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The emergence of drug resistance to targeted cancer therapies: Clinical evidence

Ana Bela Sarmento-Ribeiro[a,b,*], Andreas Scorilas[c], Ana Cristina Gonçalves[a], Thomas Efferth[d], Ioannis P. Trougakos[e,**]

[a] Laboratory of Oncobiology and Hematology and University Clinic of Hematology and Coimbra Institute for Clinical and Biomedical Research - Group of Environment Genetics and Oncobiology (iCBR/CIMAGO), Faculty of Medicine, University of Coimbra (FMUC), Center for Innovative Biomedicine and Biotechnology (CIBB), Coimbra, Portugal

[b] Hematology Department, Centro Hospitalar e Universitário de Coimbra (CHUC), Coimbra, Portugal

[c] Department of Biochemistry and Molecular Biology, Faculty of Biology, National and Kapodistrian University of Athens, Athens, Greece

[d] Department of Pharmaceutical Biology, Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany

[e] Department of Cell Biology and Biophysics, Faculty of Biology, National and Kapodistrian University of Athens, Greece

Abbreviations: α-KG, α-ketoglutarate; 2-HG, 2-hydroxyglutarate; ABL, Abelson kinase; ADCC, antibody dependent cellular cytotoxicity; ADCs, antibody-drug conjugates; ADP, antibody-dependent phagocytosis; AGP, α 1-acid glycoprotein; ALK, anaplastic lymphoma kinase; ALL, B-cell acute lymphoblastic leukemia; ALP, autophagy-lysosome pathway; AML, acute myeloid leukemia; AMPK, 5' adenosine monophosphate-activated protein kinase; APCs, antigen presenting cells; APL, acute promyelocytic leukemia; APLs, synthetic alkylphospholipids; Ara C, cytarabine; *Atg*, autophagy related gene; ATO, arsenic trioxide; BCC, basal cell carcinoma; BCRP, ABCG2, breast cancer related protein; BiTE, bispecific T cell engager; BsAbs, bivalent bispecific antibodies; BTK, Bruton's tyrosine kinase; CAFs, cancer-associated fibroblasts; CAR, chimeric antigen receptor; CDA, cytidine deaminase; CDC, complement dependent cytotoxicity; CI, cancer immunotherapy; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMML, chronic myelomonocytic leukemia; CP, 20S proteasome core particle; CRBN-CRL4, E3 ubiquitin ligase cereblon; CRC, colorectal cancer; CTCL, cutaneous T-cell lymphoma; CTLA-4, cytotoxic T lymphocyte antigen 4; Dbs, diabodies; dCK, deoxycytidine kinase; DIABLO, IAP-binding mitochondrial protein; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ER, endoplasmic reticulum; ERKs, extracellular signal-regulated kinases; FASLG, FAS ligand; FDA, US Food and Drug Administration; FGF, fibroblast growth factor; FGFR, fibroblast growth factor receptor; FLT3, fms-related tyrosine kinase 3; FOXO3, forkhead box O3; GIST, gastrointestinal stromal tumors; GRB2, growth factor bound 2; GST, glutathione S-transferase; HAT, histone acetyltransferases; hCNTs, concentrative nucleoside transporters; HCT, hematopoietic stem cell transplantation; HDAC6, microtubule-associated histone deacetylase 6; HDACis, histone deacetylase inhibitors; HDACs, histone deacetylases; hENTs, nucleoside transporters; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; Hh, Hedgehog; HMAs, hypomethylating agents; hNTs, human nucleoside transporters; hOCT1, human organic cation transporter 1; IAPs, inhibitor of apoptosis proteins; IDH, isocitrate dehydrogenase; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; IFN, interferon; IGF-1, insulin-like growth factor-1; IGF-1R, insulin growth factor-1 receptor; IKZF1, Ikaros; IKZF3, Aiolos; IL-6, interleukin 6; IMiD, immunomodulatory drugs; IMA, imatinib; InS/GF, Insulin/Growth Factor; InsR, insulin receptor; IRF4, interferon regulatory factor 4; IRS-1, insulin receptor substrate 1; IκB, inhibitors of nuclear factor-κB; JAK, Janus kinase; JNKs, Jun N-terminal kinases; KIT, stem cell growth factor receptor; LEN, lenalidomide; LSAs, lineage-specific antigens; LTK, leukocyte tyrosine kinase; mAbs, monoclonal antibodies; MAPK, mitogen-activated protein kinase; MB, medulloblastoma; MCL, mantle cell lymphoma; MDS, myelodysplastic syndromes; MDSCs, myeloid-derived suppressor cells; MET, met proto-oncogene; MHC, major histocompatibility complex; MM, multiple myeloma; MMAE, monomethyl auristatin E; MPN, myeloproliferative neoplasm; MRP1, multidrug resistance associated protein; mTOR, mammalian target of rapamycin; NFE2L2, nuclear factor, erythroid 2 like 2; NLSAs, non-LSAs; NRTK, non-receptor tyrosine kinase; NSCLC, non-small cell lung cancer; OS, overall survival; P-gp, P-glycoprotein (ABCB1); PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1; PARP1, poly(ADP-ribose) polymerase 1; PDGF, platelet derived growth factor; PFS, progression-free survival; PI3K, phosphatidylinositol 3-kinase; PIs, proteasome inhibitors; PKC, protein kinase C; PLCγ2, phospholipase c gamma 2; PLK, Polo-like kinases; PN, proteostasis network; POM, pomalidomide; PTCH1, patched 1; PTCL, peripheral T-cell lymphoma; RP, 19S proteasome regulatory particle; RTK, receptor tyrosine kinase; scDbs, single chain diabodies; scFv, single-chain variable fragment; SCLC, small-cell lung cancer; SHC, src homology 2 domain containing transforming protein 1; SLAMF7, lymphocytic activation molecule F7; SLC28, solute carrier family 28; SLC29, solute carrier family 29; SLL, small lymphocytic lymphoma; SMO, smoothened; STAT, signal transducer and activator of transcription; SUFU, hedgehog inhibitor suppressor of fused; taFvs, tandem single chain variable fragments; TAMs, tumor-associated macrophages; Tcon, conventional T cells; TCR, T-cell receptor; TET, ten eleven translocation; THAL, thalidomide; TILs, tumor-infiltrating lymphocytes; TKIs, tyrosine kinase inhibitors; TME, tumor microenvironment; TML, tumor mutational load; TNF-α, tumor necrosis factor α; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor-related apoptosis-inducing ligand; Treg, regulatory T cells; TRX, thioredoxin; UCK, uridine-cytidine kinase; UPP, ubiquitin-proteasome pathway; UPR, unfolded protein response; VEGF, vascular endothelial growth factor; XIAP, X-linked inhibitor of apoptosis

* Corresponding author at: Laboratory of Oncobiology and Hematology and University Clinic of Hematology, Faculty of Medicine, University of Coimbra, Azinhaga de Santa Comba - Celas, 3000-548 Coimbra, Portugal.

** Corresponding author at: Department of Cell Biology and Biophyscis, Faculty of Biology, National and Kapodistrian University of Athens, Athens, 15784, Greece.

E-mail addresses: absarmento@fmed.uc.pt (A.B. Sarmento-Ribeiro), itrougakos@biol.uoa.gr (I.P. Trougakos).

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ABSTRACT

For many decades classical anti-tumor therapies included chemotherapy, radiation and surgery; however, in the last two decades, following the identification of the genomic drivers and main hallmarks of cancer, the introduction of therapies that target specific tumor-promoting oncogenic or non-oncogenic pathways, has revolutionized cancer therapeutics. Despite the significant progress in cancer therapy, clinical oncologists are often facing the primary impediment of anticancer drug resistance, as many cancer patients display either intrinsic chemoresistance from the very beginning of the therapy or after initial responses and upon repeated drug treatment cycles, acquired drug resistance develops and thus relapse emerges, resulting in increased mortality. Our attempts to understand the molecular basis underlying these drug resistance phenotypes in pre-clinical models and patient specimens revealed the extreme plasticity and adaptive pathways employed by tumor cells, being under sustained stress and extensive genomic/proteomic instability due to the applied therapeutic regimens. Subsequent efforts have yielded more effective inhibitors and combinatorial approaches (e.g. the use of specific pharmacologic inhibitors with immunotherapy) that exhibit synergistic effects against tumor cells, hence enhancing therapeutic indices. Furthermore, new advanced methodologies that allow for the early detection of genetic/epigenetic alterations that lead to drug chemoresistance and prospective validation of biomarkers which identify patients that will benefit from certain drug classes, have started to improve the clinical outcome. This review discusses emerging principles of drug resistance to cancer therapies targeting a wide array of oncogenic kinases, along with hedgehog pathway and the proteasome and apoptotic inducers, as well as epigenetic and metabolic modulators. We further discuss mechanisms of resistance to monoclonal antibodies, immunomodulators and immune checkpoint inhibitors, potential biomarkers of drug response/drug resistance, along with possible new therapeutic avenues for the clinicians to combat devastating drug resistant malignancies. It is foreseen that these topics will be major areas of focused multidisciplinary translational research in the years to come.

1. Introduction

Following human genome sequencing and the massive amount of genetic information gathered from patients' tumors during the last decades, the use of targeted cancer therapies has revolutionized the treatment of this devastating disease. In general, with the term of targeted tumor therapies we primarily refer to small molecules or antibodies that block the function of individual mutated oncogenic (or non-oncogenic) proteins that drive cancer development and/or progression. These therapies target the main hallmarks of cancer (Hanahan and Weinberg, 2011) including oncogenic addiction (i.e. kinase inhibitors) or evasion of immune surveillance (i.e. monoclonal antibodies, immunomodulators and/or immune checkpoint inhibitors) (Alexa-Stratulat et al., 2019; Duplaquet et al., 2018; Kon and Benhar, 2019; Yamaoka et al., 2018; Jiang and Ji, 2019; Hui, 2019). Additional recent therapeutic approaches include inhibitors of the ubiquitin-proteasome pathway (UPP) [e.g. proteasome inhibitors (PIs)] (Niewerth et al., 2015) and apoptotic inducers; targeted nanomedicine to overcome multidrug resistance (Bar-Zeev et al., 2017; Livney and Assaraf, 2013), as well as epigenetic and metabolic modulators (Ahronian and Corcoran, 2017) (Fig. 1).

Yet, and despite the significant improvement achieved in the overall survival (OS) of patients undergoing targeted therapies, anticancer drug resistance remains a major hindrance to curative cancer therapy (Wijdeven et al., 2016; Raz et al., 2016; Zhitomirsky and Assaraf, 2016; Taylor et al., 2015; Gonen and Assaraf, 2012). Chemoresistance in the clinical oncology setting occurs either due to pre-existing mutations (intrinsic resistance) or during therapy (acquired resistance) resulting in disease progression and lethality; this phenomenon is also observed during anti-tumor immune therapies (Alexa-Stratulat et al., 2019; Kon and Benhar, 2019; Martins et al., 2019; O'Donnell et al., 2019). Acquired resistance mostly relates to the fact that although the majority of malignant cells in the tumor may contain the targeted mutation, a number of tumor subclones either harbor genetic pre-existing alterations or following exposure to the drug, acquire *de novo* mutations, supporting their survival and proliferation thus becoming resistant to the drug(s) (Burrell and Swanton, 2014; Almendro et al., 2013; Vogelstein et al., 2013; Hata et al., 2016). Resistance mostly relates to alterations in signaling modules of the targeted pathway; e.g., in BRAF mutant melanomas, only a small percentage of the detected drug resistance mutations were outside the mitogen-activated protein kinase (MAPK) pathway (Piotrowska et al., 2015). This is also evident in drugs that target the huge complexity of the receptor tyrosine kinase (RTK) family of growth factors (Ahronian and Corcoran, 2017; Yamaoka et al., 2018). Acquired resistance to targeted tumor therapies may also involve the activation of pathways that compensate for the loss of the targeted pathway as it usually occurs by the autophagy-lysosome pathway (ALP), the unfolded protein response (UPR) or molecular chaperons' activation in multiple myeloma (MM) tumors treated with PIs (Manasanch and Orlowski, 2017). Our understanding of the tremendous tumor heterogeneity has been also enhanced by approaches that include analyses of circulating tumor DNA, which is a novel mean to detect genomic alterations in metastatic tumor lesions and subclones within an individual patient; these approaches allow a frequent, non-invasive wide view of tumor heterogeneity and its evolvement vs. a single-lesion tumor biopsy (Wagle et al., 2014).

In the current review we focus on the general and often converging mechanisms that have been implicated in the development of drug resistance in cancer following treatment with targeted therapies. Also, we discuss potential biomarkers of drug response/drug resistance, as well as possible therapeutic means to overcome drug resistance in targeted therapies.

2. The emergence of drug resistance to selective inhibitors

2.1. Tyrosine kinase and other kinase inhibitors

Kinases display a fundamental role in cell proliferation, survival, and migration; hence when constitutively overexpressed and/or activated, tyrosine kinases are associated with cancer development, progression and metastasis (Bhullar et al., 2018). Tyrosine kinases transfer a phosphate group from ATP to tyrosine residues of specific proteins and together with phosphatases regulate cell growth, differentiation, and death (Bhullar et al., 2018; Jiao et al., 2018). These proteins can be divided into two categories according to their structures: RTKs and non-receptor tyrosine kinases (NRTKs) (Jiao et al., 2018).

2.1.1. Receptor tyrosine kinase (RTK) inhibitors

A series of drugs, target the huge complexity of the RTK family of growth factors. RTKs are comprised of the extracellular domain which contains the ligand-binding site and defines its specificity, a single transmembrane region and a cytosolic domain, which includes the C-terminal region that is variable in different RTK families and also contains the tyrosine kinase domain (Yamaoka et al., 2018). RTKs receive signals from the extracellular milieu by binding to their ligands which trigger their homo- or hetero-dimerization and auto-phosphorylation of the tyrosine residues; distinctly from other RTKs, the insulin receptor *α*- and *β*-subunits exist as a dimer independently of ligand binding (Yamaoka et al., 2018). The auto-phosphorylation event leads to the assembly of downstream signaling molecules containing the phosphotyrosine-binding and Src homology 2 domain; these molecules include adaptor proteins (SHC and GRB2), transcriptional factors [e.g. the signal transducer and activator of transcription (STAT)], ubiquitin ligases and phospholipases, as well as several kinases [e.g. phosphatidylinositol 3-kinase (PI3K) and SRC]. Activation of RTKs induces diverse biological responses, including cell growth, survival, inhibition of apoptosis, promotion of angiogenesis (Gacche and Assaraf, 2018) and activation of cell motility via the proto-oncogenic RAS/RAF/MAPK, PI3K/AKT/mammalian target of rapamycin (mTOR), PLC-γ/protein kinase C (PKC) and Janus kinase (JAK)/STAT pathways (Yarden and Pines, 2012).

Members of the RTKs family are the receptors of the epidermal (EGF) (i.e. EGFR, HER2 –without ligand binding domain –, HER3 – with weak or no intrinsic kinase activity – and HER4), platelet derived (PDGF), vascular endothelial (VEGF), fibroblast (FGF) and hepatocyte (HGF) (MET) growth factors, as well as the leukocyte tyrosine kinase (LTK) (ALK) (Yamaoka et al., 2018) and FLT3 a cytokine receptor that belongs to the class III RTKs. Members of the insulin receptor family, namely insulin (InsR) and Insulin Growth Factor-1 (IGF-1R) receptors recruit and phosphorylate the adaptor protein insulin receptor substrate 1 (IRS-1) after auto-phosphorylation of their tyrosine residues at the β subunit (Murakami and Rosen, 1991), leading to association with several downstream signaling molecules such as PI3K, GRB2 and SHP2 (Engelman, 2009; Ando et al., 1994). These receptors are associated with oncogenic aberrations as they undergo numerous modifications during tumorigenesis including amplification or overexpression (e.g. HER2, FGFR), deletions or mutations (e.g. EGFR, PDGFR) and translocations (e.g. ALK, FGFR) (Ahronian and Corcoran, 2017). The aberrant oncogenic activation of RTKs can be caused by ligand-dependent or ligand-independent mechanisms (Hanahan and Weinberg, 2011) and thus RTKs are suitable targets for therapy.

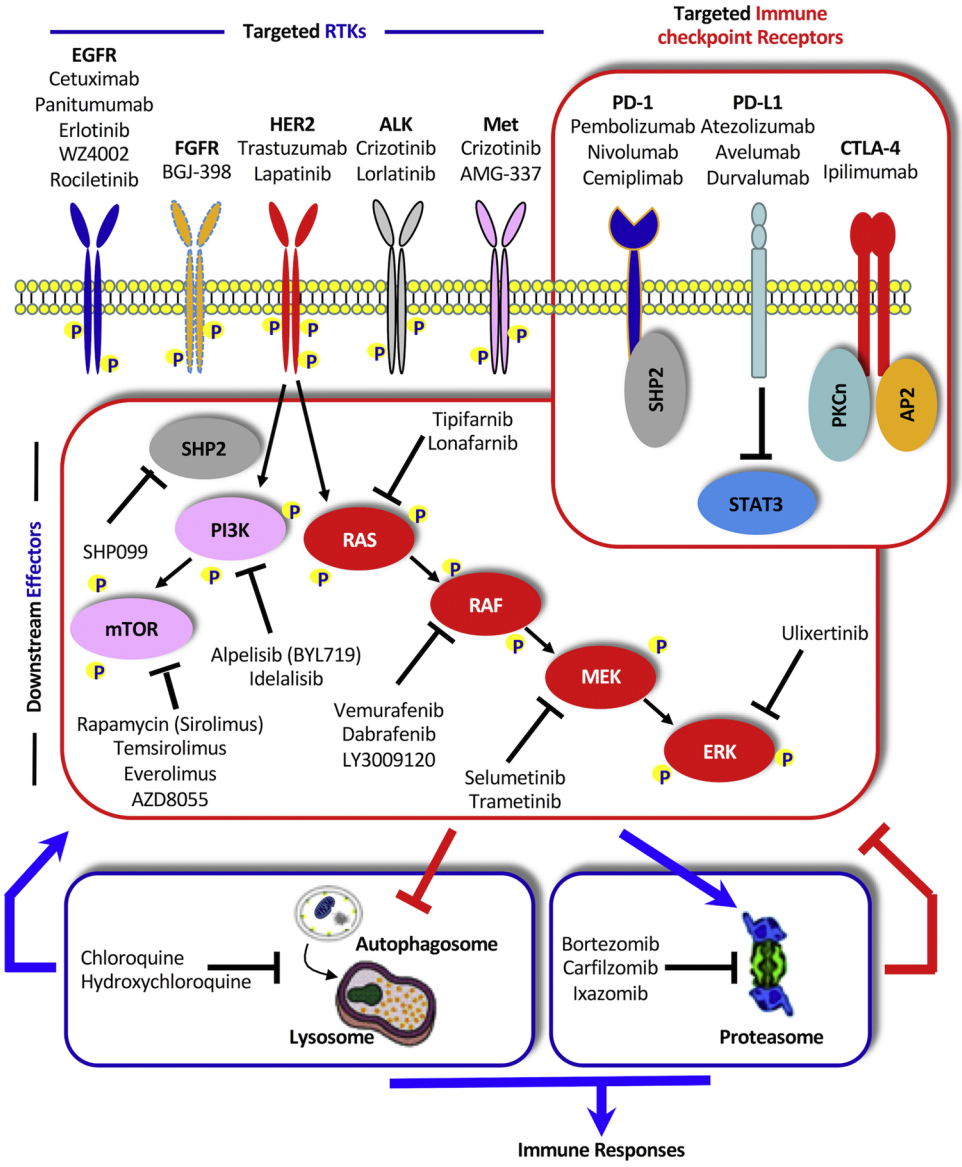

Fig. 1. Drugs that target RTKs or their downstream effectors, proteostatic pathways and immune checkpoint receptors. Drugs refer to monoclonal antibodies or kinase inhibitors targeting multiple receptors; shown are, EGFR (epidermal growth factor receptor), FGFR (fibroblast growth factor receptor), HER2 (human epidermal growth factor receptor 2), ALK (anaplastic lymphoma kinase) and MET. Inhibitors targeting downstream effectors, e.g. SHP2 and members of the PI3K (phosphatidylinositol-3-kinase) or the MAPK (mitogen-activated protein kinase) pathways, along with monoclonal antibodies targeting immune checkpoint receptors i.e. PD-1, PD-L1 and CTL4-A, and small molecules inhibiting ALP and UPP are indicated. Additional targeted therapies include apoptotic inducers, as well as, epigenetic and metabolic modulators (not shown). Reported regulatory crosstalk of the oncogenic InS/GF signaling pathways with ALP, UPP (see text) along with the positive regulation of ALP and (mostly) UPP to immune responses, e.g. via antigen presentation, are also shown (→ positive regulation; ⊣ negative regulation).

