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The multi-factorial nature of clinical multidrug resistance in cancer

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Abbreviations: ABC, ATP-binding cassette; ABCB1, ATP-binding cassette subfamily B member 1; ABCB10, ATP-binding cassette subfamily B member 10; ABCC, ATP-binding cassette subfamily C; ABCC1, ATP-binding cassette subfamily C member 1; ABCC3, ATP-binding cassette subfamily C member 3; ABCD1, ATP-binding cassette subfamily D member 1; ABCG2, ATP-binding cassette subfamily G member 2; 5-AC, 5-azacytidine; ADHFE1, Alcohol dehydrogenase iron containing 1; ADME, Absorption, distribution, metabolism and excretion; ADP, Adenosine diphosphate; AML, Acute myeloid leukemia; AP-2γ, Transcription factor activating protein-2γ; APAF-1, Apoptotic peptidase activating factor 1; APC, APC regulator of Wnt signalling pathway; ATM, Ataxia telangiectasia mutated serine/threonine kinase; ATR, ATR serine/threonine kinase; AUC, Area under the plasma concentration *versus* time curve; BAD, BCL2-associated agonist of cell death; BARD1, BRCA1 associated RING domain 1; BAX, BCL-2- associated X protein; BCL-XL, B-cell lymphoma-extra large; BCL-2, B-cell lymphoma protein 2; BCRP, Breast cancer related protein; BCRP-1, ATP-binding cassette super-family G member 2 is a protein that in humans is encoded by the ABCG2 gene; BER, Base-excision repair; BID, BH3-interacting domain death agonist; Bim, A pro-apoptotic member of the BCL-2 protein family; BMI1, Polycomb complex protein; BIRC3, Baculoviral IAP repeat-containing protein 3; BRCA, Breast cancer susceptibility protein; BRCA1, Breast cancer type 1 susceptibility protein; BRIP1, BRCA1 interacting protein C-terminal helicase 1; CALCA, Calcitonin related polypeptide alpha; CAFs, Cancer-associated fibroblasts; CBLN2, Cerebellin 2 precursor; CCBE1, Collagen and calcium-binding EGF domain-containing protein 1; CCDC8, Coiled-coil domain containing 8; CCNG1, Cyclin- G1; CD44, Cluster of Differentiation 44; CDH1, Cadherin-1; CDH13, T-cadherin also known as cadherin 13; CDKN2A, Cyclin-dependent kinase inhibitor 2A; CDKN2B, Cyclin-dependent kinase 4 inhibitor B; CH3, Methyl group; CHEK1, Checkpoint kinase 1; CHEK2, Checkpoint kinase 2; Chk2, Checkpoint kinases 2; CHODL, Chondrolectin; Cmax, Maximal plasma concentration; CML, Chronic myeloid leukemia; CRC, Colorectal cancer; CRT1, Copper transporter 1; CSCs, Cancer stem cells; CTCs, Circulating tumor cells; CYP, Cytochrome P450; CYP2A6, Cytochrome P450 family 2 subfamily A member 6; CYP2C19, Cytochrome P450 family 2 subfamily C member 19; CYP2D6, Cytochrome P450 family 2 subfamily D member 6; DAPK, Death-associated protein kinase; DDIs, Drug-drug interactions; DDR, DNA damage response; DCC, DCC netrin 1 receptor; DFS, Disease free survival; DNMT, DNA methyltransferase; DNMTi, DNA methyltransferase inhibitor; DPPA4, Developmental pluripotency associated protein 4; DPPA5, Developmental pluripotency associated protein 5; DSB, Double strand breaks; ECM, Extracellular matrix; EGFR, Epidermal growth factor receptor; EMT, Epithelial-mesenchymal transition; ERβ, Estrogen receptor β; ERCC1, Excision repair 1 endonuclease non-catalytic subunit; ERCC2, ERCC excision repair 2, TFIIH core complex helicase subunit; ESR, Estrogen receptor; EVs, Extracellular vesicles; 5-Fluorouracil, 5-FU; FA, Fanconi anemia; FAK, Focal adhesion kinase; FAM175A, Coiled-coil domain-containing protein 98; FANCD2, FA complementation group D2; FANCL, FA complementation group L; FAS, Fas cell surface death receptor; FBXO17, F-Box Protein 17; FCGR2A, Fc fragment of IgG receptor IIa; FCGR3A, Fc fragment of IgG receptor IIIa; FDA, U.S. Food and Drug Administration; FLIP, FLICE-inhibitory protein; GDF3, Growth differentiation factor 3; ɣ-GGT, Gamma-glutamyltransferase; GNAO1, G protein subunit alpha o1; GOLPH3, Golgi phosphoprotein 3; GRIK1, Glutamate receptor, ionotropic, kainate 1; GSH, Glutathione; GSTP1, Glutathione S-transferase P1; HAND2, Heart and neural crest derivatives expressed protein 2; HCC, Hepatocellular carcinoma; HDAC, Histone deacetylase; HDACi, Histone deacetylase inhibitor; HER-2, Human Epidermal Growth Factor Receptor 2; HIF1A, Hypoxia-inducible factor 1-alpha; HIPK2, Homeodomain-interacting protein kinase 2; HLA, Human leukocyte antigen; HMAs, Hypomethylating agents; HMGB1, High mobility group box 1; hMLH1, Human mutL homolog 1; hMSH2, Human MutS homolog 2; hMSH3, Human MutS homolog 3; hMSH6, Human MutS homolog 6; HOX, Homeobox; HOXA9, Homeobox A9; HOXA10, Homeobox A10; HOXA11, Homeobox A11; HR, Homologous recombination; IAPs, Inhibitor of apoptosis proteins; ILK, Integrin-linked

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ABSTRACT

Curative cancer therapy remains a major challenge particularly in cancers displaying multidrug resistance (MDR). The MDR phenotype is characterized by cross-resistance to a wide array of anticancer drugs harboring distinct structures and mechanisms of action. The multiple factors involved in mediating MDR may include host factors, tumor factors as well as tumor-host interactions. Among the host factors are genetic variants and drug-drug interactions. The plethora of tumor factors involves decreased drug uptake primarily via impaired influx transporters, increased drug efflux predominantly due to the overexpression of MDR efflux transporters of the ATP-binding cassette superfamily or due to drug efflux mediated by extracellular vesicles (EVs) or drug-loaded lysosomes undergoing exocytosis, deregulation of cell death mechanisms (i.e. anti-apoptotic modalities), enhanced DNA damage repair, epigenetic alterations and/or deregulation of microRNAs. The intratumor heterogeneity and dynamics, along with cancer stem cell plasticity, are important tumor factors. Among the tumor-host interactions are the role of the tumor microenvironment, selective pressure of various stressor conditions and agents, acidic pH and the intracellular transfer of traits mediated by EVs. The involvement of these diverse factors in MDR, highlights the need for precision medicine and real-time personalized treatments of individual cancer patients. In this review, written by a group of researchers from COST Action STRATAGEM "New diagnostic and therapeutic tools against multidrug resistant tumors", we aim to bring together these multidisciplinary and interdisciplinary features of MDR cancers. Importantly, it is becoming increasingly clear that deciphering the molecular mechanisms underlying anticancer drug resistance, will pave the way towards the development of novel precision medicine treatment modalities that are able to surmount distinct and well-defined mechanisms of anticancer drug resistance.