Therapies against deregulated RTKs include targeting of the intracellular tyrosine kinase domain by reversible or irreversible tyrosine kinase inhibitors (TKIs) or binding to extracellular domains. Thus, a number of small molecule inhibitors, such as multikinase inhibitors (in the case of VEGFR, PDGFR/KIT and FGFR which have similar structures in their intercellular kinase domains) or specific TKIs, along with several monoclonal Abs, including antibodies against EGFR (cetuximab, panitumumab and necitumumab), HER2 (trastuzumab, ado-trastuzumab, emtansine and panitumumab), VEGFR2 (ramucirumab) and PDGFRα (olaratumab) that bind to extracellular regions leading to prevention of downstream signaling have been developed; yet, apart from the rather low safety profiles of these agents and severe adverse effects, a frequent issue with their use is the development of *on-target* or *off-target* drug resistance (Yamaoka et al., 2018).

On-target drug resistance relates to mutations of the target such as the secondary mutation T790 M that is frequently seen in EGFR resistant patients (Milik et al., 2017) or to EGFR C797S and L718Q mutations that led to the development of third generation mutant-specific inhibitors (Wang et al., 2016). Prevention of drug binding to HER2 is mediated by gradual loss of its extracellular domain due to proteolytic shedding that results in a membrane-associated fragment, which has acquired constitutive activity (Christianson et al., 1998). This fragment lacks a binding site for trastuzumab and is associated with clinical resistance to this drug (Scaltriti et al., 2007), while the HER2 T798I gatekeeper mutation is associated with a high level of resistance to lapatinib (Trowe et al., 2008) and neratinib (Hanker et al., 2017) because of low binding affinity to these drugs. Regarding ALK, more than 10 mutations are related to crizotinib resistance and occur at equal frequencies (Lin et al., 2017). Ceritinib and alectinib were developed as second-generation ALK-TKIs for cases of crizotinib-resistance and were approved as breakthrough therapies by the US Food and Drug Administration (FDA) (Golding et al., 2018; Katayama, 2018). Similarly, gatekeeper mutations in FGFRs occur in the ATP-binding cleft and induce resistance to FGFR inhibitors in cell lines (Byron et al., 2013; Chell et al., 2013), while reported resistance mechanisms to MET TKIs include *MET* gene amplification (Cepero et al., 2010), point mutations in MET (Bahcall et al., 2016) and/or MET overexpression (Martin et al., 2014; Migliore et al., 2018). Furthermore, the T670I gatekeeper mutation of ATP-binding pocket of c-KIT directly inhibits imatinib (IMA) binding (Tamborini et al., 2006).

Off-target resistance mechanisms to RTKs inhibitors refer to the emergence of bypass signaling pathways which activate kinases other than the targeted RTK pro-survival pathways substituting thus the loss of the targeted molecule (Manasanch and Orlowski, 2017; Milik et al., 2017); pro-survival pathways may also be activated simply because they were inhibited by the targeted pathway. Additional mechanisms of resistance to RTKs inhibition include phenotypic transformation and resistance to apoptotic cell death or even alterations in immune responses (see below). EGFR targeting *off-target* resistance pathways mostly relate to hyper-activated MET signaling (Guo et al., 2017) and thus a combinatorial therapy with EGFR and MET TKIs is expected to overcome this resistance (Yamaoka et al., 2018). Development of resistance to third generation inhibitors of EGFR is related to gene amplification of HER-2, MET or ERBB2 (Wang et al., 2016). Inhibition of HER2 caused compensatory activation of downstream molecules mediated by HER3 up-regulation resulting in resistance to lapatinib (Garrett et al., 2011) and since trastuzumab cannot prevent the HER2/HER3 dimerization, up-regulation of HER3 also induces resistance to this drug (Wehrman et al., 2006). Additional downstream pathways related to HER2-TKIs resistance include activation of the PI3K/AKT/mTOR and SRC family of the non-receptor tyrosine kinases. In support, a mutant PI3K regulatory subunit is frequently observed in many cancers and causes constitutive activation of this enzyme (Jimenez et al., 1998; Philp et al., 2001). The molecular mechanisms of resistance to the ALK TKI crizotinib include signaling bypass by other RTKs such as EGFR, KIT, IGF-1R or downstream signaling molecules, e.g. SRC, MEK/ERK (Katayama et al., 2012; Crystal et al., 2014; Lovly et al., 2014). Similarly, VEGFR2 inhibition induced upregulation of other proangiogenic factors including FGF family members, angiopoietin, PDGF and HGF (Casanovas et al., 2005). Consistently, co-inhibition of VEGF and FGF had an inhibitory effect on angiogenesis and tumor progression in a preclinical model (Casanovas et al., 2005); yet, the therapeutic efficacy of this scheme was limited in the clinic. Tumor progression during anti-VEGF therapies can relate to an alternative pathway acting through PDGF-PDGFR which confers resistance to anti-VEGF therapy (Mamer et al., 2017) or to MET activation; similarly, KRAS gene amplification is reportedly involved in resistance mechanisms to MET TKIs (Cepero et al., 2010). Regarding the difficulty to treat triple negative breast cancer that lacks estrogen receptors, progesterone receptors and HER2 gene amplification, recent efforts include poly(ADP-ribose) polymerase 1 (PARP1) inhibitors, receptor, non-receptor tyrosine kinases and immune-checkpoints inhibitors, androgen receptor and epigenetic proteins (Lee and Djamgoz, 2018).

Another pro-survival *off-target* pathway being commonly activated upon treatment with RTKs inhibitors (Aveic and Tonini, 2016) is ALP (Klionsky et al., 2016). ALP is an intracellular self-catabolic process that in mammalian cells results in macroautophagy, microautophagy, and chaperone-mediated autophagy; in macroautophagy, double membrane vesicles (autophagosomes) being formed by the participation of autophagy related proteins (Atg) capture lipids, proteins or organelles and transfer them to lysosomes for degradation (Klionsky et al., 2016). ALP can also degrade ubiquitinated substrates (e.g. protein aggregates) via the action of microtubule-associated histone deacetylase 6 (HDAC6) and ubiquitin receptor p62/SQSTM1 which directly binds to ubiquitinated protein aggregates (Gumeni and Trougakos, 2016). ALP is tightly regulated by metabolic signaling pathways, including positive regulation by 5' adenosine monophosphate-activated protein kinase (AMPK) and sirtuins or negative regulation by growth promoting signaling, e.g., modules of the Insulin/Growth Factor (InS/GF) pathway like RTKs or their downstream effectors (Levine and Kroemer, 2008). Aberrant activation of RAS in pancreatic ductal adenocarcinoma stimulates RAF/MEK/ERK, PI3K/AKT/mTOR and RalA/B signaling pathways (Mann et al., 2016), whereas therapeutic inhibition of these pathways likely culminates in activation of autophagy (Luo et al., 2009). EGFR inhibitors can induce cytoprotective autophagy (Cui et al., 2014) via the RAS/RAF/MEK/ERK signaling pathway (Sooro et al., 2018), while acquired resistance to EGFR-TKIs, was found to induce autophagy in a dose-dependent manner following treatment of multiple cancer cell lines with EGFR-TKIs (Camidge et al., 2014); consistently, inhibition of autophagy in lung cancer cells enhanced the cytotoxic effect of EGFR-TKIs (Sui et al., 2014). Also, autophagy contributes to drug resistance following EGFR inhibition in metastatic colorectal cancer (Koustas et al., 2017) and targeted treatment of advanced non-small cells lung cancer (NSCLC) patients with afatinib in EGFR mutants, or crizotinib in ALK break positive patients. Despite profound tumor responses, inevitably induced drug resistance occurs, which was also associated with elevated autophagy (van der Wekken et al., 2016). Notably, autophagy has a decisive role in the resistance after BRAF inhibition in BRAF-mutated melanoma (Liu et al., 2018a). In anti-angiogenic treatment, increased hypoxia triggered devascularization; yet, some tumor cells survived the hypoxic insult elicited by antiangiogenic therapy through autophagy by activating the AMPK and HIF-1α pathways (Hu et al., 2012). Autophagy has been (among others) implicated in drug resistance to mTOR inhibitors such as temsirolimus and everolimus in metastatic renal cell carcinoma (mRCC) (Santoni et al., 2014). These findings have triggered several ongoing preclinical and clinical studies with autophagy inhibitors (e.g. chloroquine or hydroxychloroquine which alkalize lysosomal pH, hence disrupting lysosomal activity) to improve anti-cancer therapy, with encouraging readouts referring to some partial responses and disease stabilization (Chude and Amaravadi, 2017). Nonetheless, chloroquine and hydroxychloroquine display several *off-target* effects resulting in substantial adverse effects, as it has

emerged from clinical trials in which they were tested (Chude and Amaravadi, 2017; Zhitomirsky and Assaraf, 2016).

Finally, additional mechanisms of resistance to RTKs treatment may relate to transformation to other tumor types, as seen for instance in NSCLC patients with EGFR mutations where sampling showed the histological transformation from adenocarcinoma to small cell lung cancer (SCLC) (Sequist et al., 2011) or due to epithelial-mesenchymal transition (EMT) where AXL upregulation might be a significant mechanism of acquired resistance to EGFR-TKIs in EGFR-active mutant NSCLCs (Zhang et al., 2012). Furthermore, suppression of apoptotic pathways, e.g. due to activation of NF-κB signaling pathway conferred resistance to TKIs in EGFR mutant NSCLC cells (Bivona et al., 2011), while additional mechanism of resistance may relate to KRAS, NRAS, BRAF or PI3CA mutations, as well as PTEN deletion during resistance to anti-EGFR mAbs in colon cancer (Amado et al., 2008; Karapetis et al., 2008). Despite our understanding about the mechanisms of drug action and resistance to TKIs, much more is needed to be done in order to fully understand the drug selective and tumor microenvironment (TME) mechanisms that trigger the acquisition of resistance to TKIs.

2.1.2. *Non-receptor tyrosine kinase (NRTK) inhibitors*

NRTKs are cytoplasmic proteins or proteins anchored to cell membrane that trigger intracellular signals derived primarily from RTKs and/or other growth factor receptors (Jiao et al., 2018; Siveen et al., 2018). These tyrosine kinases can be subclassified into nine subfamilies according to kinase domains sequence similarities, namely ABL, FES, JAK, ACK, SYK, TEC, FAK, SRC and CSK (Du and Lovly, 2018; Siveen et al., 2018). NRTKs play a crucial role in several cellular mechanisms. For example, the Abelson (ABL) kinase family, which includes the ABL1 and ABL2 proteins, is essential for normal cellular function and regulates cellular growth through activation of the transcription factor Rb (Du and Lovly, 2018; Siveen et al., 2018). ABL1 (a gene which resides on chromosome 9) is mainly known for its crucial role in chronic myeloid leukemia (CML), where as a result of a translocation between chromosome 9 and 22 (where the BCR gene is located), ABL1 fuses with BCR, resulting in the oncoprotein BCR-ABL (Balabanov et al., 2014). Deregulation and abnormal expression of ABL kinases has been also implicated in several other types of cancer, namely colon cancer (Chen et al., 1999), breast cancer (Srinivasan and Plattner, 2006) and NSCLC (Rikova et al., 2007).

Given the central role of NRTKs on carcinogenesis, several specific kinase inhibitors have been developed to target mutated kinases and inhibit their activity. These TKIs revolutionized the treatment of various cancers and represented a therapeutic breakthrough. In general, TKIs exhibit excellent clinical results being efficacious and well tolerated but they trigger a strong discerning pressure for cells to acquire drug resistance; thus, acquired resistance remains a primary hindrance in TKIs therapy (Bhullar et al., 2018; Luo et al., 2018). IMA, a BCR-ABL inhibitor, was the first approved TKI by FDA, initially for CML after failure of INF-alpha therapy and later for CML as first-line therapy, ALL Ph positive and for gastrointestinal stromal tumors (GIST) due to oncogenic mutations in the RTK, KIT. Although IMA remains one of the gold standard for first-line treatment of CML, the emergence of IMA resistance led to the development of second- (nilotinib, dasatinib, and bosutinib) and third- (ponatinib) generation TKIs (Ali, 2016). Clinical and cell-based studies identified a variety of TKIs resistance mechanisms, but mutations in the kinase gatekeeper residue is the most frequent mechanism, since hydrophobic interactions on this site are critical for the binding affinity of TKIs (Bhullar et al., 2018; Sierra et al., 2010). Common molecular mechanisms of resistance are represented in Fig. 2 and include target genetic modifications, such as point mutations, as well as genomic deletions and amplifications, with point mutations being the most frequent mechanism of resistance to TKIs (Sierra et al., 2010). Frequent resistance to these drugs is associated with mutations that decrease the affinity of TKIs for the target kinase domain, mutations that alter the amino acids surrounding the TKI binding site and mutations that increase the affinity of the kinase for ATP decreasing thus the effectiveness of the ATP-competitive inhibitors (Chen and Fu, 2011; Sierra et al., 2010). A classic example of a gatekeeper mutation is the BCR-ABL T315I mutation that leads to resistance to several BCR-ABL inhibitors (except ponatinib) used in CML treatment (Ali, 2016; Balabanov et al., 2014). More than 100 different mutations have been associated with IMA resistance, and about 40–90% of IMA-resistant patients have at least one BCR-ABL mutation (Ali, 2016).

Ibrutinib, the first approved Bruton's tyrosine kinase (BTK) inhibitor, has been shown to have clinical activity against B-cell malignancies, including chronic lymphocytic leukemia (CLL), mantle cell lymphoma, Waldenstrom's macroglobulinemia, small lymphocytic lymphoma and marginal zone lymphoma (Liu et al., 2018). Resistance to ibrutinib has been mainly associated with mutations in BKT (Chiron et al., 2014; Maddocks et al., 2015; Sharma et al., 2016; Woyach et al., 2014) and PLCγ2 (Cheng et al., 2015; Furman et al., 2014; Liu et al., 2015; Maddocks et al., 2015), with most patients showing the substitution of C481 by other amino acids at the ibrutinib-binding site in BTK (Liu et al., 2018). Point mutations are also responsible for ruxolitinib resistance. This TKI was the first JAK inhibitor to be approved for the treatment of intermediate and high-risk myelofibrosis, a myeloproliferative neoplasm (MPN) (Meyer and Levine, 2014a).

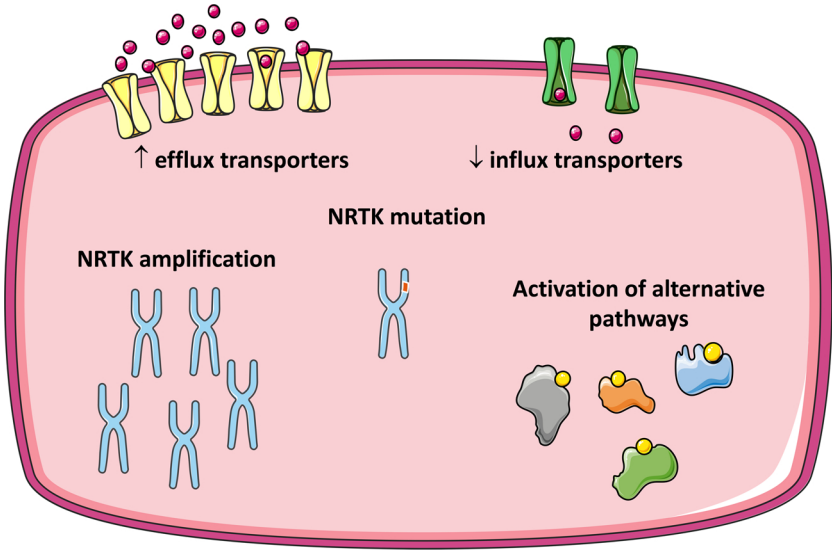

Fig. 2. Schematic representation of the most common mechanisms of resistance to non-receptor tyrosine kinase inhibitors (NRTKIs). These include mutations in the target protein (e.g. BTK mutation conferring resistance to ibrutinib), target gene amplification (e.g. BCR-ABL1 amplification that induces resistance to IMA), overexpression of multidrug efflux pumps (e.g. P-glycoprotein that is associated with resistance to several NRTKIs), downregulation of influx transporters (e.g. hOCT1/SLC22A1 that leads to decreased intracellular concentration of IMA and consequently to therapeutic failure) or activation of alternative compensatory pathways (e.g. activation of HCK, LYN, KRAS or JAK2).

Furthermore, five non-synonymous mutations in the JAK2 kinase domain of JAK2V617 F mutant cells have been identified that conferred resistance to ruxolitinib (Deshpande et al., 2012); so far however, none of these JAK2 mutations have been identified in MPN patients treated with JAK2 inhibitors suggesting that mutation-independent mechanisms may be also involved in resistance to chronic JAK kinase inhibition (Bhagwat et al., 2013; Meyer and Levine, 2014b). Gatekeeper mutations were also identified as mechanisms of resistance to other TKIs that target tyrosine kinase receptors including quizartinib (FLT3 G697R) (Pauwels et al., 2012), midostaurin (FLT3 F691) (Short et al., 2019), IMA (KIT T670I and PDGFRAT674I) (Heinrich et al., 2006; Metzgeroth et al., 2012), erlotinib and gefitinib (EGFR T790) (Godin-Heymann et al., 2008). Gene copy number alterations and protein expression level changes are additional mechanisms of TKI resistance. IMA resistance can also arise from BCR-ABL gene amplification. This resistance mechanism is less frequent than point mutations, but BCR-ABL gene amplification was detected in resistant CML patients (Gorre et al., 2001). Additionally, loss of normal ABL1 allele in CML, which resulted from a cryptic interstitial deletion in 9q34, was also associated with IMA resistance in CML patients (Virgili et al., 2011). Similarly, ibrutinib resistance is also associated with deletions in the short arm of chromosome 8 that result in tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) insensitivity (Liu et al., 2018).

Besides these target-specific resistance mechanisms, TKIs also showed other resistance mechanisms such as altered influx and efflux drug transporters and activation of alternative signaling pathways. The decrease of effective intracellular concentration of a TKI that leads to resistance can result from decreased drug influx, increased drug efflux and drug plasma sequestration (Sierra et al., 2010). Taking IMA as an example, several studies indicate that decreased expression of the organic cation transporter (hOCT1; SLC22A1), as well as increased expression of P-glycoprotein (P-gp; ABCB1) and breast cancer related protein (BCRP; ABCG2) are mechanisms of TKI resistance (Ali, 2016; Balabanov et al., 2014; Chen and Fu, 2011). These mechanisms are also associated with resistance to other TKIs, such as nilotinib and dasatinib (Sierra et al., 2010). Additionally, IMA sequestration by α 1-acid glycoprotein (AGP) decreased IMA's ability to inhibit c-ABL and was found to induce resistance to this TKI in CML patients (Gambacorti-Passerini et al., 2003; Le Coutre et al., 2002). Hydrophobic weak base TKIs including sunitinib and nintedanib have been shown to undergo efficient sequestration by lysosomes followed by lysosome exocytosis in RCC and NSCLC, hence uncovering a novel mechanism of drug resistance via lysosomal entrapment of these TKIs or other weakly basic hydrophobic anticancer drugs (Englinger et al., 2017; Gotink et al., 2011, 2014; Zhitomirsky and Assaraf, 2015, 2017). Finally, cancer cells can survive treatment with TKIs by activating alternative signaling pathways. For example, CML cells resistant to IMA can activate the PI3K signaling pathway (Burchert et al., 2005), the SRC kinase family (particularly HCK and LYN) (Donato et al., 2003; Pene-Dumitrescu and Smithgall, 2010), KRAS (Agarwal et al., 2008) and/or JAK2 (Wang et al., 2007) in order to compensate the loss of BCR-ABL activity.

2.1.3. Serine/threonine kinase and lipid kinase inhibitors

About 8% of all human cancers harbor the V600E mutation in BRAF. This mutation constitutively activates the MAPK pathway, which causes resistance to chemo- and immune-therapy and fosters metastasis. Vemurafenib and dabrafenib are *BRAF inhibitors* that have been developed against this specific mutation for melanoma treatment, and as many as 75% of all patients with the BRAFV600E mutation respond to vemurafenib. Yet, the vast majority of tumors develop drug resistance, and vemurafenib resistance is frequently linked to multidrug resistance. In this respect, improvements of progression-free survival of only 9 months on average can be reached (Griffin et al., 2017; Roskoski, 2018; Torres-Collado et al., 2018). Unexpectedly, vemurafenib and dabrafenib activate the MAP kinase pathway in tumor cells with wild-type BRAF. As the MAPK kinase pathway is activated in BRAF V600E tumors, it is a current standard practice to combine BRAF inhibitors with MEK1/2 inhibitors to achieve better response rates. A plethora of results have been generated to clarify the mechanisms underlying BRAF inhibitors resistance. Multiple mechanisms driven by genetic and epigenetic processes have been related to alterations in BRAF, MAPK and PI3K/AKT pathways and immunomicroenvironment, all of which contribute to the failure of targeted BRAF treatment (Kakadia et al., 2018). Among the known resistance mechanisms to vemurafenib and dabrafenib are *BRAF* alterations (*BRAFV600E* amplifications), *BRAF* splice variants that foster RAF dimerization, reactivation of MAPK signaling routes by secondary mutations including *NRAS* or *KRAS* mutations and *MEK1/2* mutations, activation of alternative parallel signaling routes, e.g. ERK and PI3K/mTOR, activation of negative feedback loops in the MAPK pathway, activation of non-MAP kinase pathways and other unknown mechanisms (Chapman, 2013; Welsh et al., 2016; Chan et al., 2017; Amaral et al., 2017; Pan et al., 2018).

Vemurafenib and dabrafenib target the inactive α C-helix-out and DFG-D in BRAF form. New anti-BRAF drugs (e.g. lifirafenib) inactivate the oncoprotein by binding to a different form (DFG-Din-out). Additional novel BRAF inhibitors are regorafenib and encorafenib. Ongoing clinical trials will show, whether these novel type II inhibitors demonstrate better treatment outcome and are less prone to drug resistance development.

Sorafenib is a *multi-kinase inhibitor* which inhibits several tyrosine kinases, but also the serine/threonine kinase BRAF. Although it might be expected that a drug addressing multiple targets is less prone to resistance development because of compensatory mechanisms, resistance to sorafenib is also widely seen. Among the resistance mechanisms described for sorafenib are the activation of the TGF-β pathway and EMT; activation of the PI3K/AKT, JNK, EGFR/HER3, Hedgehog, and of anti-apoptotic regulators pathways; increased cancer stem-like cells, decreased natural killer and effector T-cell activity and TME factors (Nishida et al., 2015; Chen et al., 2015).

Besides RAF kinases (including BRAF), the ERK/MAPK pathway consists of, MEK1/2 kinases and ERK1/2 kinases. As the majority of melanoma patients display MAPK pathway hyperactivation, inhibitors of this pathway are attractive drug candidates. *MEK1/2 inhibitors* include cobimetinib, binimetinib refametinib, pimasertib, selumetinib and trametinib, whereas *ERK1/2 inhibitors* are ulixertinib and ravixertinib.

Amplification, overexpression or mutations of genes involved in the MAPK pathway are main mechanisms of drug resistance. Loss of PTEN and gain of PDGFR, IGF-1R, FOXD3 and MITF have also been observed as factors contributing to drug resistance, as they compensate for the cell-killing activity of MAPK pathway inhibitors. In addition to these mechanisms related to signaling pathways in tumor cells, TME mediates drug resistance by signals conveyed by stromal fibroblasts (Poulikakos and Solit, 2011; Wellbrock, 2014). Novel *AKT inhibitors* include ipatasertib, afuresertib, uprosertib, triciribine, and AZD5363. A potential issue with AKT inhibitors is that they may induce resistance to drugs that inhibit EGFR. To overcome this impediment, a combination treatment with tyrosine kinase and serine/threonine kinase inhibitors was proposed (Tetsu et al., 2015).

Aurora A kinase plays a pivotal role in cancer cells mitosis. *Aurora kinase inhibitors* include alisertinib, danusertib, barasertib, tozasertib, hesperidin and radotinib. Resistance to mitotic spindle poisons such as paclitaxel is associated with overexpression of Aurora A and the transcription factor FOXM1. Yang et al (2019) reported that Aurora A transactivated the *FOXM1* promoter and stabilized FOXM1 expression by ubiquitin attenuation in paclitaxel-resistant triple negative breast cancer cells. Aurora A knockout inhibited proliferation of these tumor cells, which opens new avenues for overcoming drug resistance by Aurora kinase inhibitors.

Besides the role of Aurora kinase in mitosis, Aurora A activates EMT during the metastatic process and fosters the proliferation of cancer stem-like breast cancer cells. Cells overexpressing Aurora A were

resistant to conventional anticancer drugs, but treatment with the selective Aurora A kinase inhibitor alisertib reversed drug resistance. Aurora A associated drug resistance was mediated by SMAD5 and alisertib inhibited Aurora A/SMAD5 signaling (Opyrchal et al., 2017).

The expression of Aurora A also correlated with resistance to DNA-damaging agents such as cisplatin and X-ray irradiation by disturbing the repair of DNA lesions. Aurora A also fosters cell cycle progression and anchorage-independent cellular proliferation. KU-55933 is an *ATM kinase inhibitor*, which sensitizes Aurora A and ATM/Chk2 overexpressing tumor cells to cisplatin and irradiation by increasing p53 phosphorylation and decreasing Chk2, γH2AX and RAD51 levels (Sun et al., 2014). Further ATM kinase inhibitors are the natural products caffeine and wortmannin and the synthetic compounds LY294992, KU-60019, KU-59403, and CP-466722.

The activity of anticancer drugs is not only limited by resistance phenomena but also by adverse toxicity, both of which are related to each other. Non-tolerable toxicity necessitates under-dosing, which finally results in drug resistance. Among the first *CDK inhibitors* to advance to clinical trials were roscovitine (seliciclib) and the natural product derivative flavopiridol (alvocidib). Both compounds are pan-CDK inhibitors; alvocidib inhibits CDKs 1, 2, 4, 6, 7 and 9 and seliciclib inhibits CDKs 1, 2, 5, 7 and 9. The clinical responses of alvocidib in hematological tumors were limited because of non-tolerable toxicities, while seliciclib did not show objective tumor regressions at maximal tolerable concentrations. Further clinical development was discontinued, because their lack of CDK specificity prevented the selection of appropriate biomarkers to monitor tumor response during therapy and the study of their mode of action and mechanisms of resistance. The situation changed with the CDK4/6-selective drugs palbociclib, abemaciclib and ribociclib, which raised interest for the treatment of metastatic breast cancer; additional *CDK inhibitors* are dinaciclib, ronociclib, trilaciclib and voruciclib. Their selectivity facilitates biomarker monitoring and investigation of drug resistance mechanisms, as well as rationale therapy regimens in combination with other targeted protein kinase inhibitors (Whittaker et al., 2017).

Polo-like kinases (PLK) are regulators of the cell cycle and PLK1 is the most important member of this family. Interestingly, PLK1 overexpression contributes to development of resistance to chemotherapy. PLK1-mediated phosphorylation of the cell cycle related protein GTSE1 (G2 and S phase expressed 1) is needed for G2 checkpoint recovery by doxorubicin. Thus, PLK inhibition may overcome doxorubicin resistance. PLK1-mediated phosphorylation of the replication factor ORC2 promotes DNA replication in gemcitabine-treated cells. Treatment with *PLK1 inhibitors* along with gemcitabine enhanced gemcitabine efficacy in a xenograft tumor model. PLK1 conferred resistance to paclitaxel by regulating microtubule dynamics and microtubule-kinetochore attachment and PLK1 activated androgen receptor signaling, which favors resistance to androgen deprivation therapy. Furthermore, PLK1 inactivated PTEN, which increased the metabolism in prostatic tumor cells and thereby decreased the anti-cancer activity of metformin. All of these results indicate that PLK1 is an important factor in drug resistance and that inhibition of PLK1 by small molecules may sensitize tumors to standard chemotherapy. Clinical trials with rigisertib, volasertib, poloxin, GSK461364, BI2536, TAK-960, ENMD-2076 and other specific *PLK1 inhibitors* are ongoing to evaluate their clinical benefit for sensitizing tumors to chemotherapy (Gutteridge et al., 2016).

mTOR is a crucial regulator of signaling processes related to cellular growth and proliferation. It is hyperactivated in many cancers making it an attractive target for therapy. However, the clinical benefit of *mTOR inhibitors* (e.g. everolimus, temsirolimus, and ridaforolimus) is limited due to the development of drug resistance. Inherent resistance to mTOR inhibitors can occur by activation of the ERK pathway. Resistance may be acquired during therapy by downregulation of 4EBP1, a protein which is a direct target of mTOR and an inhibitor of the eukaryotic translation initiation factor 4E (eIF4E).

The PI3K/AKT/mTOR pathway exerts intense crosstalk with other signaling routes (e.g. the CXCR4/12/7 chemokine receptor axis). Feedback loops within these interwoven signaling networks dampen the efficacy of everolimus. AKT activation and mutations in FKBP-12 also cause resistance. In addition to resistance mechanisms directly associated with the signaling cascades related to mTOR, other mechanisms of resistance have also been identified such as enhanced angiogenesis, modulation of apoptosis regulators and autophagy stimulation (Carew et al., 2011; Capozzi et al., 2015; Guri and Hall, 2016). Consequently, second generation *mTOR inhibitors* (so-called “TORKinhibs”) have been developed to overcome drug resistance. Other strategies for resensitization include the dual use of mTOR and PI3K or BCL-2 inhibitors. The HDAC inhibitor vorinostat or angiogenesis inhibitors may also inhibit tumors that are resistant to mTOR inhibitors (Carew et al., 2011). Independent of resistance to mTOR inhibitors, these compounds bear a promising potential to sensitize tumors to HER2-targeting drugs such as trastuzumab. Several clinical trials revealed promising evidence showing that mTOR inhibitors (e.g. everolimus) sensitize breast carcinomas via yet unexplored mechanisms. Though the current results from clinical trials were obtained from metastatic tumors, it remains to be determined whether everolimus and other mTOR inhibitors may also reverse trastuzumab resistance in primary tumors (Nahta and O’Regan, 2010).

Activation of the PI3K signaling pathway is frequently observed in breast cancer and is associated with resistance to cytotoxic and targeted anticancer drugs, as well as to hormone therapy and radiotherapy. Most often, *PIK3CA* is amplified or mutated. PIK3CA is the α-isoform of the catalytic PI3K subunit. Other factors leading to the constitutive activation of the PI3K pathway are *AKT* amplification and *PTEN* (phosphatase and tensin homologue deeted on chromosome 10) mutation, as wild-type PTEN suppresses AKT activation (Osaki et al., 2004). Upstream of PI3K, mutations in EGFR can also activate the PI3K/AKT/mTOR pathway. Therefore, *PI3K inhibitors* raised considerable interest to improve treatment options of otherwise resistant tumors and preclinical data were promising (Burris, 2013; Gadgeel and Wozniak, 2013; Kaklamani et al., 2019). *PI3K inhibitors* include idelalisib, pictilisib, apitolisib, voxtalisib, copanlisib, and dactolisib. Unfortunately, the clinical experiences with PI3K inhibitors were rather disappointing. Among the reasons was the incomplete PI3K pathway suppression because of tumor heterogeneity and compensatory effects. Chromosomal instability is a major factor of tumor heterogeneity, which facilitates the survival of even very small subpopulations of tumor cells upon treatment with PI3K inhibitors; these subpopulations may facilitate tumor evolution and regrowth of tumor masses (Vanhaesebroeck et al., 2019). Other reasons of resistance to *PI3K inhibitors* are intrinsic drug resistance (inherent or primary resistance) and development of resistance during therapy (acquired or secondary resistance). Also, overexpression of the MYC oncogene represents one of the mechanisms, which mediated resistance to PI3K inhibitors (Dey et al., 2014). The *pan-PI3K inhibitor* buparlisib demonstrated only moderate clinical effect in combination with endocrine therapy in clinical phase III trials with aromatase inhibitor-resistant, hormone receptor-positive, human epidermal growth receptor 2 (HER2) negative breast cancer patients (Kaklamani et al., 2019). However, better treatment effects were documented in patients with PIK3CA-mutated tumors compared to those with PIK3CA-wild type cancers. Therefore, isoform-selective PI3K inhibitors may open a therapeutic window for personalized therapy settings (Yap et al., 2015). Nonetheless, it has to be tested in future clinical trials, if this hypothesis can be clinically substantiated.

2.2. Hedgehog inhibitors

Hedgehog (Hh) signaling is a highly conserved pathway that normally has a crucial role in the development and homeostasis of many organs and tissues. The canonical activation is orchestrated through binding of Hh ligands to the transmembrane receptor PATCHED 1

(PTCH1). In the absence of ligand, PTCH1 blocks pathway activity, by inhibiting the transmembrane G protein-coupled receptor SMOOTHENED (SMO), while upon ligand binding to PTCH1, both ligand and receptor are internalized and degraded and subsequently, the SMO PTCH1-mediated inhibition is relieved, leading to the activation of the GLI family of transcription factors. Thereafter, GLIs enter the nucleus and regulate the transcription of Hh target genes. Apart from the canonical pathway, ligand-independent Hh signaling pathways (non-canonical pathways) have been, also, described (Briscoe and Therond, 2013; Fattahi et al., 2018). The aberrant activation of Hh signaling leads to the expression of genes associated with the induction of cell proliferation, survival, and self-renewal and has been linked to the oncogenesis of numerous cancers, including medulloblastoma (MB), rhabdomyosarcoma, melanoma, basal cell carcinoma (BCC), and breast, lung, liver, stomach, prostate, and pancreas tumors. Therefore, drug discovery efforts have been directed against targeting Hh pathway for the treatment of patients with cancer (Lin and Matsui, 2012; Infante et al., 2015). Promising initial clinical trial results were obtained in cancers that bear mutations of the Hh pathway, such as BCC and MB, however, despite early enthusiasm, the emergence of drug resistance has been disappointing (Gan and Jimeno, 2016).

The inhibition of Hh pathway has been assessed predominantly with the development of small molecules that modulate SMO (Chahal et al., 2018). Cyclopamine, a naturally occurring alkaloid isolated from Veratrum californicum, was the first inhibitor discovered to block Hh signaling by directly binding SMO, however exhibited limitations such as toxicity and teratogenicity. Vismodegib, a second-generation cyclopamine derivative, became the first Hh pathway inhibitor to receive approval from the FDA in January 2012 for the treatment of advanced or metastatic BCC. In 2015, sonidegib was also approved for locally advanced BCC. Both drugs directly and selectively bind to SMO, thereby deactivating the Hh pathway (Wahid et al., 2016; Carpenter and Ray, 2019). Unfortunately, only 43% of advanced BCC and 30% of metastatic BCC patients responded to SMO antagonist treatment and more than 20% of patients with advanced BCC, initially responding to vismodegib treatment, developed drug resistance and, subsequently, relapse and tumor regrowth, respectively (Peer et al., 2019). Noteworthy, vismodegib-resistant patients treated with sonidegib did not benefit from the drug and experienced progressive disease (Danial et al., 2016).

Drug resistance can occur either as primary resistance, in which patients do not respond to the treatment, or as secondary resistance, in which initially treatment-sensitive patients develop resistance later on. Secondary resistance was first reported in a patient who was treated with vismodegib for metastatic MB in 2009 (Yauch et al., 2009). The initial response was followed by disease progression only 3 months after the treatment, which was attributed to a de novo D473H mutation in SMO, that impaired the ability of vismodegib to bind to SMO, conferring resistance to the drug. Additionally, in 2012, secondary resistance to vismodegib was described for advanced BCC patients. More precisely, tumor regrowth arose in 21% of the treated patients, all of which were suffering from locally advanced BCC. Since then several others have been documented for patients treated with Hh inhibitors (Danhof et al., 2018).The abovementioned acquired resistance that abolishes the therapeutic efficacy of SMO inhibitors can be attributed, according to genomic studies, to several mechanisms. More precisely, it has been reported that SMO mutations, that either impair the direct binding of the agent (e.g. SMO D473H) due to conformation changes or result in a constitutive activation of Hh signaling pathway independently of the SMO inhibitor binding, underlie treatment failure. Additionally, other resistance mechanisms proposed include mutations generating constitutively active SMO, such as loss of the gene encoding hedgehog inhibitor suppressor of fused (SUFU) or amplification of GLI2, the heterogeneity of Hh signaling pathway activity and the ligand-depend cancer and stroma interactions. Finally, the aberrant activation of other signaling pathways (PI3K-mTOR, aPKC-ι/λ, BRD4, and PDE4 signaling) that contribute to SMO-independent GLI regulation have been suggested for patients' insensitivity upon treatment (Xie et al., 2019; Gutzmer and Solomon, 2019; Dong et al., 2018).

To overcome resistance, several effective SMO inhibitors such as saridegib and taladegib have been developed (Xin et al., 2018). However, in a study with BCC patients that who had progressed after vismodegib treatment, 9 out of 94 patients did not respond to saridegib, suggesting an overlapping resistance mechanism for the two SMO inhibitors. Taladegib, which is currently in clinical trials, has been documented to be beneficial for patients bearing the D473H SMO mutation, thus providing a challenging alternative when the D473H SMO mutation restricts the application of other SMO antagonists (Zhang et al., 2017a, Zhang et al., 2017b, Zhang et al., 2017c; Ghirga et al., 2018). Additionally, two FDA-approved drugs have been identified as compelling Hh inhibitors: the anti-fungal agent itraconazole and arsenic trioxide (ATO). Itraconazole inhibits SMO at a distinct site from that bound by cyclopamine, vismodegib, or sonidegib and prevents its translocation and accumulation in the primary cilium, impairing, thus, GLI-target gene transcription. ATO hinders GLI2 ciliary accumulation at the tip, which is required for its activation and its translocation to the nucleus, and, thereafter, facilitates its degradation. Single or combination treatment with itraconazole and ATO has been effective in sensitive and resistant tumors, however, in some SMO mutant tumors, they did not ameliorate treatment (Ruat et al., 2014; Cortes et al., 2019).