1. Introduction

The efficacy of chemotherapy is a major challenge in clinical oncology. Indeed, some cancer patients fail to respond to anticancer agents, presenting either intrinsic or acquired chemoresistance (Gonen and Assaraf, 2012; Gottesman et al., 2016; Zhitomirsky and Assaraf, 2016). Multidrug resistance (MDR) is characterized by cross-resistance of cancer cells to a broad range of anticancer drugs with distinct structures and different mechanisms of action (Gottesman, 2002). This obstacle is particularly important since the majority of anticancer drugs have a narrow therapeutic window, with a small difference between the dose required to achieve a therapeutic effect and to cause untoward toxicity (Ikediobi, 2008). Clinical MDR in cancer may be caused by many factors which, for the purpose of better understanding, may be separated into host factors, tumor factors (Alfarouk et al., 2015) or factors associated with tumor-host interactions (Alaoui-Jamali et al., 2004). These multidisciplinary and interdisciplinary features of human cancers will be thoroughly reviewed in the current paper, written by a

(*footnote continued*)
kinase; IRF8, Interferon regulatory factor 8; IRI, Irinotecan; ITH, Intra-tumor heterogeneity; JNK2, C-Jun N-terminal kinases; KIT, KIT proto-oncogene, receptor tyrosine kinase; LIN28-A, Lin-28 homolog A; lncRNAs, Long non-coding RNAs; LONRF2, LON peptidase N-terminal domain and ring finger 2; MAB21L1, Mab-21 like 1; MAPK, Mitogen-activated protein kinase; MATEs, Multidrug and toxin extrusion proteins; MCL-1, Myeloid cell leukemia 1; MDR, Multidrug resistance; MGMT, Methylguanine-DNA methyltransferase; miRNAs, microRNA; MMPs, Matrix metalloproteinases; MMP2, Matrix metalloproteinase 2; MM, Multiple myeloma; MMR, Mismatch repair; MRE11A, Double-strand break repair protein MRE11A; MRP, Multidrug resistance-associated protein; MRP1, Multidrug resistance-associated protein 1; MRP7, Multidrug resistance-associated protein 7; MSI, Microsatellite instability; mTOR, Mammalian target of rapamycin; mTORC2, mTOR Complex 2; MYCL1, L-myc-1 proto-oncogene; NANOG, Nanog homeobox; NBN, Nibrin; NER, Nucleotide excision repair; NGS, Next generation sequencing; NHEJ, Non-homologous end joining; NSCLC, Non-small cell lung cancer; NER, Nucleotide-excision repair; NOVA1, NOVA alternative splicing regulator 1; OAT, Organic anion transporter; OCT, Organic cation transporter; OCT1, Organic cation transporter 1; OCT-3/4, octamer-binding transcription factor ¾; OPCML, Opioid binding protein/cell adhesion molecule like; OS, Overall survival; p16INK4A, Tumor suppressor protein p16INK4a; p53, Tumor protein p53; PALB2, Partner and localizer of BRCA2; PARP, Poly (ADP-ribose) polymerase; PARPi, Poly (ADP-ribose) polymerase inhibitor; PD, Pharmacodynamics; PDAC, Pancreatic ductal adenocarcinoma; PDCs, Patient-derived cell cultures; PDGF-D, Platelet-derived growth factor-D; PDXs, Patient derived xenografts; PFS, Progression free survival; P-gp, P-glycoprotein; PharmGKB, Pharmacogenomics Knowledgebase; PHOX2A, Paired mesoderm homeobox protein 2A; PI3K-I, Phosphatidylinositol 3-kinase-I; PIK3C2A, Phosphatidylinositol-4-phosphate 3-kinase C2 domain-containing alpha polypeptide; PK, Pharmacokinetics; PKB, Protein kinase B; PMEA, 9-(2-phosphonylmethoxynyl)adenine; POU5F1, POU domain, class 5, transcription factor 1, also known as Oct-4; PPIs, Proton pump inhibitors; PPP2R2A, Protein phosphatase 2 regulatory subunit B alpha; PTEN, Phosphatase and tensin homolog; PTGS2, prostaglandin-endoperoxide synthase 2; RAD50, Double strand break repair protein; RAD51B, RAD51 paralog B; RAD51C, RAD51 paralog C; RAD51D, RAD51 paralog D; RAD54L, DNA repair and recombination protein RAD54-like; RARβ2, Retinoic acid receptor beta 2; RASSF1A, Ras association domain-containing protein 1; RCC, Renal cell carcinoma; ROS, Reactive oxygen species; RXRG, Retinoid X receptor gamma; SCLC, small cell lung cancer; SGI-110, Guadecitabine DNMT inhibitor; SLC, Solute carrier; SLC22A1, Solute carrier family 22 member 1; SLC5A10, Solute carrier family 5 member 10; SNVs, Single nucleotide variants; SOCS1, Suppressor of cytokine signalling 1; SORCS1, Sortilin related vps10 domain containing receptor 1; SPIN3, Spindlin family member 3; SPRY4, Sprouty homolog 4 protein; SSB, Single strand break; SSRIs, Selective serotonin reuptake inhibitors; ST8SIA4, CMP-*N*-acetylneuraminate-poly-alpha-2,8-sialyltransferase; TAMs, Tumor-associated macrophages; TILs, Tumor-infiltrating lymphocytes; TKIs, Tyrosine kinase inhibitors; TLS, Translesion synthesis; TP53, Tumor protein p53; TME, Tumor microenvironment; TNF, Tumor necrosis factor; TNF-R1, Tumor necrosis factor receptor superfamily member 1A; TRAIL, TNF-related apoptosis-inducing ligand; TRAIL-R1/DR4, TRAIL receptor 1/death receptor 4; TRAIL-R2/DR5, TRAIL receptor 2/death receptor 5; TRAIL-R3/DcR1, TRAIL receptor 3/decoy receptor 1; TRAIL-R4/DcR2, TRAIL receptor 4/ decoy receptor 2; TrpC5, a transient receptor potential channel 5; TYMS, Thymidylate synthase; UCH-L1, Ubiquitin carboxyl terminal hydrolase-L1; VDR, vitamin D receptor; VEGF, Vascular endothelial growth factor; VHL, von Hippel–Lindau tumor suppressor; VLA-4, Very late antigen-4; WBP5, WW domain binding protein 5; WLS, Wntless Wnt Ligand Secretion Mediator; Wnt, Wnt signalling pathway; XAF1, XIAP associated factor 1; XIAP, X-linked inhibitor of apoptosis protein; XPA, Xeroderma pigmentosum complementation group A; XPF, Xeroderma pigmentosum complementation group F; XRCC1, X-ray repair cross complementing 1; ZEB1, Zinc finger e-box binding homeobox 1; ZNF608, Zinc finger protein 608; ZNF69, Zinc finger protein 69

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2. Host factors

2.1. Host genetic variants

Significant clinical studies aimed to identify molecular markers, namely genetic variants, to predict sensitivity or resistance to chemotherapeutic drugs have been conducted (De Mattia et al., 2015). Indeed, drug efficacy is highly variable between patients and genetic variants are estimated to account for 20–95% of response variability depending on the drug (Mukerjee et al., 2018). Driven by genomic instability of various cancers, the most abundant genetic variants influencing drug response are single nucleotide variants (SNVs), but insertions, deletions, repeats, and copy number variations also have an impact in the efficacy of therapy (Deenen et al., 2011a; Olivera et al., 2019; Turajlic et al., 2019). These genetic variations are predominantly located in genes encoding for drug-metabolizing enzymes (e.g. *CYP2A6*, *CYP2C19*, and *CYP2D6*), drug uptake/efflux (e.g. *SLC22A1*, *ABCB1*, *ABCG2*), drug targets (e.g. *TYMS*, *ESR*, *VDR*), DNA repair mechanisms (e.g. *ERCC1*, ERCC2, and *XRCC1*), cell cycle control (e.g. *TP53*), and immune system related alleles (e.g. HLA class I genes, *FCGR2A*, and *FCGR3A*) (Chowell et al., 2018; Daigo et al., 2002; Kim et al., 2009; Kjersem et al., 2014; Li et al., 2007; Marin et al., 2012; Mathijssen et al., 2003; Mukerjee et al., 2018; Rodriguez-Antona et al., 2010). However, the role of genetic variants in cancer resistance is associated with well-known response factors that interact with the genetic background, such as age, co-morbidities, drug-drug interactions (DDIs), diet, among others (Alfarouk et al., 2015). Several germline variants have been significantly associated with the efficacy of cancer therapy. Pharmacogenomics Knowledgebase (PharmGKB), a free access online database created, curated and managed by the University of Stanford, assembles a collection of clinically relevant drug-gene associations related to dosage, efficacy, toxicity/adverse drug reactions and metabolism/pharmacokinetics (Whirl-Carrillo et al., 2012). However, more than 93% of the associations between genetic variants and chemotherapy efficacy recorded in PharmGKB are qualified as low or preliminary (www.pharmgkb.org; 16th May 2019). These promising germline variants have failed clinical validation in independent studies and/or their level of evidence is low due to conflicting results that cannot provide clear conclusions about the predictive value of a specific genetic variant. The genetic variants affecting the response to anticancer drugs with potential clinical interest are summarized in **Supplementary Table S1** and will be presented below.