Targeting molecules downstream of SMO or independently of SMO has ascended as a novel therapeutic strategy for the treatment of Hh-dependent tumors that can overcome drug resistance and adverse effects (Ruat et al., 2014). GLI2 expression during vismodegib or sonidegib treatment and aberrant activation of GLI signaling pathway have been reported to be implicated in the emergence of resistance, while GLI inhibitor and GLI2 antagonist could restrain the activation of Hh pathway, suggesting that the inhibition of GLI might be beneficial in SMO inhibitor-acquired drug resistance. Beside the abovementioned FDA-approved ATO, numerous other molecules directed against GLI, the final and crucial effector of the Hh signaling pathway, have been described; yet, they should be fully evaluated in clinical studies. GANT61 was the first GLI inhibitor discovered, acting via impairing the DNA binding ability of the transcription factors, however some pharmaceutical limitations, regarding its suitability, opposed its entrance in clinical trials. Additionally, the hedgehog pathway inhibitors (HPIs; HPI-1/2/3/4) have been described to hinder GLI activity downstream of SUFU and impair tumor growth, however the exact mode of action has not yet been completely elucidated. Moreover, the GLI-targeting molecules pyrvinium, imiquimod, and nanoquinacrine are under assessment. Pyrvinium, an anti-helmetic drug, decreases the stability of the GLI transcription factors and imiquimod, an agonist of the TLR7 and the TLR8, benefits the PKA-induced GLI2 phosphorylation and its followed degradation. Nanoquinacrine, a spherical nanoparticle form of quinacrine, reduces GLI1-dependent proliferation and tumor growth via augmenting GLI inhibitors and modulating the GLI1 binding to DNA (Didiasova et al., 2018). Furthermore, the aPKC-i/l-mediated enhancement of BCC growth seems to contribute to the induction of SMO inhibitor resistance and preclinical data have reported that a peptide that inhibits PKC activity is beneficial for sensitive and resistant BCCs. Finally, it has been demonstrated *in vivo* that phosphodiesterase inhibitors impede tumor growth once SMO resistance occurs, by blocking cAMP degradation and, thereby, increasing the activity of PKA, that negatively regulates Hh pathway (Pak and Segal, 2016; Niewiadomski et al., 2019).

Finally, a novel therapeutic approach that has arisen, recently, to overcome the emergence of resistance, is targeting alternative pathways responsible for non-canonical GLI activation. Among them, the RAS-RAF-MEK pathway seems to have a critical role in sustaining Hh-GLI signaling beyond SMO. The combination of SMO and MEK inhibitors (SANT-1 and PD325901 respectively) demonstrated augmented efficacy in restraining prostate tumor growth *in vitro*, compared to each agent

alone. Similarly, synergistic effect was observed in cholangiocarcinoma cells upon treatment with SMO and MAPK inhibitors (Cyclopamine and MEKi U0126). Other targeted signaling pathways that are implicated in SMO-independent GLI activation include PI3K-AKT-mTOR, TGF-β, DYRK1B and HDAC. Mounting evidence from pre-clinical studies has unveiled that directing against several pathways simultaneously is a powerful and challenging therapeutic approach to overcome the acquired resistance. Further clinical studies will elucidate the adequate combinations (Pietrobono et al., 2019; Wu et al., 2017).

2.3. Proteasome inhibitors

Downstream to plasma membrane receptors and their signaling cascades that transfer information from the extracellular milieu to cells lie the proteostasis network (PN), a modular, yet highly integrated network of proteome stability curators (Sklirou et al., 2018). Specifically, following their synthesis in ribosomes, polypeptides are folded by molecular chaperons and are targeted for chaperon-mediated assembly to complex protein machines, plasma membrane receptors, cytoskeletal

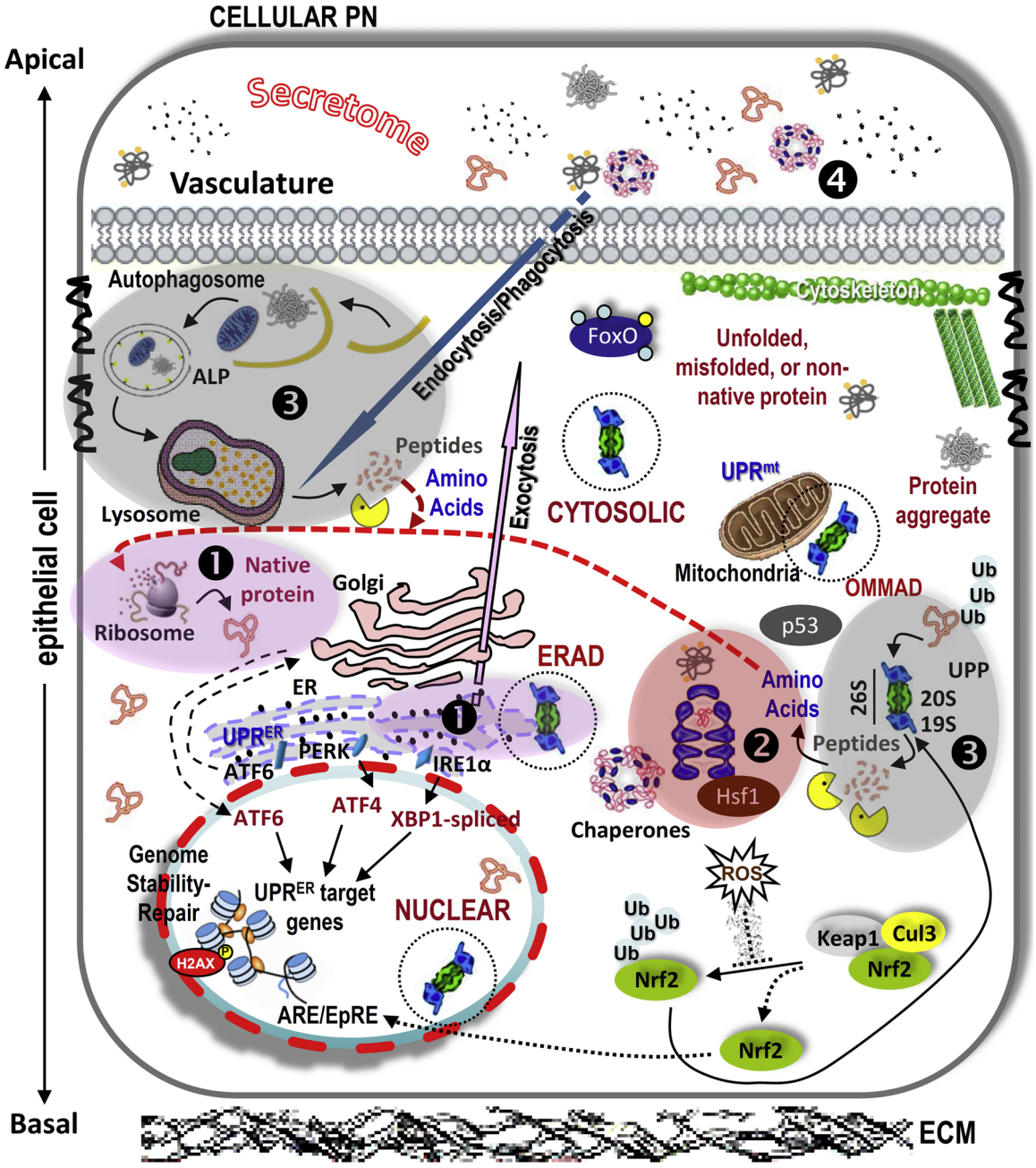

Fig. 3. The main proteostatic modules. Following their synthesis in ribosomes, polypeptides are folded by molecular chaperons and (in most cases) are targeted to protein machines or to complex cellular structures composed of several different subunits; the assembly process is also catalyzed by chaperons. The appearance of proteome instability in cells (also referred to as, proteotoxic stress), promotes highly regulated alarming responses which slow down synthesis of polypeptides and also *hold*, *fold* or *degrade* (e.g. in UPP and ALP) unfolded polypeptides and/or protein aggregates; UPP and ALP are also subject to tight regulation by the aberrantly activated during tumorigenesis InS/GF signaling modules (*oncogenic* addiction). Cancer cells are characterized by significant proteome instability (also due to severe genome instability that results in highly mutated polypeptides) and thus in several cases they hijack the proteostatic module machinery in order to suppress proteotoxic stress. Given that both UPP and ALP are involved in immune responses (e.g. via antigen presentation), it is expected that their deregulation will also have an impact on the functionality of the immune system. This *non-oncogenic* addiction of tumor cells to elevated activities of UPP or ALP can be exploited for the development of novel anti-tumor drugs or for the treatment of cancer cells being resistant or refractory to targeted tumor therapies. Shaded circles indicate main components of the proteostatic network, i.e. protein synthesis in the cytosol (❶) and the ER (❶), intra- (❷) and extra- (❹) cellular chaperones and degradation machineries (❸).

structures, etc. The appearance of proteome instability (also known as, proteotoxic stress) promotes highly regulated alarming responses which apart from slowing down polypeptides' synthesis, they also *hold*, *fold* or *degrade* unfolded polypeptides and/or protein aggregates in the UPP or in ALP (Fig. 3).

UPP is composed of the ubiquitin-conjugating enzymes and the 26S proteasome; the latter consists of a catalytic 20S core particle (CP) bound to 19S regulatory particles (RP) (Tsakiri and Trougakos, 2015). The 20S CP is composed of four stacked heptameric rings (two α- surrounding two of β-type) that form a barrel-like structure; the caspase-, trypsin- and chymotrypsin-like peptidase activities are located at the β1, β2, and β5 proteasomal subunits, respectively. The 19S RP is involved in substrate recognition, deubiquitination, unfolding and translocation into the 20S CP (Tsakiri and Trougakos, 2015). UPP is a key regulator of numerous cellular processes, including development, metabolism, signal transduction, cell cycle and cell death, as well as immune responses since the short peptides that are produced following polypeptides degradation can be trimmed to 8–10 amino acid long peptides for presentation at cell surface on major histocompatibility complex (MHC) class I molecules to initiate an immune response (Reits et al., 2003; Tsakiri and Trougakos, 2015). A variant to constitutive proteasomes is the immunoproteasome that is expressed in hematopoietic cells (Groettrup et al., 2010; Niewerth et al., 2013; Parlati et al., 2009; Roccaro et al., 2010) and differs from the constitutive proteasome in the 11S RPs and the replacement of the catalytically active subunits by PSMB9/LMP2, PSMB10/MECL-1 and PSMB8/LMP7 (Huber et al., 2012). Immunoproteasome (or other hybrid proteasomes that can process different tumor antigens) expression is induced upon stimulation by inflammatory cytokines such as interferon (IFN)-γ and to a lesser extent by TNFα (Vigneron and Van den Eynde, 2012).

Both UPP and ALP are subject to tight regulation by the InS/GF signaling modules (Fig. 1) and also respond to high protein synthesis rates and to significant proteome instability seen due to increased mutational load (i.e. genomic instability) in most tumors (Gorgoulis et al., 2018). Given that UPP and ALP are involved in antigen presentation on MHC class I molecules (Reits et al., 2003), it is expected that their deregulation will have a significant impact on immune responses. Therefore, it is not surprising that cancer cells hijack the proteostatic machinery in order to reduce proteotoxic stress (Roeten et al., 2018; Sklirou et al., 2018); this *non-oncogenic* addiction of tumor cells to over-activated UPP or ALP can be exploited for the development of either novel anti-tumor drugs or for the treatment of cancer cells being resistant or refractory to classical or targeted therapies. Nonetheless, despite encouraging preclinical data with PIs treatment in solid tumors including findings demonstrating that cancer cells with mutant KRAS were selectively addicted to increased proteasome activities (Steckel et al., 2012), proteasome inhibition was not effective against solid tumors in the clinical setting. On the other hand, PIs had proven very effective against hematological cancers such as MM and mantle cell lymphoma (MCL) (Manasanch and Orlowski, 2017); the former is an incurable malignancy of plasma cells being characterized by extensive proteotoxic stress due to abundant synthesis of monoclonal immunoglobulins and/or free light chains (Kyle and Rajkumar, 2014; Röllig et al., 2015). First generation (bortezomib; BTZ) or second generation (carfilzomib; CFZ) PIs, along with orally administered novel PIs (oprozomib and ixazomib) take advantage of the heavy reliance of myeloma cells on the proteasome for the degradation of excessive and/or misfolded proteins (e.g. immunoglobulins) (Bianchi and Anderson, 2019). Yet, despite the significant improvement regarding progression-free survival (PFS) and OS of MM patients, development of resistance is an emerging problem which hinders the therapeutic value of PIs; notably, CFZ overcomes BTZ resistance indicating that this drug could improve treatment of relapsed and/or refractory MM patients (Dimopoulos et al., 2011).

Several mechanisms have been implicated in intrinsic or acquired resistance to PIs. These may include mutations in proteasomal subunits that make cells insensitive to PIs (Robak et al., 2018), as well as higher expression levels of the targeted PSMB5 proteasomal subunit or of the constitutive and/or immunoproteasomes levels in tumor cells (Balsas et al., 2012). Notably, although BTZ-resistance in cell models may relate to acquired mutations to *PSMB5* gene (de Wilt et al., 2012; Franke et al., 2012; Niewerth et al., 2014a, b; Oerlemans et al., 2008; Ri et al., 2010), patients' polymorphisms at the *PSMB5* gene had no effect on sensitivity to PIs (Wang et al., 2008; Lichter et al., 2012); thus whether mutations in proteasome subunits contribute to BTZ resistance in the clinical setting remains elusive. Higher expression levels of proteasomal genes mostly relate to activation of antioxidant responses by the nuclear factor, erythroid 2 like 2 (NFE2L2) pathway (Tsakiri et al., 2013, 2019a; 2019b) and indeed, BTZ resistance-related gene expression signatures revealed enrichment for NFE2L2 transcriptional targets (Stessman et al., 2013). Proteasome over-activation, e.g. due to proteasomal genes upregulation or to increased assembly rates, was the most frequent alteration found in cells intrinsically resistant to BTZ or in acquired BTZ-resistant cells (Bianchi et al., 2009; Niewerth et al., 2013, 2014c; Wallington-Beddoe et al., 2018). Proteasomal genes and enzymatic activities upregulation was noted in PBMCs from patients treated with PIs (Papanagnou et al., 2018) and solid tumors with higher intrinsic proteasome activity were more inherently resistant to PIs (Gu et al., 2012). Also, as a response to PIs treatment, tumor cells have the capacity to modulate immunoproteasome function to escape immune surveillance (Heink et al., 2006; Johnsen et al., 1998; Niewerth et al., 2013, 2014c). Other mechanisms involved in the resistance of MM cells to PIs relate to P-glycoprotein induction (Abraham et al., 2015); however, its contribution to acquired BTZ-resistance remains unclear since BTZ is a poor substrate for P-gp (Minderman et al., 2007; Oerlemans et al., 2008). On the contrary, CFZ is a P-gp substrate, albeit with relatively low affinity, but nevertheless patients treated with CFZ show increased P-gp expression (Verbrugge et al., 2012). Also, resistance to PIs may involve defects in apoptotic mechanisms, senescence and/or DNA repair mechanisms (Wallington-Beddoe et al., 2018) or in exosome-transmittance of proteasomal subunits (Xu et al., 2019a) as it was previously reported that bone marrow stem cells-derived exosomes inhibited BTZ-induced cell death to protect MM cells from apoptosis (Wang et al., 2014).

Resistance to PIs may also be associated with activation of compensatory proteostatic pathways due to extensive proteome instability and accumulation of protein aggregates. These pathways may include the endoplasmic reticulum UPR, ALP or chaperons' network (Mitsiades et al., 2002a; Catley et al., 2006; Papanagnou et al., 2018). In support, co-administration of BTZ and the HDAC (a molecule involved in protein aggregates removal) inhibitor panobinostat was approved by the FDA for the treatment of relapsed/refractory MM patients (San-Miguel et al., 2014). Moreover, chloroquine, an ALP inhibitor and a lysosomotropic agent which alkalizes lysosomal pH, is being evaluated for its activity against solid tumors, as well as in combination with BTZ in relapsed and refractory MM patients showing some clinical benefit (Wallington-Beddoe et al., 2018). As for chaperons, resistance to BTZ may be conferred by induction of HSP70 and small HSPs (Chauhan et al., 2003; Hamouda et al., 2014; Bailey et al., 2015), while inhibition of Grp78 (an ER and UPR involved chaperone) enhanced the anti-MM effects of BTZ (Abdel Malek et al., 2015). Moreover, HSP90 inhibition exerted anti-myeloma activity (Mitsiades et al., 2006) and treatment of BTZ-resistant MCL cells with an HSP90 inhibitor together with Grp78 knockdown enhanced cell death (Roué et al., 2011); nonetheless, clinical trials where HSP90 inhibitors and BTZ were combined, have failed to produce promising clinical readouts (Seggewiss-Bernhardt et al., 2015).

Beyond upregulation of proteostatic pathways, development of resistance to PIs may relate to insulin-like growth factor-1 (IGF-1)-mediated activation of PI3K or AKT that are induced in MM cell lines and patients' tumor cells resistant to BTZ (Hideshima et al., 2007; Markovina et al., 2008; Podar et al., 2009). In support, an IGF-1R

inhibitor re-sensitized MM cells to BTZ (Kuhn et al., 2012) and EGFR inhibition suppressed proteasome expression levels in a STAT3-dependent manner (Zhang et al., 2016). However, considering that PD-L1 (see below) inhibits STAT3 in tumor cells (Gato-Cañas et al., 2017), PD-L1 inhibitory immune therapies may enhance proteasomal activities.

Finally, the bone marrow microenvironment including both the non-cellular (i.e. ECM proteins and soluble factors such as cytokines, chemokines and growth factors) and cellular (i.e. hemopoietic and non-hemopoietic cells) compartments is likely involved in resistance to PIs therapy (Manier et al., 2012). Specifically, the interaction between bone marrow stromal cells and ECM proteins with MM cells plays a crucial role in MM drug resistance via secretion of growth factors, adhesion proteins, cytokines and exosomes; it was shown that interleukin 6 (IL6) secretion by stromal and MM cells enhanced VEGF-mediated angiogenesis leading to BTZ resistance (Vacca et al., 2003; Hao et al., 2011). Also, the HGF/c-MET signaling pathway is constitutively activated in MM cells and endothelial cells from patients with relapsed/refractory MM, likely mediating drug resistance (Moschetta et al., 2016). Nonetheless, the anti-IL6 antibody siltuximab (Voorhees et al., 2013), the c-MET inhibitor tivantinib (Baljevic et al., 2017), a monoclonal IGF-1R antibody (Moreau et al., 2011) or the AKT inhibitor afuresertib (Spencer et al., 2014) did not show promise for further development in clinical trials in relapsed/refractory MM patients.

Given these findings, apart from novel second or third generation PIs, additional strategies to overcome PIs resistance may include novel highly specific autophagic, chaperon or proteasome deubiquitinase inhibitors; redox modulators, new epigenetic-targeted drugs or therapeutic monoclonal antibodies targeting RTKs or other modules of the InS/GF signaling cascade.

2.4. Inducers of apoptosis

Apoptosis represents a finely regulated form of programmed cell death that is defined by distinct morphological characteristics (e.g. chromatin condensation, nuclear fragmentation, plasma membrane blebbing, and apoptotic body formation), as well as by biochemical alterations (e.g. activation of caspases). The two major apoptotic pathways, namely intrinsic (via release of cytochrome c) and extrinsic (stimulation of death receptors), are activated as a response to intracellular and extracellular signals, respectively. The balance between the proapoptotic and antiapoptotic members of the BCL2 family is a key factor for the regulation of the intrinsic apoptotic pathway. The activation of the extrinsic pathway occurs when death ligands such as tumor necrosis factor α (TNFα), TRAIL and FAS ligand (FASLG) bind to TNFα-family death receptors. Both cellular apoptotic pathways converge on the activation of caspases, a family of cysteine proteases, which are crucial mediators of apoptosis. Cancer cells employ different mechanisms to suppress apoptotic machinery, including the recruitment of endogenous inhibitors of apoptosis and increased expression of anti-apoptotic members of the BCL2 family. As a result, several compounds have been studied in preclinical and clinical trials regarding their ability to induce apoptosis of malignant cells (Czabotar et al., 2014; Kiraz et al., 2016; Kontos et al., 2014).