Phase I drug metabolizing enzymes catalyze drug oxidation, reduction and hydrolysis reactions, resulting in drug activation or inactivation depending on the specific drug (Deenen et al., 2011b). The human cytochrome P450 (CYP) superfamily encompasses approximately 60 enzymes that are responsible for 80–90% of phase I drug metabolism (Marin et al., 2012). CYP2D6, a highly polymorphic phase I drug metabolizing enzyme, is one of the primary enzymes responsible for the metabolic activation or inactivation of exogenous compounds and is particularly important in breast cancer treatment with tamoxifen (Hertz et al., 2015). This enzyme metabolizes tamoxifen to 4-hydroxytamoxifen and endoxifen, both of which display higher anti-estrogenic activity than tamoxifen, and probably interferes with the effectiveness of therapy outcomes (Goetz et al., 2018; Hertz et al., 2015). Several studies explored the influence of *CYP2D6* variants on the efficacy of tamoxifen treatment in breast cancer patients, and there is a strong association between *CYP2D6* genotype and endoxifen concentrations (Hertz et al., 2015; Saladores et al., 2015). According to PharmGKB, these studies provide evidence that patients with two non-functional alleles (such as *CYP2D6*3*, **4*, **5*, **6*) or a **10* or **41* allele in combination with a non-functional allele or another **10* or **41* allele, may have decreased metabolism of tamoxifen, leading to lower endoxifen concentrations, increased likelihood of recurrence, and decreased event-free and recurrence-free survival, in comparison to patients with a *CYP2D6*1/*1* genotype or normal metabolizers (Hennig et al., 2015; Rangel et al., 2014). The *CYP2D6* genotype explains 34–52% of endoxifen concentration variability (Schroth et al., 2017); however, the association of the *CYP2D6* genotype and outcome measures (recurrence and survival) may also be influenced by other genetic and clinical factors since there are some contradictory findings regarding this association (Dezentje et al., 2013; Trojan et al., 2012).

Plasma membrane transporters are key players in the uptake as well as efflux of a multitude of chemotherapeutic drugs and are strongly associated with drug resistance. The large solute carrier (SLC) family of membrane transporters determines the intracellular concentration of most drugs, influencing drug uptake. On the other hand, the ATP-binding cassette (ABC) superfamily is responsible for drug efflux, and some members of this family also participate in intracellular drug sequestration (Marin et al., 2012). ABC transporters, particularly ABCB1 (ATP-binding cassette subfamily B member 1, also known as P-glycoprotein; P-gp), ABCC1 (multidrug resistance-associated protein 1; MRP1), and ABCG2 (ATP-binding cassette subfamily G member 2, also known as breast cancer resistance protein; BCRP), are major determinants of drug resistance since they modulate drug absorption, distribution and elimination, or restrict membrane permeability through the blood-tissue barrier (Bruhn and Cascorbi, 2014). Several genetic variants have been identified in the ABC transporter family, but *ABCB1* genetic variants showed the highest clinical impact. A frequent *ABCB1* haplotype, comprising the variants c.3435C > T (p.Ile1145=; rs1045642), c.2677 G > T/A (p.Ser893Ala; rs2032582), and c.1236C > T (p.Gly412=; rs1128503), has been associated with sunitinib resistance and lower overall survival (OS) in patients with renal cell carcinoma (RCC). Three studies explored the influence of *ABCB1* haplotypes in response to sunitinib treatment in metastatic RCC patients and suggested with a moderate level of evidence, that RCC patients with the *ABCB1*2/*2* diplotype may show decreased response to sunitinib, compared to patients with other diplotypes, namely *ABCB1*1/*1* and *ABCB1*1/*2* (Chu et al., 2015b; Diekstra et al., 2015; van der Veldt et al., 2011).

The cytotoxicity of several chemotherapeutic agents, such as platinum compounds, is mediated by the formation of different DNA adducts, triggering intra- and interstrand breaks, that lead to DNA replication arrest and cell death (De Mattia et al., 2015; Xiong et al., 2017). However, cells have different DNA damage repair pathways to repair these lesions, including nucleotide-excision repair (NER) and base-excision repair (BER), among others (Perez-Ramirez et al., 2017). The ability of cancer cells to repair the DNA damage induced by chemotherapeutic agents determines the clinical outcome of several drugs such as platinum compounds (Beheshti et al., 2018). X-ray repair cross-complementing 1 (XRCC1) is one of the BER proteins involved in the detection and repair of DNA damage induced by platinum compounds (Perez-Ramirez et al., 2017; Xiong et al., 2017). One of the most investigated genetic variants of *XRCC1*, considering the prediction of platinum-based regimens, is the c.1196A > G (p.Gln399Arg; rs25487). Cancer patients harboring the TT genotype that were treated with platinum-based chemotherapeutic regimens showed decreased response to these platinum drugs (Goricar et al., 2017; Lai et al., 2013; Perez-Ramirez et al., 2019). Controversially, a few studies reported no association between decreased response to platinum compounds and the TT genotype in cancer patients (Giovannetti et al., 2011; McLeod et al., 2010). This inconsistency may be due to ethnic differences since chemoresistance to these drug regimens was mainly found in Chinese patients and to a lesser extent in Caucasian patients (Gu et al., 2015; Perez-Ramirez et al., 2019; Shahnam et al., 2016; Xiong et al., 2017).

In summary, many genetic variants have been investigated as potential biomarkers of cancer drug response but, so far, the obtained results have been inconsistent. This lack of strong evidence is probably due to the multifactorial nature of drug resistance and to the cancer

type and stage, indicating that the clinical relevance of genetic variants as response biomarkers to chemotherapeutic agents needs further elucidation.

2.2. Drug-drug interactions (DDIs)

Among host-related factors, DDIs play a key role in the onset of anticancer drug resistance. A DDI, defined as the change in efficacy or toxicity of one drug by prior or concomitant administration of a second drug, can be classified into pharmacokinetic (PK) or pharmacodynamic (PD) interaction (Scripture and Figg, 2006). Moreover, other factors such as food, herbal supplements, environmental factors (e.g. cigarette smoking) can alter the drug's PK and PD (Scripture and Figg, 2006). The PK DDIs involve alterations in drug absorption, distribution, metabolism and excretion (ADME), whereas the PD DDIs can result in synergistic, antagonist or additive responses.

Cancer patients are very susceptible to DDIs since they usually take several medications including anticancer drugs, supportive care drugs (antiemetics, analgesics, antifungals, anxiolytics, antidepressants, gastric acid-reducing agents, and cholesterol reducing statins), and drugs to treat additional comorbidities (Riechelmann et al., 2007). Moreover, the ADME/PK properties of drugs may be affected by altered liver and/or renal function, particularly in elderly patients that are at increased risk of developing cancer and other chronic diseases (Riechelmann and Del Giglio, 2009).

Three retrospective studies demonstrated that 27–58% of patients receiving i.v. anticancer treatment (Riechelmann et al., 2007; van Leeuwen et al., 2011) and 46% of patients treated with oral anticancer regimens (van Leeuwen et al., 2013), had at least one potential DDI. Two prospective studies found clinically relevant DDIs in 17–27% of oncological patients (Ramos-Esquivel et al., 2017; van Leeuwen et al., 2015). Recently, by using a DDI screening tool, one study detected moderate to major DDIs in 24.2% of subjects enrolled in clinical trials at the University of Michigan Rogel Cancer Center (Marcath et al., 2018).

Some representative examples of PK DDIs that have a major impact on drug disposition and treatment outcome in cancer patients will be presented here. Of note, even though factors that influence absorption have little effect on antineoplastic agents administered i.v., the absorption of oral anticancer agents (e.g. tyrosine kinase inhibitors, TKIs) may be significantly influenced by altered intra-gastric pH values as well as by the activity of drug transporters and intestinal enzymes. Most of the TKIs are characterized by a poor and variable oral bioavailability. They are weak bases, protonated, and most soluble in acidic environments; therefore, an increase in pH values dramatically decreases their solubility (Herbrink et al., 2015; Mathijssen et al., 2014). It is known that up to 30% of cancer patients take gastric acid-reducing agents [proton pump inhibitors (PPIs), H_2-antagonists, and anti-acids] to relieve gastro-esophageal reflux and dyspepsia symptoms, with PPIs being the most commonly prescribed agents (Sharma et al., 2019; Smelick et al., 2013). Therefore, absorption of several TKIs (e.g. gefitinib, erlotinib, dasatinib, nilotinib, nintedanib and sunitinib) may be significantly reduced by concomitant use of such agents (Budha et al., 2012; Hussaarts et al., 2019; van Leeuwen et al., 2014). For example, in healthy volunteers, co-administration of 150 mg erlotinib with either 40 mg omeprazole or 300 mg ranitidine, once daily, decreased erlotinib's area under the plasma concentration *versus* time curve (AUC) by 46 and 33% and the maximal plasma concentration (Cmax) by 61 and 54%, respectively. However, when the TKI was administered 2 h before or 10 h after 150 mg ranitidine, taken twice daily, its AUC and Cmax decreased only by 15 and 17%, respectively (Budha et al., 2012; EMA, 2019). Therefore, label guidelines advise to avoid the concomitant treatment with PPIs or to switch to H_2 antagonists, taken 2 h after erlotinib (EMA, 2019). Moreover, it was shown that the intake of erlotinib with an acidic beverage (Coca Cola®) enhanced bioavailability by almost 40% in non-small cell lung cancer (NSCLC) patients also taking esomeprazole (van Leeuwen et al., 2016).

However, so far there are no prospective controlled trials, but only conflicting retrospective analyses regarding the clinical significance of this important DDI. In NSCLC patients randomized in the BR.21 trial (Shepherd et al., 2005), a *post hoc* analysis showed that co-administration of PPIs/H_2 receptor antagonists and erlotinib did not have a significant impact on the median plasma drug levels, nor on OS and progression free survival (PFS) (Hilton et al., 2013). Comparable results on patient outcome were obtained in 130 NSCLC patients harboring EGFR mutations (Zenke et al., 2016). In contrast, two retrospective observational studies demonstrated that PFS and OS in patients who received gastric acid-suppressing agents along with erlotinib, were significantly reduced (Chu et al., 2015a; Nieves Sedano et al., 2018). Very recently, a large population-based study including 12,538 patients taking PPIs and several TKIs to treat different cancer types, reported a 21% increased risk of death among lung cancer patients who were receiving erlotinib with a concurrent PPI (Sharma et al., 2019). However, concomitant treatment with PPIs and TKIs was not significantly associated with discontinuation of the anticancer therapy, indicating that discontinuation may not be responsible for the reduced survival of those patients (Sharma et al., 2019).

The DDIs involving agents that reduce gastric acid secretion are not limited to TKIs. Many oral non-targeted anticancer agents require an acidic environment to properly dissolve for systemic absorption. A negative interaction between capecitabine and PPI, for example, has been reported in several retrospective studies (Chu et al., 2017; Rhinehart et al., 2018; Sun et al., 2016; Wong et al., 2019a). These findings have been raising a concern in view of the widespread use of PPIs, also available as over-the-counter drugs, without a prescription from a healthcare professional.

Drug absorption is a complex phenomenon also modulated by drug transporters active within the enterocyte. Either inhibition of influx transporters or induction of efflux transporters may reduce the extent of drug absorption and, subsequently, its bioavailability (Hussaarts et al., 2019). In healthy male subjects, co-administration of nintedanib, a TKI approved for locally advanced, metastatic or recurrent NSCLC, and the P-gp inducer rifampicin caused a decrease of 50% in the AUC and 60% in C_{max} (Luedtke et al., 2018). As nintedanib is metabolized essentially via hydrolytic ester cleavage with subsequent glucuronidation whilst the oxidative CYP-metabolism is of negligible importance, this effect is likely due to P-gp induction (Wind et al., 2019). Moreover, induction of efflux transporters localized either at the brush-border membrane of the proximal renal tubule or in the canalicular membrane of hepatocytes may lead to increased drug excretion into the urine and bile, respectively, with consequently decreased drug exposure (Scripture and Figg, 2006).

Although drug metabolism may occur within the gastrointestinal tract, the primary site for drug biotransformation is the liver. Drugs capable of inducing CYPs, via increased transcription, can reduce the serum concentration of drug substrates of the induced enzymes. Contrariwise, the activity of a prodrug, which is metabolized into a pharmacologically active drug, will be decreased by CYP inhibitors (Scripture and Figg, 2006). Furthermore, several CYP inducers or inhibitors are also inducers or inhibitors of ABC transporters (Hussaarts et al., 2019). Moreover, metabolic DDIs may be complicated by the CYP genotype. Most TKIs undergo CYP-dependent metabolism and some of them can also act as an inducer or inhibitor of the CYP isoenzymes (Teo et al., 2015). Co-administration of TKIs with CYP inducers like anticonvulsants (carbamazepine, phenobarbital, and phenytoin), glucocorticoids and rifampicin may significantly decrease the exposure to the TKI being converted to the inactive form through CYP metabolism. Rifampin, for example, was shown to reduce bosutinib AUC and C_{max} by about 90% (Abbas et al., 2015), and increasing the dose of bosutinib when co-administering strong CYP3A inducers is unlikely to compensate for the loss of drug exposure (Hussaarts et al., 2019).

As stated above, CYP2D6 plays a key role in metabolic activation of tamoxifen (Goetz et al., 2018). Frequently, women taking tamoxifen

also take selective serotonin reuptake inhibitors (SSRIs) for depression and vasomotor symptoms (Dusetzina et al., 2013). Some SSRI, like fluoxetine, duloxetine and paroxetine are potent CYP2D6 inhibitors, capable of reducing 4-hydroxytamoxifen and endoxifen formation (Jin et al., 2005; Stearns et al., 2003). Several studies have investigated the clinical meaning of this DDI, although with controversial results: some suggested an increased risk of either breast cancer recurrence or mortality (Busby et al., 2018; Chubak et al., 2008; Dezentje et al., 2010; Kelly et al., 2010), whilst other studies produced negative results (Donneyong et al., 2016; Haque et al., 2016; Siegelmann-Danieli et al., 2011).

Taken together, DDIs are of paramount importance in cancer patients taking drugs with narrow therapeutic index and inherent toxicity. However, beyond DDIs affecting drug efficacy, those causing increased toxicity can reduce patient compliance, contributing to treatment discontinuation and therapeutic failure. Although most of the findings reviewed here warrant further investigation in order to better clarify their clinical relevance, they have important implications for patients and health care professionals, because they increase awareness of the DDIs and their possible impact on drug bioavailability and therapeutic outcomes in cancer patients.