Pharmacological inducers of apoptosis: Most of the classical chemotherapeutic agents (e.g. alkylating agents, anti-mitotic agents, antimetabolites, anthracenediones and topoisomerase inhibitors) affect DNA synthesis and/or cell division, triggering apoptosis by causing a cytotoxic effect. Consequently, they activate key molecular pathways [e.g. Jun N-terminal kinases (JNKs), extracellular signal-regulated kinases (ERKs) or the TP53 tumor suppressor] to trigger the apoptotic response (Kontos et al., 2014; Korbakis and Scorilas, 2012; Scorilas, 2014). However, only a small portion of cytotoxic drugs directly target members of the apoptotic machinery. Arsenic trioxide is a FDA approved regimen used to treat acute promyelocytic leukemia (APML), while it is tested in phase II clinical trials to assess its efficacy in the treatment of acute T cell leukemia and lymphoma. Arsenic trioxide disrupts mitochondrial matrix and activates caspase-3 to induce apoptosis of leukemic promyelocytes (Cai et al., 2000). Inhibitor of apoptosis proteins (IAPs) serve as endogenous negative regulators of apoptosis. X-linked inhibitor of apoptosis (XIAP) is the only member of IAPs that can bind and modulate directly the activity of caspases, keeping them inactive and preventing apoptosis of malignant cells. Several companies have developed XIAP inhibitors exerting the same binding sites for IAPs, like the IAP-binding mitochondrial protein (DIABLO), to suppress IAPs and reactivate the apoptotic pathways; however, clinical trials have illustrated limited efficacy of these compounds (Fulda and Vucic, 2012).

More promising results were obtained upon preclinical and clinical trials of both proteins and small molecules that target BCL2 family members. Venetoclax has shifted the paradigm of treatment in refractory or relapsed chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) patients, gaining accelerated approval from the FDA in 2016 based on overall response rate. Venetoclax is a selective inhibitor of antiapoptotic BCL2 protein which antagonizes the interaction between BCL2 and proapoptotic protein BIM leading to recruitment and subsequent oligomerization of BAX and BAK in the outer mitochondrial membrane to induce caspase-mediated apoptosis (Roberts and Huang, 2017). Elevated expression of antiapoptotic members of BCL2 family confers resistance to apoptosis in malignant cells. Obatoclax (GX15-070) is a selective antagonist which disrupts the interactions of BCL2 family pro-survival proteins (BCL2, BCL2L1, BCL2L2, MCL1) with BAX and BAK (Nguyen et al., 2007). Obatoclax has been evaluated in phase I and/or II clinical trials as a standalone antitumor agent in AML, relapsed or refractory Hodgkin's lymphoma and myelodysplastic syndromes (MDS), as well as in combination with carboplatin and etoposide in randomized phase II trials for the treatment of SCLC (Oki et al., 2012; Arellano et al., 2014; Langer et al., 2014; Schimmer et al., 2014). In the era of antisense oligonucleotide BCL2-inhibitors, encouraging results have been obtained for oblimersen, which binds to BCL2 mRNA and attenuates its expression. Oblimersen has been studied for the treatment of various malignancies, while in some of them it was tested in combination with other anticancer agents to enhance the activity of these cytotoxic agents (Baig et al., 2016; Montero and Letai, 2018).

TP53 is a key tumor-suppressor gene that can be found mutated in about 50% of human malignant neoplasms. Upon activation by various cellular stress stimuli (DNA damage, activation of oncogenes, etc.) TP53 regulates directly the transcriptional activation of proapoptotic members of the BCL2 family, such as NOXA and PUMA. Thus, the restoration of *TP53* gene and, by extension, of the TP53 protein expression and functionality, is crucial to suppress the uncontrolled cell division and growth and to promote programmed cell death in malignant cells (Aubrey et al., 2018). Advexin is a recombinant adenoviral *TP53* gene therapy, that restores TP53 activity in cancer patients and triggers apoptosis (Ghobrial et al., 2005). Moreover, other strategies include the use of small compounds that bind directly either to mutant TP53, facilitating its activation, or to well-known regulators of TP53 such as MDM2 (Lane et al., 2010).

Death receptors and their ligands represent a well-studied group of molecules that can be targeted by drugs to induce apoptosis. Death receptors are members of the TNF superfamily characterized by a cytoplasmic "death domain". When a ligand binds to the death receptor, it causes receptor aggregation and enables a proteolytic cascade which leads to the activation of effector caspases (caspase 8 and caspase 10). TNFα has been used as an isolated limb perfusion therapy to treat sarcomas and non-resected melanomas with an increased response rate. Other strategies employ the cytokine TRAIL or agonistic monoclonal antibodies to target TRAILR1 and TRAILR2 to cause TRAIL-dependent apoptosis by activating caspase 8 and subsequently downstream effector caspases (Takeda et al., 2007).

Synthetic alkylphospholipids (APLs) constitute a group of structurally related molecules that interact with cell membranes to exert their

antitumor effects. APLs are similar to endogenous phospholipids and they interfere with lipid metabolism and lipid-mediated signaling, thus facilitating apoptosis. Several novel APLs such as perifosine, erucylphosphocholine and erufosine exhibit antitumor activity in hematological malignancies and solid tumors in preclinical studies (Rios-Marco et al., 2017). Interestingly, they can be used to sensitize malignant cells to chemo- and radio-therapy. These regimens exert their antiproliferative actions mainly by targeting the PI3K/AKT/mTOR pathway. For example, perifosine inhibits activated/phosphorylated AKT, which is crucial for the downstream activation of mTOR and subsequent inactivation of pro-apoptotic molecules (Kostadinova et al., 2015; Rios-Marco et al., 2017).

Bortezomib is a boronic acid dipeptide PI that was initially approved by FDA to treat relapsed and refractory MM (see also above), but it has also shown promising antitumor activity, as monotherapy or combined with other cytotoxic drugs, in other solid and hematologic malignancies (Selimovic et al., 2013), being now aproved for first-line treatment of patients with MM and mantle-cell lymphoma. The proteasome degrades (among others) endogenous inhibitors of nuclear factor-κB (IκB) and it is critical for the survival of cancer cells. The degradation of IκB by the proteasome promotes cell survival by reducing susceptibility to apoptosis. More specifically, inhibition of proteasome increases the cytoplasmic concentration of IkB, which is forming heterodimers with NF-KB preventing its translocation into the nucleus hence provoking apoptosis (Manasanch and Orlowski, 2017).

Last but not least, several FDA approved monoclonal antibodies as well as small molecule drugs such as cetuximab, trastuzumab, gefitinib, erlotinib, IMA, and pazopanib have been used to treat a wide spectrum of malignant neoplasms enabling apoptosis (Green and Kroemer, 2005). For example, trastuzumab, targets HER2, a well-studied activator of the PI3K-AKT signaling pathway (see also above), to treat breast cancer patients with HER2/neu overexpression. A proapoptotic BCL2 family protein, BAD, is directly phosphorylated by AKT which limits BAD efficacy to access outer mitochondrial membrane and, by extension, to promote apoptosis (Fink and Chipuk, 2013; Valabrega et al., 2007). Furthermore, the small molecule drug pazopanib (an effective multitargeted receptor TKI) has demonstrated promising clinical utility in a variety of malignant neoplasms. Recently, it has been illustrated in preclinical studies that the antitumor effect of pazopanib is mediated through PUMA induction. Pazopanib is a potent inhibitor of the AKT signaling pathway, leading to the downstream activation of forkhead box O3 (FOXO3) that induces the expression of PUMA, stimulating the intrinsic apoptotic pathway (Xu et al., 2019b; Zhang et al., 2017a). Similarly, ipatasertib is a novel AKT inhibitor that induces the transcription factors FOXO3A and NF-KB regulating PUMA-dependent apoptosis; supporting the strong antitumor effect that ipatasertib shows in a variety of cancers (Sun et al., 2018).

2.5. Epigenetic and metabolic modulators

Epigenetic and metabolic alterations are mechanisms highly associated with cancer development and progression and thus related enzymes and regulators are potential drug targets for cancer treatment (Dong and Cui, 2019; Miranda-Gonçalves et al., 2018). The production of oncometabolites as 2-hydroxyglutarate (2-HG), fumarate, and succinate by the mutated metabolic enzymes isocitrate dehydrogenase (IDH), fumarase and succinate dehydrogenase, respectively, deregulates DNA and histone methylation (Wang and Lei, 2018). On the other hand, epigenetic mechanisms induce alterations in the metabolome by regulating the expression of metabolism-related genes, which

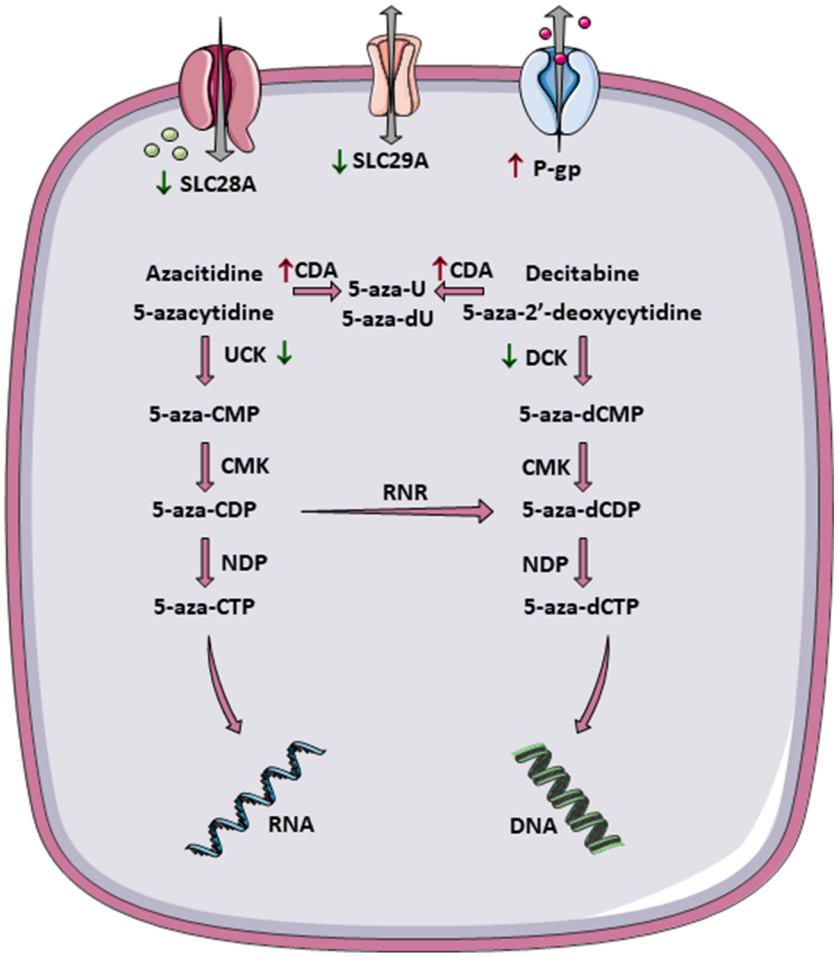

Fig. 4. Membrane transport and intracellular metabolism of azacytidine and decitabine. The uptake of azacytidine and decitabine across the cell membrane is mediated by solute carrier 29 (SLC29) and solute carrier 28 (SLC28) family members. Following cellular uptake, azacytidine (5-azacytidine) and decitabine (5-aza-2′-deoxycytidine) are modified by different metabolic pathways and are incorporated into RNA and DNA, respectively. Excess azanucleotide is rapidly deaminated to uracil by cytidine deaminase (CDA). Resistance mechanisms are related to a decrease in the levels of SLC transporters and deoxycytidine kinase (dCK), uridine-cytidine kinase (UCK) and an increase in P-glycoprotein (P-gp) and CDA. CMK, Cytidine monophosphate kinase; NDP, nucleotide diphosphate kinase; RNR, ribonucleotide reductase.

may also be targeted by epigenetic drugs (Miranda-Gonçalves et al., 2018).

2.5.1. Epigenetic modulators

Epigenetic modifications working in concert with genetic mechanisms are deregulated in many diseases, including cancer. Cancer epigenetics are related with a wide range of heritable changes in gene expression, which do not originate from any alteration in DNA sequences. The key epigenetic mechanisms associated with tumor initiation, cancer progression and metastasis are aberrant DNA methylation, histone modifications (e.g. histone deacetylation), and the expression of non-coding RNAs (Fardi et al., 2018; Park and Han, 2019). The reversible nature of epigenetic changes has led to the emergence of novel epigenetic therapeutic approaches (Fardi et al., 2018), known as epidrugs and several hypomethylating agents (HMAs) and histone deacetylases inhibitors (HDACi) have been already approved by the FDA and the European Medicines Agency (EMA) for the treatment of some hematological neoplasias.

In hematopoietic malignancies, several tumor suppressor genes, transcription factor genes, and pro- or anti-apoptotic genes are hypermethylated (Wang et al., 2018). Inducing hypomethylation of these genes will promote their reexpression, consequently inducing antitumor effects (Sripayap et al., 2014). Azacytidine and decitabine are HMAs approved by the FDA in 2004 and 2006, respectively, for use in all subtypes of MDS (Ball et al., 2017; Kaminskas et al., 2005). Currently, they were approved for the treatment of some subtypes of MDS, chronic myelomonocytic leukemia (CMML) and AML (Derissen et al., 2013). These HMAs are cytidine nucleoside analogs with similar mechanism of action, but while azacytidine is a ribonucleoside that is incorporated into both RNA and DNA, decitabine is incorporated only into DNA (Ball et al., 2017). Besides their hypomethylating mechanism of action, which reactivates several genes, HMAs also induce DNA damage and consequent apoptosis; it also modulates several signaling pathways that regulate stem cell renewal, differentiation, cell cycle arrest, apoptosis, immune recognition, angiogenesis and invasion (Cruijsen et al., 2014; Stresemann et al., 2008). Furthermore, the role of epigenetics in immune evasion may be the basis for the use of epigenetic drugs in combination with immunotherapeutic agents to treat cancer (Dunn and Rao, 2017). Despite the success of HMAs, only about 50% of patients respond to these drugs and most responding patients eventually relapse, since these drugs are unable to eradicate the drug resistant malignant clone (Ball et al., 2017; Derissen et al., 2013). Nonetheless, although resistance to HMAs is a major obstacle, the underlying mechanisms remain poorly understood.

Azacytidine and decitabine are subject to cellular uptake by membrane transporters of two different families of human nucleoside transporters (hNTs), namely, solute carrier family 29 (SLC29) or human equilibrative nucleoside transporters (hENTs) and the solute carrier family 28 (SLC28) or human concentrative nucleoside transporters (hCNTs) (Damaraju et al., 2012). An overview of azacytidine and decitabine membrane transport and intracellular metabolism that are also associated with drug resistance, is shown in Fig. 4. hENTs and hCNTs mediate the uptake of azacytidine, while decitabine is transported mainly by hENT1 or hENT2 (Damaraju et al., 2012). Also, cell-based studies showed that decitabine resistant cell lines have lower expression of hENT1 (Qin et al., 2009). In MDS patients, the low expression levels of hENT1 were strongly correlated with poor response to decitabine and shorter survival (Wu et al., 2015, 2016). Following cellular uptake, azacytidine is phosphorylated by uridine-cytidine kinase (UCK) and decitabine is phosphorylated into its active forms initially by deoxycytidine kinase (dCK) (Pleyer and Greil, 2015). In this context, insufficient intracellular concentration of HMAs may result from several factors including low uptake through membrane transporters, DCK deficiency and high deamination by cytidine deaminase (CDA) (Qin et al., 2011). dCK deficiency has been reported as a major mechanism of resistance to decitabine and cytarabine (Ara C), while UCK is responsible for azacytidine resistance (Levin et al., 2019; Qin et al., 2011; Valencia et al., 2014).

In this respect, MDS patients expressing lower levels of UCK1 were shown to be resistant to azacytidine, and had lower response rates and shorter OS (Valencia et al., 2014). CDA is a major enzyme in HMAs metabolism and increased CDA expression/activity contributes to poor prognosis of MDS and AML patients (Mahfouz et al., 2013). Moreover, it was reported that the CDA/dCK ratio was higher in MDS patients that did not respond to decitabine as compared to responders, suggesting that this could be a mechanism of primary resistance (Qin et al., 2011). Additionally, the expression or activity of CDA is relatively higher in males than in females (Mahfouz et al., 2013), which may explain why male patients treated with HMAs present lower OS and response rates (DeZern et al., 2017).

Resistance to HMAs treatment may also be associated with patient's methylation status. Some studies have evaluated the relationship between methylation and the outcome of MDS and AML patients treated with HMAs. The increased methylation of BCL2L10, a BCL2 family member with anti-apoptotic function, was associated with poor response to azacytidine or lower survival in high-risk MDS patients (Voso et al., 2011). In MDS or AML patients, resistance to azacytidine was also linked to the percentage of BCL2L10 positive cells in bone marrow (Cluzeau et al., 2012). Furthermore, high expression levels of miR-21 (Kim et al., 2014), miR-181 (Butrym et al., 2016) and miR-331 (Butrym et al., 2015) were correlated with poor response to HMAs and survival of MDS and AML patients. The increase in c-MYC (Brondfield et al., 2015) and PD-1 (Yang et al., 2014; Zhang et al., 2017b) along with the decrease of PI-PLCβ1 (Cocco et al., 2015) and MLL5 (Zhang et al., 2017c) gene expression levels were also associated with poor response to HMAs treatment.

Cell-based models also showed that azacytidine-resistant SKM1 myeloid cells are defective for azacytidine-induced mitochondrial apoptosis and autophagy (Cluzeau et al., 2011); moreover, studies in resistant cell lines revealed that azacytidine resistance was associated with increased activity of glutathione S-transferase (GST) and P-glycoprotein overexpression (Messingerova et al., 2015). However, further studies are needed to decipher the complex mechanisms of HMAs resistance.

The HDAC inhibitors (HDACis) are a promising class of chemotherapeutic agents that prevent the deacetylase activity of histone deacetylases (HDACs) leading to unrestricted histone acetyltransferases (HAT) activity and increased gene transcription (Robey et al., 2011). Some HDACis comprise isoform-selective inhibitors and others are active against all types of HDACs (pan-inhibitors), being classified into five classes, namely hydroxamic acids (e.g. vorinostat, belinostat, panobinostat); aliphatic acids (e.g. valproic acid); benzamides (e.g. entinostat); cyclic tetrapeptides (e.g. romidepsin) and sirtuin (e.g. nicotinamide and EX-527) inhibitors (Eckschlager et al., 2017). Numerous clinical trials have been testing HDACis for the treatment of many diseases, including cancer, diabetes, heart, inflammatory and neurological diseases. Vorinostat and romidepsin have been approved for the treatment of cutaneous T-cell lymphoma (CTCL) while belinostat has been approved for peripheral T-cell lymphoma (PTCL) and panobinostat for MM (Li and Sun, 2019).

Although the exact mechanism of action of HDACis is not completely understood, HDAC inhibition leads to the accumulation of acetylated proteins including histones, transcription factors, tubulin and HSP90, and consequently to alterations in transcription, mitosis and proteome stability (Fantin and Richon, 2007). These changes trigger cellular responses that ultimately cause tumor cell death and all can display a role in resistance to HDACis. Despite the fact that distinct HDACis have been developed over multiple years, a limited number of resistant cell lines have been established and only few clinical studies have been conducted. Nevertheless, several mechanisms have been implicated in HDACis resistance, including drug efflux, target overexpression and desensitization, chromatin/epigenetic alterations,

changes in the expression of DNA repair proteins, stress response mechanisms and anti-/pro-survival mechanisms (Robey et al., 2011).