3. Tumor factors

3.1. An overview of the mechanisms underlying MDR

3.1.1. Alterations in intracellular drug concentration

3.1.1.1. Drug efflux/influx transporters. A significant part of the success of current cancer treatment has been based on increasing therapeutic drug dose and scheduling intensity, in an attempt to circumvent chemotherapeutic drug resistance (Yardley, 2013). To achieve therapeutic effectiveness, anticancer drugs need to be active and reach their targets at an adequate concentration. Regarding drugs with intracellular targets, they must enter tumor cells by crossing the plasma membrane through passive diffusion (e.g. doxorubicin), facilitated diffusion, and active transport (e.g. nucleoside analogues) (Mansoori et al., 2017). Early studies to explain the mechanisms involved in drug resistance were performed by Biedler in 1971 (Kolata, 1986) as well as by Assaraf and Schimke (Assaraf and Schimke, 1987) and their observations suggested that impaired plasma membrane transporters might act as a barrier leading to decreased drug accumulation within the cell, resulting in therapeutic failure in the clinic. Three theories attempted to explain the decrease in intracellular drug concentration in drug-resistant cancer cells. One of this hypotheses proposes that drug diffusion is reduced by a barrier to drug permeability that leads to a decreased intracellular drug concentration (Ramu et al., 1989). The second hypothesis suggested that an influx transporter that normally takes up a reduced folate vitamin and recognizes antifolates like methotrexate, is impaired due to the frequent emergence of inactivating mutations in this influx transporter (Assaraf and Schimke, 1987). The third hypothesis postulated that drug resistant cancer cells have an active efflux process mediated by proteins from ATP-binding cassette (ABC) transporter superfamily that extrude a wide variety of substrates, including a large number of hydrophobic compounds and metabolites (among others) across extra- and intracellular membranes, leading to decreased intracellular drug concentration (Kolata, 1986; Ramu et al., 1989).

During malignant transformation and drug resistance development, several alterations occur in the membrane lipid composition as well as in its biophysical features (Peetla et al., 2013). Resistant cells display decreased intracellular drug concentration mainly achieved by decreased drug influx, increased efflux, and drug sequestration in intracellular vesicles and compartments (Peetla et al., 2013). These mechanisms have been associated with common membrane lipid changes, including increased sphingolipids and cholesterol membrane content and changes in membrane lipid organization, that lead to less permeable plasma membrane, hence, impairing lipophilic drug diffusion (Peetla et al., 2013). For example, glycosylceramide was shown to be consistently present in drug resistant tumor cell lines, as well as melanoma, and breast cancer patients who had failed chemotherapy, a phenomenon which was absent in cognate drug-sensitive cells and patients with a known positive clinical response to chemotherapy (Lucci et al., 1998). The functionality of efflux pumps, like P-gp, also depends on the lipid composition of the plasma membrane and on its biophysical characteristics (Peetla et al., 2013). The decreased rate of drug influx is considered to be one of the major contributors to the reduced intracellular drug concentration in drug-resistant tumor cells. Since most conventional anticancer drugs are weak bases, with pK_a values ranging from 7.4 to 8.5 and are lipophilic in neutral form, they cross passively the cell membrane (Mayer et al., 1986). However, when the extracellular tumor microenvironment is acidic, these drugs become highly protonated, and the rate of cellular uptake markedly decreases since charged drugs cross the cellular membrane in a much lesser efficient manner (Manallack, 2007). In this respect, changes in the biophysical and physico-chemical properties of the plasma membrane modulate drug influx. Besides these properties of the plasma membrane, anticancer drug influx and efflux are also modulated by cell membrane transporters that regulate intracellular drug accumulation and ability to reach their cellular targets (de Klerk et al., 2018). The lower intracellular drug levels observed in chemoresistant cancer cells can result from the decrease in drug influx via influx transporters, such as solute carriers (SLC), for example, inactivating mutations and decreased expression of the reduced folate carrier (RFC/SLC19A1), the dominant transporter for antifolate chemotherapeutics (Assaraf, 2007; Gonen and Assaraf, 2012; Kaufman et al., 2006; Rothem et al., 2002). In addition, enhanced drug efflux predominantly via ABC transporters like P-gp, MRP1 and BCRP have been well documented (Hoffmann and Lambert, 2014; Li et al., 2016c).

The key SLC family members involved in chemoresistance include: folate transporters (SLC19A1 and SLC46A1), which have an important role in antifolate drugs (Assaraf, 2007; Gonen and Assaraf, 2012;

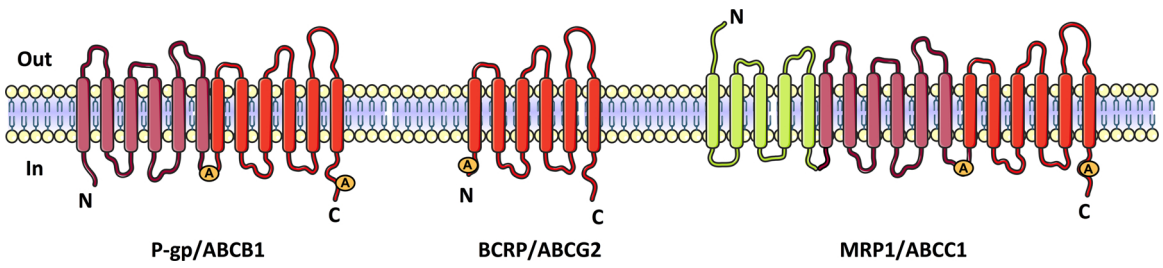

Fig. 1. Schematic representation of structural domains of ABC transporters: P-gp, BCRP, and MRP1. P-gp contains two transmembrane domains, each with six hydrophobic α-helices and two ATP-binding sites (nucleotide-binding domain, NBD). ABCG2 has one transmembrane domain of 6 α-helices and one NBD on the amino-terminal side. MRP1 has two transmembrane domains with six α-helices, one transmembrane domain with five α-helices and two ATP-binding sites. C, carboxyl terminus; N, amino terminus; A, nucleotide-binding domain.

Kaufman et al., 2006; Ma et al., 2014a; Rothem et al., 2002) including methotrexate, pemetrexed and pralatrexate (Gonen and Assaraf, 2012); organic cation transporters (OCT) (SLC22A1-3) involved in the uptake of platinum compounds; organic anion transporters (OAT) (SLC22A6-8) that facilitate the delivery of methotrexate to cancer cells; organic cation/carnitine transporters (SLC22A4-5) involved in oxaliplatin and imatinib influx; copper transporters (SLC31A) that take up cisplatin; multidrug and toxin extrusion proteins (MATEs) (SLC47A), which have double function as influx and efflux transporters of cisplatin in certain tissues; oligopeptide transporters (SLC15A1/2) with a role in floxuridine transport; and amino acid transporters (SLC7A and SLC3A) involved in acivicin uptake (Ma et al., 2014a). One of the most studied influx transporters is OCT1 (SLC22A1). Several studies evaluated the relationship between *OCT1* gene expression and imatinib response in chronic myeloid leukemia (CML) patients, and about half of them found that *OCT1* gene expression is a predictor biomarker of imatinib response in the chronic phase of CML patients (Gromicho et al., 2013; Nardinelli et al., 2012; Watkins et al., 2015). Additionally, a study conducted by Kim et al., showed that CML patients that develop imatinib resistance have a significant decrease in *OCT1* gene expression compared to the expression before therapy, suggesting a potential role for this transporter in imatinib resistance (Kim et al., 2014). Platinum-based drug resistance is often caused by decreased drug accumulation via the copper transporter 1 (CRT1), a member of SLC subfamily 31, and several clinical studies demonstrated that decreased expression of CTR1 is correlated with decreased intratumor platinum compound concentration and with the outcomes of patients with solid cancers treated with platinum-based therapies (Kilari, 2016). In recent years, several reports have shown that ion channel overexpression also influences cancer drug resistance (Hoffmann and Lambert, 2014).

However, drug efflux is the more studied mechanism of cancer drug resistance and increased drug efflux mechanisms are a common cause of MDR (Perez, 2009; Yardley, 2013). ABC transporter proteins induce the MDR phenotype by pumping anticancer agents out of tumor cells into the extracellular milieu, thereby preventing the drugs from reaching their minimally effective concentrations inside cells (Li et al., 2016c; Yardley, 2013). These transmembrane pump proteins transport a multitude of structurally and mechanistically distinct compounds across cellular membranes; these multidrug efflux pumps were classified by the presence of two distinct domains – a highly conserved nucleotide-binding domain and a more variable transmembrane domain (Fig. 1) (Housman et al., 2014). ABC transporters couple ATP hydrolysis to the active extrusion of a wide spectrum of substrates across the plasma membrane (Locher, 2004). Overexpression of members of the ABC superfamily including P-gp (ABCB1), MRP1 (ABCC1), multidrug-resistance-associated protein 7 (MRP7/ABCC10), and BCRP (ABCG2), was found to be involved in drug resistance in different types of cancer (Assaraf, 2007; Schinkel and Jonker, 2003; Wong and Goodin, 2009). The overexpression of P-gp confers MDR to a wide variety of neutral and cationic hydrophobic antitumor drugs, including paclitaxel, docetaxel, etoposide, teniposide, vinblastine, vincristine, doxorubicin, daunorubicin, actinomycin D, gefitinib, sunitinib, and tacrolimus (Gottesman and Ambudkar, 2001; Tiwari et al., 2011; Schinkel and Jonker, 2003; Sodani et al., 2012). ABCB1 (P-gp) overexpression was associated with low response rates of NSCLC patients treated with paclitaxel (Yeh et al., 2003) as well as with SCLC patients treated with cyclophosphamide, doxorubicin, and vincristine or cisplatin and etoposide (Hsia et al., 2002; Kawasaki et al., 1998). Overexpression of MRP1 confers MDR to a large number of drugs including etoposide, teniposide, vinblastine, vincristine, doxorubicin, daunorubicin, mitoxantrone, camptothecin, methotrexate and saquinavir (Anreddy et al., 2014; Assaraf et al., 2003; Sodani et al., 2012; Wang et al., 2014b). MRP7 overexpression induces MDR to several anticancer drugs including paclitaxel, docetaxel, vincristine, vinblastine, vinorelbine, cytarabine, gemcitabine, 2′,3′-dideoxycytidine, 9-(2-phosphonylmethoxynyl)adenine (PMEA) and epothilone B (Bessho et al., 2009; Hu et al., 2011; Kruh et al., 2007; Malofeeva et al., 2012; Oguri et al., 2008; Rudin et al., 2011; Sun et al., 2013b). For example, *ABCC1* (MRP1) overexpression is associated with poor survival of neuroblastoma patients and *ABCC3* (MRP3) overexpression was found to be a drug resistance marker in NSCLC patients (Balaji et al., 2016; Zhao et al., 2013). *ABCC1* and *ABCC3* overexpression was also observed in breast cancer patients (Balaji et al., 2016). Finally, overexpression and mutations in BCRP (ABCG2) lead to MDR to mitoxantrone, doxorubicin, daunorubicin, camptothecin, and methotrexate (Mao, 2005; Sun et al., 2012b; Wang et al., 2014a). For example, CML patients with a high expression of the *ABCG2* gene were shown to have a 2-fold higher risk of relapse than patients with low expression, suggesting that high *ABCG2* expression might enhance TKIs efflux and diminish the efficacy of chemotherapeutic drug treatment in CML patients (Rinaldetti et al., 2018).

Since overexpression of ABC transporters has been correlated with poor chemotherapeutic response and prognosis of patients with different cancer types, the inhibition of these transporters emerges as a logical approach to circumvent MDR and improve patient's outcome. In recent years, concentrated efforts have been invested in order to identify or design modulators that can either block or inactivate these ABC transporters and thereby increase the intracellular concentration of anticancer drugs, hence achieving the reversal of MDR (Kathawala et al., 2015). Several MDR chemosensitizers were already tested in clinical trials, namely cyclosporine A and tariquidar, both P-gp and MRP1 inhibitors, which were already tested in clinical settings/clinical trials (Jaramillo et al., 2018). However, these clinical trials with ABC pump inhibitors showed a limited therapeutic success in overcoming MDR in cancer therapy (Kathawala et al., 2015; Palmeira et al., 2012), mainly due to their high toxicities, drug-interactions, and clinical trial design problems (Gottesman and Pastan, 2015; Robey et al., 2018). Nevertheless, novel approaches to inhibit ABC transporters are being developed, such as drug delivery systems, siRNAs and microRNAs delivered by nanoparticles, monoclonal antibodies against P-gp, among others (Bar-Zeev et al., 2017; Jaramillo et al., 2018; Li et al., 2016c). Another possible route to surmount drug resistance is the manipulation of plasma membrane as well its composition and function. This approach, which is currently being developed, may provide powerful tools to treat cancer in combination with conventional and targeted anticancer agents (Zalba and ten Hagen, 2017). Only concentrated efforts from experts of different and complementary fields, including physicians, biophysicists, pharmacists, and cell biologists will improve our understanding of the mechanisms underlying anticancer drug resistance and their clinical implications, thereby leading to the development of new and effective therapeutic modalities that evade and/or overcome cancer MDR.

3.1.1.2. Extracellular vesicles (EVs). EVs have been described as a notable vehicle of dissemination of cancer drug resistance (Namee and O'Driscoll, 2018). EVs are nanosized particles (30–1000 nm) enclosed by a phospholipid bilayer, which cannot replicate (Thery et al., 2018). EVs have traditionally been named exosomes, microvesicles, microparticles, apoptotic bodies, etc., depending on their biogenesis, size and content (Colombo et al., 2014). Drug efflux pumps including P-gp, MRP1 and BCRP have been found in the cargo of EVs (Namee and O'Driscoll, 2018; Sousa et al., 2015). It is believed that the orientation of such drug transporters may be inverted in the membranes of some (but probably not all) EVs shed by MDR cells, which would contribute to the influx of drugs into the EVs (Gong et al., 2013). Indeed, EVs have the capacity to sequester chemotherapeutic drugs in their cargo (Gong et al., 2013; Samuel et al., 2017). Once EVs are released from tumor cells, they may extrude drugs to the extracellular milieu, thus reducing the available intracellular drug concentration and consequently contributing to a reduction in the antitumor effect of such drugs (Gong et al., 2013; Samuel et al., 2017; Sousa et al., 2015).

In fact, several studies with different cancer cell lines have demonstrated that drug accumulation within EVs may influence the acquisition of a drug-resistance phenotype (Ferrao et al., 2001; Goler-Baron and Assaraf, 2011; Goler-Baron et al., 2012; Muralidharan-Chari et al., 2016). These *in vitro* findings on the sequestration of cytotoxic drugs within EVs support this novel mechanism of EVs-mediated resistance to therapy. However, there is very little clinical evidence to support this novel mechanism of drug resistance. A study using a reduced number of clinical samples demonstrated that rituximab, given to lymphoma patients, bound to EVs isolated from their plasma, suggesting a decrease in the availability of the drug for therapeutic benefit (Aung et al., 2011). Another study demonstrated that EVs isolated from the serum of Human Epidermal Growth Factor Receptor 2 (HER-2)-positive early breast cancer patients presented lower-level binding to trastuzumab when compared to EVs circulating in the serum of advanced disease patients, suggesting that EVs might contribute to drug sequestration, thereby leading to trastuzumab resistance in advanced breast cancer patients (Ciravolo et al., 2012).