One of the molecular mechanisms most frequently associated with the resistance to HDACis in cancer cells is P-glycoprotein overexpression (Fantin and Richon, 2007; Robey et al., 2011). Romidepsin is the only HDACi found to be a P-glycoprotein substrate and efflux mechanisms do not seem to constitute a major mechanism of resistance to the hydroxamate or carboxylic acid classes of HDACis (Fantin and Richon, 2007). In tumor biopsy samples from patients with CTCL, *ABCB1* gene (that encodes for P-glycoprotein) expression, was not correlated with romidepsin resistance (Bates et al., 2010), suggesting that other mechanisms of resistance might play a role in the clinical setting. As mentioned, changes in HDACs expression is involved in HDACis resistance. Cell-based studies showed that overexpression of HDAC1 (Bandyopadhyay et al., 2004) and inactivating HDAC2 mutations were sufficient to induce resistance to HDACis (Ropero et al., 2006). The detection of the same mutation in tumor samples from patients with colon, gastric and endometrial tumors suggests that HDAC2 changes may play a role in clinical response to selective HDACis (Ropero et al., 2006). Furthermore, the redox pathway plays an important role in HDACis resistance; and a negative correlation between thioredoxin (TRX) levels and the sensitivity to vorinostat, entinostat, and romidepsin was observed (Marks, 2006), since high TRX levels protect cells from the damage induced by ROS generated by HDACis. HDACis resistance is also linked to cell signaling changes in apoptosis, NF-kB and JAK-STAT pathways, retinoic acid, autophagy and endoplasmic reticulum (ER) stress (Fantin and Richon, 2007; Robey et al., 2011). Additional studies showed that cells resistant to vorinostat, dacinostat and panobinostat have increased BCL-2 and BCL-XL expression levels, while those being resistant to romidepsin express higher levels of BCL-2 (Ellis et al., 2009; Newbold et al., 2008; Shao et al., 2010; Vrana et al., 1999). These models also showed that constitutive activation of NF-kB was linked to panobinostat resistance (Shao et al., 2010). It was also found that vorinostat sensitivity was associated with the expression of STAT1, -3, and -5 (Fantin et al., 2008); in this study, the lymphoma cell lines being resistant to vorinostat displayed higher expression and phosphorylation levels of these STAT proteins (Fantin et al., 2008). The association of HDACi resistance with STAT3 expression was confirmed in a series of skin biopsy samples from patients with cutaneous T-cell lymphoma (Fantin et al., 2008). A recent study showed that low expression of the growth factor independent 1 (GFI-1), a transcriptional repressor with an important role in cell proliferation, apoptosis and differentiation of hematopoietic stem cells, was linked with panobinostat resistance in AML patients (Cheng et al., 2018). Although studies conducted in cell lines provided some insights in the molecular mechanisms of resistance to HDACis, further studies involving patients in clinical settings are needed. Additionally, several clinical trials are ongoing using new epigenetic drugs as the EZH2, DOT1L and BET inhibitors, suggesting the promising therapeutic potential of these new drugs in human cancers besides hematopoietic malignancies; particularly, in selected populations and in combination with other drugs (Mohammad et al., 2019) to provide the most effective cancer treatment.

2.5.2. Metabolic modulators

Metabolic changes have for long been linked to carcinogenesis and are considered a cancer hallmark. Specifically, the expression and activity of metabolic genes is frequently altered in cancer due to gene amplification, deletion or epigenetic changes (Luengo et al., 2017). In recent years, recurrent mutations of isocitrate dehydrogenase 1 (IDH1) and isocitrate dehydrogenase (IDH2) genes, have been identified in several cancers suggesting a key role in oncogenesis and a possible new molecular target (Upadhyay et al., 2017). At diagnosis, IDH mutations are somatically acquired; are generally monoallelic, rarely resulting in loss of heterozygosity and are mostly mutually exclusive (Clark et al., 2016; Platt et al., 2015; Rakheja et al., 2012; Upadhyay et al., 2017). IDH1 mutations are more frequent in solid cancers, such as low-grade gliomas, chondrosarcomas and cholangiocarcinomas, while IDH2 mutations are more frequent in hematological malignancies such as AML, MPN, and MDS (Dang et al., 2016; Molenaar et al., 2014; Upadhyay et al., 2017; Ward et al., 2010). The majority of mutations in IDH1 and IDH2 genes occur at an arginine residue within the catalytic pocket of the enzyme. IDH1 mutations typically occur at arginine 132 with substitutions including R132H, R132C, R132 L, R132S and R132 G, while IDH2 mutations occur at arginine 172 or arginine 140 (which is analogous to R132 in IDH1) (Clark et al., 2016).

IDH enzymes catalyze the oxidation of isocitrate to α-ketoglutarate (α-KG); however, IDH1/IHD2 mutants act as oncogenes producing 2-HG in a NADPH-dependent manner (Luengo et al., 2017; Upadhyay et al., 2017). 2-HG is a competitive inhibitor of α-KG- dependent enzymes, including the ten eleven translocation (TET) family of 5-methyl cytosine hydroxylases, the jumonji domain containing (JmjC) family of histone lysine demethylases, as well as enzymes involved in nucleic acid metabolism, namely ALKB and FTO (Amatangelo et al., 2017; Clark et al., 2016; Upadhyay et al., 2017). This inhibition of α-KG–dependent enzymes leads to DNA hypermethylation, increased repressive histone methylation and impaired hematopoietic differentiation (Amatangelo et al., 2017; DiNardo et al., 2018). Moreover, the accumulation of certain metabolites in cancer can induce metabolic recoding of epigenetics resulting in aberrant gene expression (Wang and Lei, 2018).

The identification of 2-HG as an oncometabolite reinforced the hypothesis that IDH mutations are oncogenic and led to the development of new-targeted therapies such as ivosidenib and enasidenib (Clark et al., 2016). Ivosidenib (AG-120) and enasidenib (AG-221) are oral small-molecule inhibitors that target mutated IDH1 and IDH2, respectively; these molecules have been approved for the treatment of AML relapsed/refractory with mutated IDH (DiNardo et al., 2018). Enasidenib is a small-molecule inhibitor of mutated IDH2 that reduces serum 2-HG, induces DNA hypermethylation and repressive histone marks, and promotes hematopoietic differentiation in patients with IDH2 R140 and IDH2 R172 mutations (Quek et al., 2018). Ivosidenib is a potent inhibitor of 2-HG production by cells with the mutated IDH1, and its main clinical activity occurs through increased differentiation of malignant cells (DiNardo et al., 2018).

The mechanisms that mediate response and resistance to ivosidenib and enasidenib are not fully understood (Amatangelo et al., 2017; Harding et al., 2018; Intlekofer et al., 2018; Quek et al., 2018). Primary resistance and consequent failure to respond to enasidenib has been associated with baseline high mutation burden and with the presence of co-mutations including FLT3-ITD, FLT3-TKD, NRAS and PTPN11 (Amatangelo et al., 2017; Bullinger, 2019; Quek et al., 2018; Stein et al., 2019). On the other hand, acquired resistance to these IDH-targeted therapies may arise from a mutation at a second-site in IDH2 gene (Intlekofer et al., 2018), from clonal evolution or clonal selection (Quek et al., 2018), and from a mutated IDH isoform switch, from mutant IDH2 to mutant IDH1 and vice versa (Harding et al., 2018). The mechanisms of resistance to enasidenib were investigated in two AML patients (Intlekofer et al., 2018). At diagnosis, these patients harbored the oncogenic IDH2 R140Q mutation and acquired a second IDH2 missense mutation in *trans* (IDH2 Q316E or IDH2 I319 M) on the allele that was not affected by the R140Q mutation. These second mutations occured on the interface where enasidenib binds the IDH2 dimer, blocking the drug-target interaction (Intlekofer et al., 2018). These authors also reported a case of a patient with an IDH1 R132C mutation that acquired resistance to ivosedenib through an IDH1 S280 F in *cis* mutation (an analogous residue to IDH2 I319), suggesting that resistance to enasidenib and ivosidenib can occur through second site mutations in *cis* or in *trans* (Intlekofer et al., 2018). In another study it was reported that patients which developed resistance to enasidenib showed differentiation arrest and relapse not induced by second-site mutations in IDH2 but through clonal evolution or selection of terminal

or ancestral clones, with at least seven different mutations leading to reestablishment of differentiation arrest (Quek et al., 2018). Finally, it was found that resistance to isoform-selective IDH inhibitors may be due to mutant isoform switching (Harding et al., 2018); in this study it was reported that three AML patients with the mutation IDH1 R132C acquired resistance to ivosedenib through development of IDH2 R140Q or IDH2 R172 V mutations. Additionally, another AML patient with an IDH2 R140Q mutation treated with enasidenib developed resistance due to a new IDH1 R132C mutation (Harding et al., 2018). The frequency of each resistance mechanism to IDH inhibitors remains unknown and as larger numbers of patients with mutated IDH clones are treated with these drugs, it will be important to elucidate the mechanisms underlying inherent and acquired resistance.

3. Resistance to immunotherapies

It has been known for many years that the immune system plays a major role in neoplastic development and control; thus, evasion to immune destruction is considered a major cancer hallmark (Hanahan and Weinberg, 2011; Vinay et al., 2015). In this context, there are currently several strategies globally termed cancer immunotherapies (CIs) that act by stimulating/educating the immune system to recognize and attack specific cancer cells, boost immune cells to help them eliminate cancer or provide the body with additional components to enhance the immune response. Cancer immunotherapy marks an entirely different way of treating cancer, by targeting the immune system and not the tumor itself (Couzin-Frankel, 2013). This concept is not new as the oldest form of CI is allogeneic hematopoietic stem cell transplantation (HCT) used to treat some hematologic malignancies; the first allogeneic transplant was performed in 1968 by E. Donnall Thomas (Im and Pavletic, 2017).

Several CI agents are now approved, some of which target the tumor whereas others activate immune cells. The first category includes monoclonal antibodies and the second includes cancer vaccines, oncolytic viruses, immune checkpoint antagonists, stimulatory agonists, various forms of cellular therapies (Sathyanarayanan and Neelapu, 2015; Kelly, 2017; Oiseth and Aziz, 2017) and immunomodulating drugs. Many clinical trials of all of these approaches, including combinations of the various CI strategies, are currently ongoing, which open new avenues for the treatment of cancer patients (Vinay et al., 2015), where CI is now considered the “fifth pillar” of cancer therapy (Oiseth and Aziz, 2017). However, only a small subset of some cancer patients respond to these treatments and, until now, it is difficult to determine precisely which patients will benefit from these therapies; also, resistance is frequently a barrier to CI success (Draghi et al., 2019).

The resistance to immunomodulatory drugs (IMiDs) and monoclonal antibodies (MoAbs) is multifactorial and could be innate; develop during treatment or after a short period of remission. Moreover, MDR cancer cells exhibit cross-resistance to a broad spectrum of structurally unrelated drugs. At this point, it is crucial to identify the molecular events responsible for inherent or acquired resistance in order to predict and prevent patient therapeutic failure and untoward toxicity, apart from creating new therapeutic options that restore the response.

3.1. Monoclonal antibodies

The use of MoAbs in cancer therapy relies on the specific binding to well defined targets mainly expressed on the surface of cancer cells. However, despite the remarkable clinical success, some patients acquire resistance following initial treatment, due to continuous genetic alterations that attenuate the initial therapeutic efficacy (Reslan et al., 2009).

The pharmacokinetic and pharmacodynamic properties of MoAbs are frequently complex, since they affect multiple cytotoxic mechanisms and have a complex disposition (Reslan et al., 2009). Similar to conventional agents, MoAbs undergo degradation/clearance and they induce apoptosis, but they also cause their anticancer effect by complement dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and/or antibody-dependent phagocytosis (ADP) (Reslan et al., 2009; Freeman and Sehn, 2018).

The first MoAb approved for cancer therapy was rituximab which received approval in 1997 for relapsed or refractory low-grade or follicular CD20-positive B-cell non-Hodgkin's lymphoma. Rituximab is a genetically engineered chimeric murine/human anti-CD20 containing a glycosylated immunoglobulin G1 (Pérez-Callejo et al., 2015). Ofatumumab and obinutuzumab are newer MoAbs directed against CD20 that have been developed for use in B cell malignancies. Ofatumumab is a second-generation type I anti-CD20 antibody, fully humanized, that binds to a different site than rituximab. Obinutuzumab is a second-generation glycoengineered type II anti-CD20 MoAb, differing from the others because it induces direct cell death and has an enhanced ADCC (Im and Pavletic, 2017).

Since the approval of rituximab, a number of effective MoAbs targeting lineage-specific antigens (LSAs) have been successfully developed, along with a plethora of MoAbs that target non-LSAs (NLSAs) and act by neutralizing oncogenic pathways, block tumor-related chemotactic pathways, mobilize malignant cells from the TME to peripheral blood; modulate immune-checkpoints, or deliver cytotoxic drugs into tumor cells (Cuesta-Mateos et al., 2018).

During the last two decades, rituximab has showed significant clinical activity as a single agent and in combination with chemotherapy as first line induction therapy or in maintenance treatment against non-Hodgkin’s lymphoma, diffuse large B cell lymphoma, chronic lymphocytic leukemia and follicular lymphoma (Salles et al., 2017). The effectiveness of rituximab is dependent on diverse host and tumor cell-related factors, including pharmacokinetic parameters, accessory effector mechanisms, intracellular signaling pathways, changes in CD20 levels and in lipid raft domains, as well as on the development of resistance (Reslan et al., 2009; Freeman and Sehn, 2018). The incidence of rituximab resistance depends on the definition and degree of resistance which is frequently difficult to determine. The generally accepted definition of rituximab resistance is a lack of response or disease progression within six months of treatment with a rituximab-containing regimen, with disease progression during rituximab therapy the most clearly defined form of resistance (Rezvani and Maloney, 2011). Several mechanisms of resistance to rituximab have been reported including downregulation or loss of CD20 expression; CD20 mutations, structural changes affecting the binding region to rituximab, changes in cell membrane composition (e.g. cholesterol membrane depletion), trogocytosis or CD20 “shaving” mechanisms, ADDC inhibition by deposition of C3 activating fragments, polymorphism of the FcγRIIIa on cytotoxic cells, inhibition of CDC by upregulation of complement inhibitor proteins (e.g. CD55 and CD59), overexpression of antiapoptotic members of the BCL-2 family (e.g. BCL-2), shedding of CD20/rituximab complexes, as well as changes in TME and in NF-kB, p38 MAPK, MEK1-2/ERK1-2 and PI3K/AKT pathways (Bonavida, 2014; Freeman and Sehn, 2018; Pérez-Callejo et al., 2015; Reslan et al., 2009). The overexpression of CD55 and CD59 in malignant cells plays a role in tumor immune evasion and resistance against therapeutic antibodies including rituximab and ofatumumab (Robak et al., 2018).

Daratumumab is the first CD38-targeting antibody approved as single agent and in combination with several other treatments in MM (van de Donk and Usmani, 2018). However, not all patients respond durably to daratumumab and the mechanism of resistance is not clear yet. Mechanisms of resistance to CD38 monoclonal antibodies include decreased CD38 cell surface expression levels, trogocytosis, and high levels of complement inhibitor proteins (CD46, CD55, and CD59) (Nijhof et al., 2016; van de Donk and Usmani, 2018; Robak et al., 2018). The soluble form of CD38 (Funaro et al., 1996) and differences in frequency or activity of effector cells may also contribute to clinical efficacy of daratumumab (Nijhof et al., 2015). Furthermore, genetic

variants of Fc gamma receptors (*FCGR*) receptor (van de Donk et al., 2019), KIR and HLA genotypes (Marra et al., 2015), and the microenvironment that protects MM cells from CD38 antibody-induced ADCC by upregulation of anti-apoptotic molecules, like survivin, are also factors contributing to the clinical efficacy of CD38 monoclonal antibodies (van de Donk and Usmani, 2018). In addition, the high levels of CD45 in MM patients' clonal plasma cells (PCs) were shown to independently predict inferior OS, being probably a marker of a very aggressive and resistant disease; furthermore, a decrease in CD56 expression was observed in the nonresponding patients (Pick et al., 2018).

Elotuzumab is a humanized mAb against signaling lymphocytic activation molecule F7 (SLAMF7) that directly enhances natural killer cell cytotoxicity via SLAMF7 ligation (Cook et al., 2018; van de Donk et al., 2016). This antigen is a cell-surface glycoprotein expressed on MM cells, natural killer cells and other immune cells (van de Donk et al., 2016). Elotuzumab was approved for treatment of relapsed MM in combination with lenalidomide and dexamethasone (Cook et al., 2018). However, to date, no specific mechanisms of resistance to elotuzumab have been reported.

Brentuximab vedotin is an anti-CD30 antibody conjugated with the cytotoxic drug monomethyl auristatin E (MMAE) with proven efficacy in patients with $CD30^+$ malignancies, including Hodgkin lymphoma and anaplastic large cell lymphoma (Ansell, 2014). The conjugation of small molecules to MoAbs through chemical linkers gave rise to an entirely new class of anti-cancer drugs known as antibody-drug conjugates (ADCs). ADCs recognize tumor-specific cell surface antigens and are internalized into endosomes and lysosomes where proteolytic enzymes release theircytotoxic contents (Liu-Kreyche et al., 2019). Despite initial encouraging clinical results, ADCs encounter a number of challenges including drug resistance due to overexpression of efflux transporters in tumor cells (Loganzo et al., 2016). Brentuximab resistance was studied in cell-based models and it was found that tumor cells that express high levels of P-gp on the plasma membrane and/or lysosomal membrane, show resistance to the cytotoxic MMAE drug of the ADC (Liu-Kreyche et al., 2019). This resistance occurs through sequestration of MMAE released from brentuximab vedotin in the lysosomes, which prevents it from reaching its cytosolic targets (Liu-Kreyche et al., 2019). Consistently, given the hydrophobicity and weakly basic properties of MMAE, this agent is expected to undergo high sequestration in lysosomes as previously described (Zhitomirsky and Assaraf, 2016). However, the role of this resistance mechanism in the clinical setting remains largely unclear.

Gemtuzumab ozogamicin is another ADC that comprises a calicheamicin derivative and a recombinant humanized antibody directed against the CD33 antigen. It is approved for the treatment of adult patients with newly diagnosed CD33-positive AML in combination with daunorubicin and cytarabine (Ara C) or in monotherapy (Jen et al., 2018; Takeshita, 2013). *In vitro* cell-based studies showed that cells persistently exposed to low-dose gemtuzumab ozogamicin acquired resistance through P-gp overexpression (Naito et al., 2000); results from phase I studies confirmed that good responders to this ADC have low efflux activity *in vitro* (Linenberger, 2005; Sievers et al., 2001). Other cell-based studies showed that gemtuzumab ozogamicin resistance is complex and comprises several mechanisms including increased expression of antiapoptotic proteins (such as BCL-2), activation of survival signaling pathways (e.g. PI3K/AKT, MEK/ERK, and JAK/STAT) and reduction of CD33 on the surface of leukemia cells (Takeshita, 2013).

MoAbs can also block the inhibitory signals that protect tumors from immune cells. Although showing excellent results, these molecules only prevent the binding of growth factors to the receptors. To overcome this limitation, Abs that bind two or more antigens known as bivalent bispecific "antibodies" (BsAbs) being also conjugated to chemo- and radiotherapy agents were developed (Labrijn et al., 2019). BsAbs come in many formats, ranging from relatively small proteins, merely consisting of two linked antigen-binding fragments, to large immunoglobulin G (IgG)-like molecules with additional domains attached. An attractive bsAb feature is their potential for novel functionalities, that is, activities that do not exist in mixtures of the parental or reference antibodies. To date, more than 20 different commercialized technology platforms are available for bsAb creation and development; 2 bsAbs are marketed and over 85 are in clinical development. Recently, some of these novel targeted therapies have been approved, namely the BsAbs blinatumomab, the antibody-drug conjugate inotuzumab ozogamicin (among others), and the chimeric antigen receptor (CAR) T-cell tisagenlecleucel (Hathaway et al., 2018).