3.1.2. Deregulation of cell death mechanisms: apoptosis, autophagy and anoikis

The cytotoxicity of antineoplastic drugs depends mainly on their ability to induce cell death. The major mechanisms of cell death are apoptosis, necrosis, and autophagy, which are essentially defined by their morphologic, biochemical, and molecular attributes (Green and Llambi, 2015; Hotchkiss et al., 2009). Chemotherapeutic drugs can induce cell death through several molecular and cellular mechanisms such as reactive oxygen species (ROS) induction, DNA damage, activation of pro-apoptotic receptors, induction of autophagy-associated cell death, and immune cell effector response (Tarasov et al., 2019; Yang et al., 2018). However, cancer cells are undergoing constant evolution and adaptation that confers upon them the ability to evade cell death (Indran et al., 2011). Fig. 2 summarizes the common deregulated mechanisms of cell death observed in cancer patients.

Deregulation of apoptosis is a fundamental characteristic of cancer cells that is linked to both carcinogenesis and drug resistance. A key feature of apoptosis is the cleavage of cytoskeletal proteins by caspases, which thereby induce the destruction of subcellular components (Hotchkiss et al., 2009). Activation of caspases is mediated by death receptor pathways (extrinsic pathway), which are activated when members of the tumor necrosis factor (TNF) superfamily bind to cell-surface death receptors, such as TNF-R1, FAS (CD95/Apo-1), TRAIL-R1 (DR4) and TRAIL-R2 (DR5) (Green and Llambi, 2015). Apoptosis is also activated by the mitochondrial pathway (intrinsic pathway) that is controlled by the interplay between pro- and antiapoptotic members of the BCL2 family (Green and Llambi, 2015; Hotchkiss et al., 2009). Survival of cancer cells is usually dependent on antiapoptotic proteins, such as BCL-2 family members, decoy receptors (such as TRAIL-R3/DcR1 and TRAIL-R4/DcR2), inhibitor of apoptosis proteins (IAPs), and FLIP (Holohan et al., 2013b; Tarasov et al., 2019). The intricate balance between anti- and proapoptotic proteins is the key regulator of cell survival, controlling the sensitivity of cancer cells to apoptosis (Safa, 2016). In this context, the mechanisms of resistance to chemotherapy and targeted therapies are linked to genetic abnormalities like mutations, gene amplifications, and chromosomal translocations, as well as to the overexpression of genes encoding for these proteins (Holohan et al., 2013b). The upregulation of antiapoptotic proteins, such as BCL2, BCL-X_L, and MCL-1, induces chemotherapy resistance in cancer cells (Campbell and Tait, 2018; Wilson et al., 2009; Zheng, 2017). In the clinical setting, the relationship between response to therapy and BCL2 family members, death receptors of the TNF family, and IAPs is still controversial due to contradictory findings. BCL-2 expression in cancer cells was found to be a poor prognosis marker for chemoradiotherapy in patients with bladder cancer (Hussain et al., 2003), associated with lower PFS and OS in diffuse large B cell lymphoma patients (Urun et al., 2018), and associated with poor chemotherapy response in chemotherapy-naïve primary bladder cancer (Kiss et al., 2015). Estrogen receptor positive breast cancer patients with low BAD expression levels had a significantly lower OS and disease free survival (DFS) (Al-Bazz et al., 2009; Cannings et al., 2007). Death receptor pathways were also

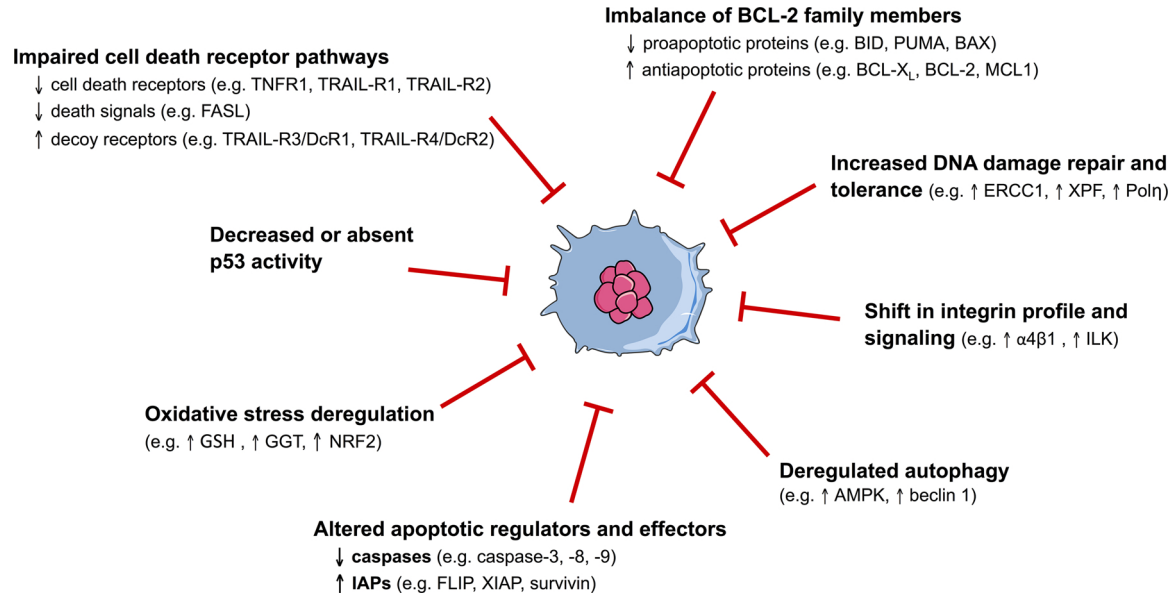

Fig. 2. Mechanisms of drug resistance due to cell death deregulation. Resistance to cell death induced by chemotherapeutic drugs can arise from the deregulation of several molecular and cellular mechanisms that modulate apoptosis, autophagy, and anoikis. AMPK, AMP-activated protein kinase; BAX, BCL-2- associated X protein; BCL-XL, B-cell lymphoma-extra-large; BCL-2, B-cell lymphoma protein 2; BID, BH3-interacting domain death agonist; ERCC1, excision repair cross-complementation group 1; FASL, Fas ligand; FLIP, FLICE-inhibitory protein; GGT, ϒ-glutamyltransferase; GSH, glutathione; IAPs, inhibitor of apoptosis proteins; ILK, integrin-linked kinase; MCL1, myeloid cell leukemia 1; NRF2, nuclear factor erythroid 2-related factor 2; PUMA, p53 upregulated modulator of apoptosis; TNF-R1, tumour necrosis factor receptor superfamily member 1A; Pol η, DNA polymerase eta; TNF, tumor necrosis factor; TRAIL-R1/DR4, TRAIL receptor 1/death receptor 4; TRAIL-R2/DR5, TRAIL receptor 2/death receptor 5; TRAIL-R3/DcR1, TRAIL receptor 3/decoy receptor 1; TRAIL-R4/DcR2, TRAIL receptor 4/ decoy receptor 2; TRAIL, TNF-related apoptosis-inducing ligand; XIAP, X-linked inhibitor of apoptosis protein; XPF, DNA repair endonuclease XPF.