Recombinant techniques have also led to the creation of the BsAbs, small fragment molecules that combine single chain variable fragments from two different monoclonal antibodies. Some examples of these are the bispecific T cell engager (BiTE), tandem single chain variable fragments (taFvs), diabodies (Dbs), single chain diabodies (scDbs) and triplebodies. As mentioned, only Blinatumomab, a bi-specific antibody, is approved by the FDA (December 2014) for the treatment of B-cell ALL. Blinatumomab is a novel bi-specific T-cell engager which binds sites for both CD19 (antigen expressed on all stages of B cell lineage) and CD3 T cell receptor complex (is a BsAbs anti-CD19/CD3 T-cell), promoting the activation and expansion of CD8 cytotoxic and CD4 helper T-cells, resulting thus in lysis of malignant and normal B-cells (Runcie et al., 2018; Braig et al., 2017; Hathaway et al., 2018). Since CD19 is expressed in almost all B-cell lineages, except in plasma cells, blinatumomab is an option for most patients with B-cell ALL (Hathaway et al., 2018; Labrijn et al., 2019). It was found that in adult patients with primary refractory or relapsed Philadelphia negative ALL, surface CD19 antigen expression became negative in relapsed patients after blinatumomab treatment (Topp et al., 2015). Furthermore, in blinatumomab-treated ALL patients it was showed that disruption of CD19 trafficking to the plasma membrane may be a novel mechanism of resistance that may account for loss of CD19 surface positivity leading to BITE resistance (Braig et al., 2017). This fact suggests that CD19 downregulation is a possible mechanism of blinatumomab resistance. In this context, after failure of blinatumomab, CD19 expression should be measured and taken in consideration when choosing an alternative immunotherapy approach. Other mechanisms of blinatumomab resistance that have been reported include increased number of regulatory T cells, up-regulation of programmed death 1 (PD-L1), and extramedullary tumors (Duell et al., 2017; Köhnke et al., 2015; Topp et al., 2012). Moreover, it has been reported that the decreased response to blinatumomab was associated with high disease burden defined as BM blasts higher than 50%; history of prior extramedullary disease anytime during ALL course and presence of extramedullary disease at the time of blinatumomab therapy (Aldoss et al., 2017). However, the mechanisms underlying this BITE resistance are insufficiently understood, but in patients treated with CART-19, genetic alterations and alternatively spliced and truncated CD19 variants, have been described to account for the observed resistance. In addition, in patients with mixed lineage leukemia, a myeloid lineage shift has been shown to drive resistance to blinatumomab and CAR-T-cell therapy (Braig et al., 2017).

Moxetumomab pasudotox-tdfk, is a recombinant immunotoxin targeting CD22 that is composed of a single-chain variable fragment (scFv) fused to a truncated form of pseudomonas exotoxin PE38. This drug was approved by the FDA in 2018 for the treatment of adult patients with relapsed or refractory hairy cell leukemia who have received at least two prior systemic therapies, including treatment with a purine nucleoside analog (Kaplon and Reichert, 2019). This immunoconjugate binds CD22 on the surface of B-cells and is internalized to bring about ADP-ribosylation of elongation factor 2, inhibition of protein synthesis and apoptotic cell death. The density of CD22 and the ability of CD22 to undergo internalization are related with drug response and likely contribute to Moxetumumab resistance (Kreitman and Pastan, 2015); yet, further studies are needed to confirm this notion.

The first therapeutic monoclonal antibody to receive FDA approval for a solid tumor was trastuzumab in 1998. This drug targets the human

epidermal growth factor receptor 2 (HER2) overexpressed in approximately 20% of breast cancers and which is linked to poor prognosis and higher recurrence rates. Unfortunately, resistance mechanisms have been reported (see also above) which are associated with the acquisition of a HER2 receptor mutation (p95HER2), that lacks the trastuzumab-binding domain, as well as the increased expression of mucin 4, that can sterically impede the binding of the antibody to HER2, leading to decreased sensitivity to trastuzumab; additionally, increased AKT signaling has been linked to resistance (Jin et al., 2017; Nahta et al., 2006).

There is convincing evidence of acquired resistance in patients with colorectal cancer (CRC), head and neck cancer, or NSCLC treated with cetuximab. Cetuximab is a monoclonal chimeric antibody targeting EGFR, which is overexpressed in many different cancers. The emergence of cetuximab resistance is correlated in vitro and in vivo with the aberrant activation of ERBB2 signaling, which leads to ERK 1/2-mediated growth, differentiation, and survival. Additionally, patients suffering from advanced CRC tumors, containing KRAS or BRAF V600E mutations, do not respond to anti-EGFR therapies such as panitumumab and cetuximab (Yonesaka et al., 2011). Besides KRAS and BRAF mutations, the oncogenic activation of other downstream EGFR effectors such as PIK3CA and PTEN, can influence response to therapy. Authors suggest that CRCs lacking oncogenic alterations in these four genes have the highest probability of response to anti-EGFR therapies and are defined as “quadruple negative” (Bardelli and Siena, 2010; De Stefano and Carlomagno, 2014).

Although the use of antibodies to guide drugs to a specific target has been explored for over 30 years, advances in the knowledge of linker and drug properties, as well as in antibody engineering, design and selection, have led to the development of a new generation of molecules that are demonstrating promising clinical results. One example is trastuzumab emtansine (T-DM1), a humanized anti-HER2 antibody conjugated to the anti-mitotic chemotherapeutic drug emtansine (DM1) (Simpson and Caballero, 2014). In February 2013, the FDA approved T-DM1 for the treatment of “positive metastatic breast cancer that previously received trastuzumab and a taxane, separately or in combination”. In addition to its ability to deliver DM1 selectively to tumor cells, T-DM1 retains the effector functions of trastuzumab, including inhibition of HER2-mediated signal transduction and activation of ADCC (Krop and Winer, 2014). Despite the clinical outcome improvement observed in many patients, several patients who initially responded to T-DM1 treatment, eventually develop progressive disease. The mechanisms that contribute to T-DM1 resistance are not fully understood, but it has been proposed that the levels of HER2 at the surface of tumor cells (Li et al., 2018) and the abnormal function of lysosomes are among the major mechanisms of resistance to T-DM1 therapy (Ríos-Luci et al., 2017). Furthermore, upregulation of MDR1 and/or PTEN deficiency can contribute to T-DM1 resistance (Li et al., 2018). Recent clinical trials involving the use of bispecific antibodies in solid tumors (Runcie et al., 2018) and several other monoclonal antibodies have been approved by the FDA and/or are in clinical trials for the treatment of solid tumors (Chiavenna et al., 2017; Kaplon and Reichert, 2019). Furthermore, for the treatment of unresectable or malignant melanoma, FDA approval was first granted in 2011 for ipilimumab, a human MoAb specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA4). Since then, many MoAbs have been developed and received FDA approval for the treatment of several solid tumors, including MoAbs against programmed death 1 (PD-1) (see below).

3.2. Immunomodulators

Immunomodulatory drugs (IMiD) are a novel class of oral antineoplastic agents that have made an important impact on the treatment of patients with hematological malignancies, particularly MM. The first IMiD to demonstrate antineoplastic activity among patients with MM was thalidomide (THAL), but its secondary toxicity led to the development of less toxic analogs, namely the second and third generation of IMiDs, lenalidomide (LEN) and pomalidomide (POM), respectively. While the major impact of the IMiDs is observed among MM patients, notable clinical benefit has been also observed in several other hematologic cancers including MDS, non-Hodgkin lymphoma and CLL (Chanan-Khan et al., 2013).

LEN is a more potent immunomodulatory THAL derivative, and POM is the most recent and potent IMiD molecule. Both were approved by the FDA for MM treatment in 2006 and 2013, respectively. The use of LEN and POM in MM patients, especially in combination with other anti-MM agents, has significantly improved the treatment response and the long-term outcome of these patients compared with traditional chemotherapies. Previous cell-based and preclinical studies have suggested that the anti-MM effect of LEN involves pleiotropic biologic effects such as immunomodulation, modulatory effects on the TME and direct cytotoxic effects, but its precise mode of action remains to be elucidated.

The previous related anti-MM effects of IMiDs are related to their binding to the E3 ubiquitin ligase cereblon (CRBN-CRL4) and subsequent ubiquitination and degradation of two lymphoid B-cell transcription factors, Ikaros (IKZF1) and Aiolos (IKZF3) (Robak et al., 2018; Shi and Chen, 2017). The depletion of IKZF1 and IKZF3 induce IL2 production in T cells and studies have demonstrated that a single amino acid substitution of IKZF3 conferred resistance to LEN (Shi and Chen, 2017). The binding of an IMiD to cereblon alters its substrate specificity, resulting in aberrant proteasomal degradation of the transcription factors Ikaros and Aiolos which leads to downregulation of the promyeloma interferon regulatory factor 4 (IRF4) (Shaffer et al., 2008). LEN is the only IMiD that has been shown to cause cereblon-mediated degradation of casein kinase 1α, which leads to p53 activation (Ito and Handa, 2016).

Subsequently, it was shown that the anti-MM efficacy of IMiDs is directly related to CRBN expression (Robak et al., 2018; Shi and Chen, 2017) and clinical studies showed a lower expression of CRBN in patients resistant to IMiDs (Zhu et al., 2011; Krönke et al., 2014). Although the first described mechanism behind IMiD resistance was downregulation of CRBN expression (Zhu et al., 2011; Krönke et al., 2014), in a recent study performed in relapsed patients previously treated with lenalidomide, CRBN mutations have been confirmed to play an important role in MM resistance to IMiD (Kortüm et al., 2016). In these patients, three CRBN mutations were identified only when MM patients became refractory, suggesting a clonal selection during prolonged IMiD therapy; this could also contribute to IMiD resistance. However, other mechanisms of resistance to IMiD compounds have also been proposed including a decrease in the expression of IRF4, a member of the interferon regulatory factor family (Shaffer et al., 2008). In a recent study in Waldenström's macroglobulinemia patients, IRF4 was found to be a potential mechanism of resistance to LEN POM (Bertrand et al., 2017; Robak et al., 2018).

The disruption of the E3 ubiquitin ligase complex, observed in cells resistant to IMIDs, also leads to deregulation of the WNT/β-catenin pathway. This causes β-catenin accumulation and overexpression of various pro-survival and anti-apoptotic factors that may be responsible for IMiDs resistance, particularly to THAL and LEN (Nass and Thomas, 2018). One of these factors is the hyaluronan (HA)-binding protein CD44, which was shown to be overexpressed in a LEN-resistant preclinical model. CD44 promotes a greater adhesion to bone marrow stromal cells protecting MM cells from IMiDs. Another cell signaling pathway involved is RAS/RAF in which activating mutations result in resistance to IMiDs (Wallington-Beddoe et al., 2018).

Efflux transporters from ABC family are factors involved in drug resistance towards many drug classes used in MM treatment and other malignancies including PIs, anthracyclines, alkylating agents and immunomodulatory drugs (Bar-Zeev et al., 2017; Bram et al., 2009a, b; Li et al., 2016; Nass and Thomas, 2018). P-gp is the best studied MDR pump, but other members as multidrug resistance associated protein

(MRP1) and BCRP may also be involved (Niewerth et al., 2015; Wallington-Beddoe et al., 2018; Nass and Thomas, 2018). It has been suggested that LEN is a substrate of P-gp, but there are currently no published research studies investigating the role of P-gp in resistance to POM (Abraham et al., 2015).

In addition to their direct anti-MM effect, IMiDs target the BM microenvironment, alter the adhesion of MM cells to BM stromal cells and directly induce apoptosis or growth arrest of MM cells (Gorgun et al., 2010). The indirect mechanisms of IMiDs include immunomodulation mediated through enhancement of CD4+ and CD8 + T cell co-stimulation, downregulation of inflammatory cytokines and increase in natural killer cell activity (Cook et al., 2018). They selectively inhibit the production of the pro-inflammatory cytokine TNF-α (Sampaio et al., 1991), and suppress angiogenesis by inhibiting the production of interleukin-6 and VEGF in bone marrow (Hu et al., 2017); moreover, they stimulate T-cell proliferation, IL-2 and IFN production, and enhance cytotoxic T lymphocyte (Gorgun et al., 2010) and natural killer effector cell activity (Mitsiades et al., 2002b; Gorgun et al., 2010). However, lenalidomide is more potent than THAL in stimulating T-cell proliferation via the T-cell receptor (TCR) and in enhancing IL-2 and IFN-α production. In addition, LEN decreases secretion of TNF-α and IL-10, and POM increases serum IL-2 receptor and IL-12 levels, with the activation of T cells, monocytes, and macrophages (Gorgun et al., 2010). Furthermore, LEN and POM also inhibit regulatory T cells (Cook et al., 2018).

Moreover, it was demonstrated that IMiDs may act primarily via peroxidase inhibition which result in increased intracellular hydrogen peroxide (H_2O_2) levels (Sebastian et al., 2017). It was found that MM cells with lower H_2O_2 decomposition capacity were more vulnerable to the cytotoxicity induced by lenalidomide (Sebastian et al., 2017). Furthermore, in lower-risk MDS patients' mononuclear cells it was observed that CRBN expression is mediated by NRF2, a transcription factor involved in antioxidant response by reducing oxidative stress. Expression of both NRF2 and CRBN is stimulated by LEN and even more intensely by the combination of LEN and recombinant erythropoietin contributing to drug resistance (Bokorová et al., 2018); the major mechanisms involved in IMiDs resistance are depicted in Fig. 5.

3.3. Immune check-point inhibitors (ICIs)

As mentioned, evasion of immune responses by cancer cells is a major hallmark of cancer (Hanahan and Weinberg, 2011). Also, although the tumor-immune system interplay is mostly studied for T cells, natural killer cells, dendritic cells, neutrophils, and macrophages are also implicated in anti-tumor immune responses (Cassidy et al., 2017). Conventional T cells (Tcon) target tumor cells via two types of signals (Fig. 6). The first is antigen-unspecific and is mediated by Tcon cells receptors that stimulate or inhibit Tcon cells activity; these stimuli are triggered by either tumor-infiltrating antigen presenting cells (APCs) or by tumor cells, and include the Tcon stimulating receptor CD28 and the Tcon inhibitory receptor CTLA-4 (Chen and Flies, 2013). CD28 binding to its costimulatory ligands, namely B7.1 or B7.2 that are being displayed by antigen presenting cells (APCs), results in its phosphorylation, recruitment of downstream kinases (e.g. PI3K) and activation of TCR and the immune adaptor LAT signaling. The second signal that regulates Tcon cells depends on specific antigens and it is mediated by TCR which is activated by MHC molecules on APCs and/or tumor cells that present antigens (Fig. 6). Upon antigen binding to TCR in Tcon cells, the TCR bound CD3 subunits become phosphorylated, triggering the activation of ZAP70 which then activates LAT signaling, cytoskeleton remodeling, activation of the MAPK signaling cascade and the activation of the Tcons transcriptional program which, among others, leads to IFNs secretion-mediated toxicity in tumor cells (Huse, 2009).

The programmed cell death 1 ligand 1 (PD-L1) activates programmed cell death 1 (PD-1) in Tcon cells. PD-L1 binding to PD-1 triggers its phosphorylation and recruitment of the SHP2 phosphatase which dephosphorylates CD28 and TCR signaling components to inhibit Tcon cell activation. Under normal conditions, PD-1 expression in Tcon cells is induced via a negative feedback loop by TCR signaling to suppress Tcon cell overactivation and autoimmunity; consequently, PD-1 expression decreases to basal levels upon antigen clearance. In the TME however, sustained antigen stimulation can lead to constitutively high

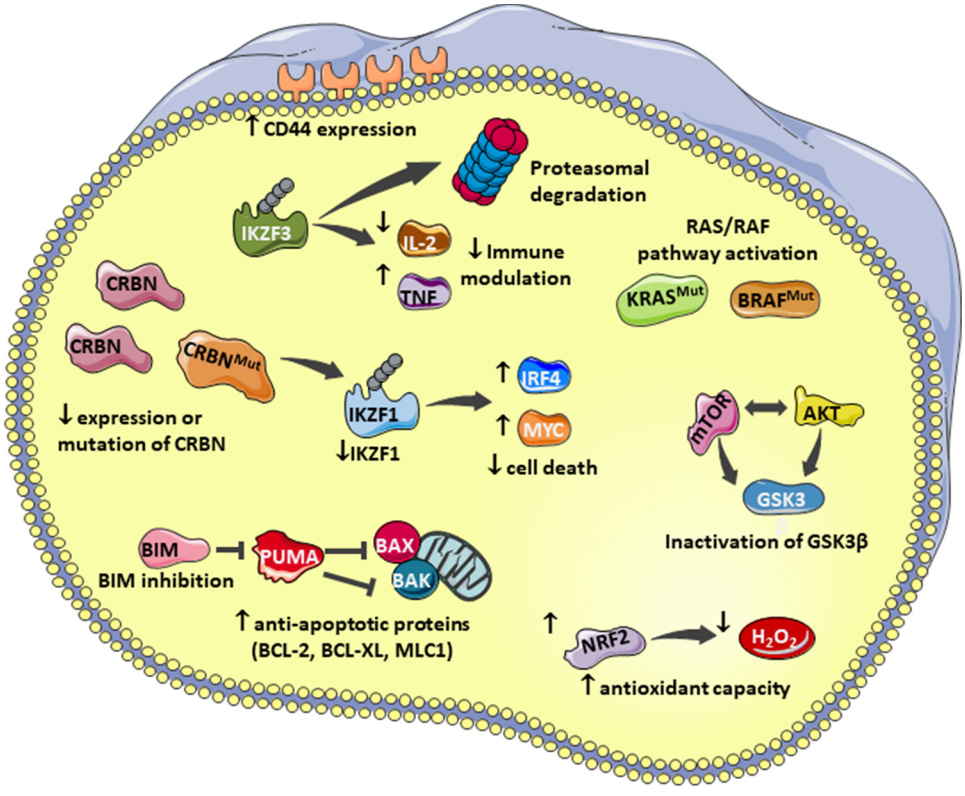

Fig. 5. Mechanisms of resistance to immunomodulatory agents. The common mechanisms of resistance to IMIDs, namely thalidomide, lenalidomide and glucocorticoids, such as dexamethasone, involve reduction of cereblon (CRBN) expression, mutations in the CRBN pathway components, activation of the RAS/RAF pathway through $KRAS^{G12D}$ and $BRAF^{V600E}$ mutations, increased WNT/β-catenin signaling by overexpression of CD44, overactivation of the NRF2 pathway and antioxidant responses, decrease in immune modulation and Ikarus (IKZF1), resistance to apoptosis through upregulation of anti-apoptotic proteins BCL2, BCL-XL and MCL1, inactivation of GSK-3β and inhibition of BIM.

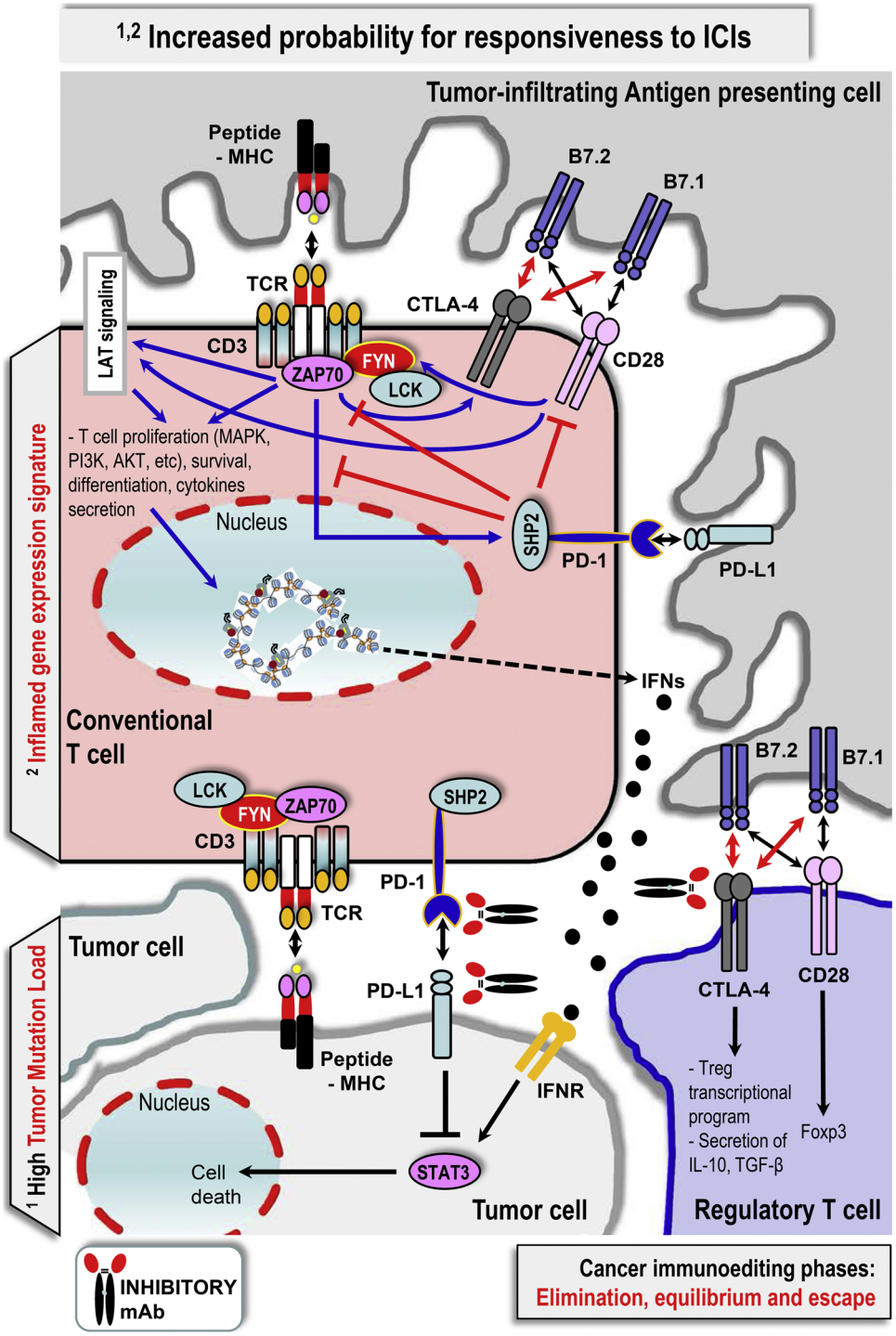

Fig. 6. Inhibitors that target immune checkpoint modules. Main cell types in TME, signaling receptors and downstream regulatory pathways, along with therapeutic inhibitory antibodies (targeting the CTLA-4, PD-1 and PD-L1 molecules) that exploit immune checkpoints are shown (see also text).

PD-1 expression levels that can then be hijacked by tumors to evade immune surveillance. Interestingly, PD-L1 also suppresses the IFNγ/STAT3-mediated apoptosis of tumor cells (Gato-Cañas et al., 2017) and thus it also directly suppresses cytolytic activity of Tcon cells on tumor cells.

Tcon cells overactivation is also suppressed by cytotoxic T lymphocyte antigen 4 (CTLA-4) that is delivered to the plasma membrane upon TCR activation (Walker, 2017), where due to its higher (compared to CD28) affinity for the B7.1 and B7.2 molecules, it suppresses CD28 signaling. CTLA-4 is upregulated shortly after Tcon cell activation, downregulating the immune response to maintain tolerance. CTLA-4 has also a significant role in the suppressive activity of the regulatory T (Treg) cells as it depletes B7 molecules from APCs (Kong et al., 2014; Hou et al., 2015); notably, Tregs in the TME express higher levels of CTLA-4 in the plasma membrane as compared to Tregs at other sites (Simpson et al., 2013). Intriguingly, intrinsic in Tregs, CD28 appears to support Tregs function via activation of the Treg-maintaining transcription factor FOXP3 (DuPage et al., 2015) (Fig. 6).

In line with these findings, several drugs (also referred to as immune checkpoint inhibitors; ICIs) that target PD-L1/PD-1 (Fig. 6) aiming to

harness the immune system to fight cancers, have been approved for cancer immunotherapy including anti-PD-L1 (Atezolizumab, Avelumab, Durvalumab), anti-PD-1 (Pembrolizumab, Nivolumab, Cemiplimab) and anti-CTLA-4 (Ipilimumab) blocking antibodies (Figs. 1 and 6). These antibodies have indeed yielded impressive clinical activities against a variety of tumors (Sharma and Allison, 2015; Ribas and Wolchok, 2018; Zappasodi et al., 2018; Hui, 2019), including lasting responses in a proportion of patients with advanced-stage melanoma or NSCLC, suggesting the formation of a long-lasting tumor-specific immunological memory (Schadendorf et al., 2015; Wolchok et al., 2017). Responses to ICIs are affected by the location, type and density of the immune cells in the TME; these parameters are now recognized to be predictive of patients' treatment response (Fridman et al., 2012) and have been incorporated in a scoring system termed *immunoscore* (Pagès et al., 2009).

Nonetheless, treatment with ICIs may either not promote antitumor immune responses or the tumor-induced immune suppression is not overcome, indicating the existence of intrinsic resistance (Sharma et al., 2017). This output is frequently seen in patients with systemic immunosuppression or in tumors with low mutational load (TML), which are thus less immunogenic; in other words, the same mechanisms that allow immune *escape* during tumorigenesis may also prevent activation of the immune system during cancer immunotherapy (Shin et al., 2017). On the contrary, complete immunotherapy responses relate to the so-called tumor *elimination* phase, whereas during partial responses an *equilibrium* is induced due to partial failure of ICIs to completely overcome tumor cell-mediated suppression of the immune system. Eventually, the *equilibrium* phase results in the selection of tumor clones capable of evading or suppressing anti-tumor immunity; this output is known as the *secondary escape* phase of cancer immunoediting processes and is clinically marked as acquired resistance to therapy, leading to disease progression (Mittal et al., 2014; Teng et al., 2015a; O'Donnell et al., 2019). Overall, the cancer immunoediting processes, namely *elimination*, *equilibrium* and *escape* phases occur during both tumorigenesis or as a response to therapeutic treatment (Schreiber et al., 2011).

Reportedly, better prognosis and response to ICIs is seen when T cells' transcriptional signature is enriched in IFNγ-responsive genes (inflamed or "*hot*" tumors) (Chen and Mellman, 2017; Thorsson et al., 2018). This readout is usually combined with tumors bearing a high mutational load (Kreiter et al., 2015; Linnemann et al., 2015; Schumacher and Schreiber, 2015) such as cutaneous melanomas, lung carcinomas or urothelial carcinomas (O'Donnell et al., 2019) and relates with antigens (e.g. from gene amplification of tumor-associated antigen genes, neoantigens, oncoviruses or germ cell antigens) that are efficiently cross-presented on APCs and tumor cells (Montgomery et al., 2005; Coulie et al., 2014; Schumacher and Schreiber, 2015). These tumors tend to express PD-L1 suggesting the induction of immunosuppressive factors in the TME (Tumeh et al., 2014; Gajewski et al., 2013; Gajewski, 2015). On the other hand, tumors in which T cells are detected within the surrounding stroma but are absent within the tumor tissue (*immune cell-excluded* tumors) or tumors where T cells are absent in both the tumor tissue and the TME (*immune-deserted* tumors) (Chen and Mellman, 2017; Gajewski, 2015), are defined as immunologically "*cold*" tumors and are characterized by either the absence of pre-existing antitumor immune responses or from immune cells that are selectively excluded from the malignant tissue. Patients with these tumor types tend to have poor responses to anticancer immunotherapies (Chen and Mellman, 2017) (Fig. 6).

TME is critically affecting the outcome of therapeutic interventions with ICIs and it can be categorized into four types based on PD-L1 expression and the abundance of tumor-infiltrating lymphocytes (TILs) (Teng et al., 2015b; Ock et al., 2016). The *type 1* TME is characterized by high TML (Hellmann et al., 2018a, b) and an inflammation gene signature, indicating the existence of an ongoing, but functionally suppressed, immune response (Chen et al., 2017); a *type 1* TME usually correlates with good responses to ICIs (Prat et al., 2017). *Type 2* tumors are characterized by relatively low TML and thus minimal (if any) antigen presentation, as well as by no inflammatory gene expression indicating the absence of an adaptive immune response (Taube et al., 2012; Spranger et al., 2015); tumors with either an *immune-desert* or an *immune cell-excluded* phenotype fall into this category (Chen and Mellman, 2017) and patients with such tumors are expected to have minimal responses upon treatment with ICIs. The TML of *type 3* tumors is lower than that of *type 1* tumors but higher than that of *type 2* tumors (Ock et al., 2016); yet, the absence of an inflammatory gene signature in these tumors reflects the exclusion of tumor-specific T cells from tumor tissue (Chen et al., 2016; Chen et al., 2017) indicating that these tumors are likely insensitive to ICIs. Finally, *type 4* tumors contain low TML but express inflammatory genes suggesting innate immune cells activation and/or suppressive immune cells infiltration (Ock et al., 2016), and thus the PD-1–PD-L1 immunosuppressive mechanisms are likely less dominant (Taube et al., 2012). Given however, the increased inflammatory responses, these tumors are likely prone to growth and metastasis (Taniguchi and Karin, 2018).

Tumors with good responses to ICIs may develop acquired immune resistance due to IFNγ-mediated upregulation of PD-L1 expression in tumor cells and tumor-infiltrating immune cells (Taube et al., 2012), resulting in a state often referred to as T cell exhaustion (Pauken et al., 2016; Sen et al., 2016). PD-L1 on immune cells and tumor cells in the TME can be also induced by other inflammatory or immunosuppressive cytokines (e.g. IL-6, IL-12 or TGFβ), while exosomes originating from tumors may carry PD-L1 and contribute to immunosuppression (Chen et al., 2018). Therapies that inhibit the PD-1/PD-L1 molecules may also have a direct effect on tumor-associated macrophages (TAMs), which are subcategorized into M1-type and M2-type macrophages, which suppress or enhance tumor progression, respectively. It was reported that TAMs from mouse and human tumors express PD-1, which impaired their antitumor activity via phagocytosis (Gordon et al., 2017), while in another study TAMs inhibited T cell function, supported metastasis and promoted neovascularization via IL-10 and TGFβ secretion (Mantovani et al., 2017). Reportedly, the pro-tumorigenic functions of TAMs and the adaptive immune resistance to ICIs can be also mediated via T cell-induced production of macrophage colony-stimulating factor 1, a key regulator of monocyte and macrophage differentiation (Neubert et al., 2018). Immunosuppressive myeloid cells, such as myeloid-derived suppressor cells (MDSCs) are recruited into tumor tissue by tumor cells-secreted chemokines (Kumar et al., 2016) supporting tumor progression (Condamine et al., 2015). Similarly, the presence of dendritic and natural killer cells in the tumor can also determine responsiveness to ICIs in patients with melanoma (Barry et al., 2018). Moreover, specific stromal components such as cancer-associated fibroblasts (CAFs), within the TME may also have a major role in immunosuppression (Mondino et al., 2017), as it was found that TGFβ expressed and secreted by CAFs, prevented T cell entry into tumor tissue (Tauriello et al., 2018). The levels of TGFβ in the TME have been shown to suppress the activity of tumor-infiltrating NK cells by promoting their conversion into *type 1* innate lymphoid cells; this conversion negatively affected tumor progression in mice (Gao et al., 2017). Also, CAFs produce immunosuppressive cytokines and promote tumor cell proliferation and production of excess collagen, which impairs immune cell infiltration (Costa et al., 2018).

Interestingly, despite being a critical regulator of antitumor immunity, IFNγ produced by $CD8^+$ T cells within the TME can also promote tumor resistance by inducing neoantigen downregulation or complete loss, thereby leading to tumor *escape* (Takeda et al., 2017). Immune *escape* may also involve the outgrowth of tumor cells with genetic or epigenetic alterations in the IFNγ receptor kinases JAK1/JAK2 and the STAT molecules (Dunn et al., 2005; Gao et al., 2016); mutations in these genes have also been detected in patients with melanoma who displayed intrinsic or acquired resistance to ICIs (Zaretsky et al., 2016; Sade-Feldman et al., 2017). In support, targeting

STAT3, the main transcription factor responsible for the immunosuppressive activity of myeloid cells (Su et al., 2018), by short interfering RNA-loaded nanoparticles or small-molecule inhibitors (Yu et al., 2009; Kortylewski and Moreira, 2017), has demonstrated efficacy in preclinical studies (Woods et al., 2017) and is currently being assessed in phase I/II clinical trials. Notably, a hypoxic environment in the TME can promote the accumulation of metabolites that apart from promoting tumor growth, they also interact with immune cells, impairing lymphocyte function and inducing strong immunosuppression within the TME (Vijayan et al., 2017). Other mechanisms promoting adaptive resistance to ICIs may also relate to loss of tumor antigen expression due to mutations affecting the antigen-presenting machinery (e.g. in the proteasome or autophagy), chaperons responsible for folding and subcellular translocation of MHC molecules (Campoli and Ferrone, 2008; Seliger, 2014) or transporters being associated with antigen processing. Consistently, deficiencies in these pathways affect the recognition of tumor antigens by immune cells (Hicklin et al., 1998; Restifo et al., 1996) and it was found that loss of the chaperone β2-microglobulin is associated with resistance to cancer immunotherapies (Hugo et al., 2016; Zaretsky et al., 2016; Sade-Feldman et al., 2017).

Given these therapeutic readouts, the extreme genetic heterogeneity of human tumors and the adaptive resistance to monotherapies, it was proposed that new combinatorial immunotherapies targeting multiple non-redundant immune pathways and fully activating endogenous tumor immunity should be developed (Smyth et al., 2016; Chen and Mellman, 2017; Marrocco et al., 2019). Consistently, co-treatment with chemotherapy and an anti-PD-1 antibody overcomes adaptive immune resistance (Gandhi et al., 2018), while a combination of both the anti-CTLA-4 and anti-PD-1 antibodies has been associated with higher (compared to monotherapy) overall response rates in advanced-stage melanoma (Wolchok et al., 2013, 2017).

4. Concluding remarks

Classical anti-cancer therapies for many decades included surgery, radiation, and chemotherapy. Yet, in the last two decades, following the identification of genomic drivers and main hallmarks of cancer (Hanahan and Weinberg, 2011), the introduction of targeted therapies that inhibit specific tumor promoting oncogenic (e.g. kinases, steroid hormones, etc.) or non-oncogenic (e.g. the proteasome) pathways has revolutionized cancer therapy. Yet, the emergence of chemoresistance due either to activation of compensatory pathways or because of pre-existing or newly acquired mutations in the targeted pathways, limits the efficacy of these drugs, contributing significantly to cancer mortality. Specifically, it is now becoming evident that beyond the well-described contribution of ABC efflux transporters to MDR, several additional mechanisms evolve in cancer cells being under sustained stress and extensive genomic/proteomic instability due to the applied therapeutic regimen; these responses eventually fuel drug resistance as they provide additional means for continuous supplementation of cancer cells with bioenergetics and survival. In general, the mechanisms of resistance can be classified into: a) inherent, where the tumor is resistant to the drug(s) from the very beginning; and b) acquired, where tumors are initially responsive but become drug resistant upon repeated drug treatment cycles; c) TME-mediated resistance, where immune cells, CAFs, TAMs and vascularization cross-talk with tumor cells contributes to chemoresistance; and finally, d) those the relate to pharmacokinetic factors, where detoxification determines the actual drug concentration that reach the tumor or the drug target.

Studies on the mechanisms involved in drug resistance revealed new mechanistic insights in the basic biology, function of oncogenes (e.g. kinases), the plasticity of transcriptional programs and the wiring of signal transduction and proteostatic/mitostatic modules in human cells. Future research should focus on new methodologies that will permit the early detection of drug resistance mechanisms and common genetic/epigenetic alterations that lead to chemoresistance. Also, studies should focus on precise interventions to overcome resistance particularly for refractory and relapsed patients. Given that targeted therapies which inhibit oncogenic modules of the InS/GF pathway (e.g. TKIs) or proteostatic modules (e.g. PIs) would likely activate as an adaptive or compensatory response pro-survival autophagy (Fig. 7), clinical trials with either existing autophagy inhibitors or with new highly specific and less toxic molecules that inhibit autophagy should be designed. Furthermore, advances in the discovery and clinical development of unique next-generation, highly specific PIs, offer important possibilities for the future of cancer treatment; intriguingly however, promising preclinical data obtained with PIs in solid tumor models have not been confirmed in the clinic (Yuan et al., 2018). Given that proteasome is mostly induced under conditions of increased proteome instability (such as the one seen in MM or after chemotherapy/radiotherapy), as

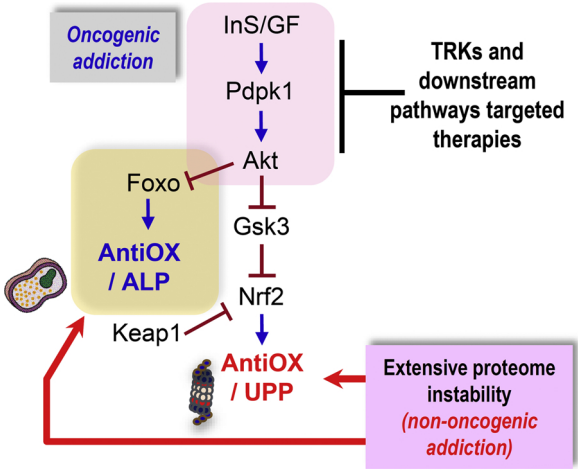

Fig. 7. Basic regulatory functional links between oncogenic and proteostatic pathways. Excluding cases of extensive proteome instability, e.g. in MM or during chemotherapy/radiotherapy (where both UPP and ALP are expected to be induced), PIs will likely not add much to therapies targeting oncogenic modules of the InS/GF pathway in cancer cells, since it is expected that treatment of tumor cells with TKIs will likely also suppress proteasome activity. On the other hand, inhibition of autophagy -which is expected to be activated following the use of TKIs- will likely synergistically enhance the toxicity of TKIs. As tumor cells likely exhibit minimal basal survival-promoting autophagy, its activation may be most significant as an adaptive response to anticancer therapies; thus, autophagy inhibition will be of minimal utility as monotherapy. Therefore, clinical trials with autophagy inhibitors (e.g. chloroquine or hydroxychloroquine) should combine these compounds with other targeted therapies of oncogenic addiction (e.g. TKIs) (→ positive regulation; ⊣ negative regulation).

well as that UPP is likely positively regulated by oncogenic modules of the InS/GF pathway (Luo et al., 2009) (Figs. 1 and 7) we propose that the combined application of PIs with therapeutic interventions targeting RTKs or related downstream pathways will not confer further improvement of the therapeutic index.

Additionally, prospective validation of biomarkers should be used to identify patients that will benefit from certain drug classes including those with drug resistant disease. The development of the new gene editing techniques (e.g. CRISPR-Cas9 system) (Gupta et al., 2019) may also speed up the elucidation of specific resistance mechanisms in tumor cell lines that can be then validated in patient-derived xenografts (Lampreht Tratar et al., 2018) for different classes of targeted inhibitors. Furthermore, for the evaluation of small molecules targeting cancer-related protein kinases, clearly defined stratification criteria will be needed not only based on the use of suitable biomarkers but also on appropriate clinical end points (Fedele et al., 2012).

It is anticipated that the use of novel combinatorial therapies, e.g. TKIs in combination with other types of pharmacologic inhibitors and/or immunotherapy, will likely improve therapeutic indexes. In the exciting field of immunotherapy, combination drug regimens will comprise *homo-combinations*, i.e. two-three antibodies engaging non-overlapping epitopes of the same protein antigen, or *hetero-combinations*, i.e. two or more antibodies, each blocking distinct antigens. Regarding immune therapies, future efforts should focus on the targeting of additional elements of resistance such as TAMs, CAFs or the combined anti-PD-1 and/or anti-CTLA4 therapies with tumor vaccines; the latter will likely enhance tumor recognition and anti-tumor responses in poorly immunogenic tumors models.

Overall, despite exciting findings and the new era of targeted anticancer therapies that has significantly increased cancer patients' OS, drug resistance remains a primary hindrance in the clinic that should be addressed with focused multidisciplinary translational research in the years to come.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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