associated with chemotherapy resistance. The high expression of TRAIL-R1, TRAIL-R2, and FAS was associated with poor response to chemotherapy at disease recurrence in metastatic ovarian carcinoma (Dong et al., 2008) and the overexpression of TRAIL-R2 was correlated with poor prognosis and low DFS and OS in acute myeloid leukemia (AML) patients (Costa et al., 2017). Moreover, TRAIL-R1 overexpression was associated with better survival in colon cancer and pancreatic ductal adenocarcinoma (PDAC) (Gundlach et al., 2018; Sträter et al., 2002); however, a similar study, showed that high TRAIL-R1 expression was associated with worse DFS, worse OS, and shorter time to recurrence in colorectal cancer (CRC) patients (Van Geelen et al., 2006). The high expression of XIAP, an inhibitor of apoptosis protein, was found to be a marker of poor prognosis in AML (Tamm et al., 2004), RCC (Mizutani et al., 2007), gastric cancer, and head and neck cancer (Gao et al., 2019), but no association was found with response to chemotherapy and OS in NSCLC (Ferreira et al., 2001). Since some of these studies showed opposite effects and controversial results, the biologic mechanisms behind these findings need to be further studied and elucidated. The p53 protein is the most frequently mutated tumor suppressor gene in human cancers. This central protein can also contribute to apoptosis resistance since it activates the expression of proapoptotic proteins (e.g. BAX and BID), death receptors (e.g. FAS and DR5), and suppresses antiapoptotic proteins (e.g. survivin) (Indran et al., 2011). For example, Ellis and colleagues found that estrogen receptor positive breast cancer patients resistant to aromatase inhibitors have higher frequency of *TP53* mutations than those sensitive to this treatment (Ellis et al., 2012). Furthermore, the majority of chemotherapeutic drugs induce cell death by increasing ROS levels (Yang et al., 2018). However, the increase in glutathione (GSH), a key player in cellular antioxidant defense systems and in many metabolic processes, is a major contributing factor to drug resistance by decreasing ROS levels, preventing damage to proteins or DNA, and participating in DNA damage repair (Nitti et al., 2013; Yang et al., 2018). High GSH levels were correlated with early relapse and short OS in patients with childhood and adult acute lymphoblastic leukemia (ALL) (Hall et al., 2001; Sarmento-Ribeiro et al., 2012). Moreover, ϒ-glutamyltransferase (GGT), an enzyme involved in GSH metabolism, also regulates apoptotic balance. High GGT levels were found to be correlated with therapy resistance and worse PFS and OS in patients with breast cancer (Staudigl et al., 2015), gastric cancer (Wang et al., 2017a) and RCC (Hofbauer et al., 2014).

Autophagy is a conserved adaptive cellular survival mechanism that involves lysosomal degradation and recycling of unnecessary or damaged cellular components, which is essential for cell survival in response to hypoxia, genome instability, endoplasmic reticulum stress, and nutrient deprivation (Ferreira et al., 2017; Mohammad et al., 2015). Autophagy occurs frequently during tumorigenesis and cancer chemotherapy, being also responsible for drug resistance and cancer refractoriness (Ferreira et al., 2017; Mohammad et al., 2015; Sun et al., 2017). Damaged proteins and organelles are removed from cancer cells by autophagy, providing energy for their survival against anticancer therapy (Cordani and Somoza, 2019; Kumar et al., 2015). Regulation of autophagy is a very complex process that includes several signaling pathways, such as mammalian target of rapamycin (mTOR), phosphatidylinositol 3-kinase-I (PI3K-I)/protein kinase B (PKB), GTPases, calcium, and protein synthesis (Yang et al., 2005). Although the role of autophagy in chemoresistance has been extensively studied in *in vitro* models, its importance in the clinical setting remains unclear. A study by Ueno et al. (2016) demonstrated that the expression of BECLIN 1 was associated with worse clinical and pathological responses in breast cancer patients (Ueno et al., 2016). In another study, Valente et al. (2014) found that low expression of BECLIN 1 in ovarian cancer was associated with a dismal prognosis, but they did not find any correlation with response to therapy (Valente et al., 2014). In CRC patients, *ABCB1* gene expression was positively associated with the expression of *LC3*, *Beclin1*, and *Rictor* genes and negatively correlated with *Raptor* gene (Shuhua et al., 2015), strongly suggesting the involvement of autophagy in the development and progression of cancer as well as drug resistance (Sun et al., 2017).

Anoikis is a particular apoptotic process due to loss or incorrect cell adhesion that is also linked to tumorigenesis and chemotherapy resistance (Paoli et al., 2013; Taddei et al., 2012). Although different pathways mediate the initiation and execution of anoikis, this process culminates with caspase activation, DNA fragmentation, and cell death through the intrinsic or extrinsic apoptotic pathways (Paoli et al., 2013; Taddei et al., 2012). In general, cancer cells are resistant to anoikis and do not require adhesion to extracellular matrix (ECM) to survive and proliferate (Taddei et al., 2012). This resistance can be achieved by several mechanisms, including a specific shift in integrin profile, epithelial-mesenchymal transition (EMT), constitutive activation of pro-survival signaling, and deregulation/adaptation of metabolic pathways (Warburg metabolism or autophagy) (Paoli et al., 2013). The same mechanisms are involved in chemotherapy resistance. For example, Gao and collaborators (2013) found that integrin subunit αv was overexpressed in ovarian cancer tumors resistant to paclitaxel and carboplatin treatment but subunit β3 had similar expression levels in both resistant and sensitive patients (Gao et al., 2013). In childhood ALL, the higher expression of integrin α4β1 (very late antigen-4; VLA-4; ITGA4) was associated with relapse or absence of response to therapy (Shalapour et al., 2011). Additionally, the overexpression of integrin-linked kinase (ILK) is associated with resistance to 5-fluorouracil (5-FU)-based chemotherapy in metastatic CRC patients (Tsoumas et al., 2018) and to a worse PFS in NSCLC patients with mutated EGFR (Karachaliou et al., 2019).

The heterogeneous response to chemotherapy treatments frequently observed in cancer patients is determined by the complexity of drug resistance mechanisms and also by patient-specific features. It is worth noting that studies exploring drug resistance in the clinical setting present conflicting and sometimes-unexpected results. Since cell fate is orchestrated by the balance between opposite regulators, for example pro- and antiapoptotic proteins, the use of a single biomarker to study drug resistance may explain these conflicting results. The in-depth understanding of the complex network of interactions that constitute chemotherapy resistance in cancer patients will open new opportunities, not only towards new therapeutic strategies to overcome resistance, but also to identify new molecular targets in cell death pathways.

3.1.3. DNA damage response (DDR) and repair

It is essential for any cell to have functional DDR and thus maintain genomic stability, in order to keep cellular homeostasis and prevent cancer development. When normal regulation of DDR is lost, mutations accumulate, leading to carcinogenesis, rapid tumor evolution and resistance to different DNA damaging agents. The most conventional cancer treatments induce DNA damage and various chemotherapeutics including platinum drugs such as cisplatin, carboplatin and oxaliplatin, as well as nitrogen mustard, or chloroethylnitrosoureas, form DNA adducts which interfere with active DNA replication in cancer cells (Ghosh, 2019). Failure in DNA replication and repair of the damaged DNA, generates replication stress, hence driving cells towards apoptosis. DNA lesions, single strand breaks (SSB) and double strand breaks (DSB), are repaired by different DDR pathways including BER, NER, mismatch repair (MMR), homologous recombination (HR), non-homologous end joining (NHEJ), translesion synthesis (TLS) and Fanconi anemia (FA) pathway (Bellon et al., 1991; Tian et al., 2015; Yamanaka et al., 2017; Zhang and Walter, 2014). In cancer cells, critical components of DDR pathways often carry mutations, being responsible for repair deficiencies and activation of compensatory mechanisms (Heyer et al., 2010; Shibata et al., 2011).

Development of drug resistance may be strongly associated with deregulated expression in DDR pathways and substantially increased capacities of the cell to repair damaged DNA and avoid apoptosis.

Several studies have shown a correlation between altered expression and mutations in individual DDR proteins including BRCA1/2, TP53, ATM, BARD1, BRIP1, CHEK1, CHEK2, FANCD2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, RAD54 L, ATR, BARD1, NBN, RAD50, FAM175A, MRE11A with compromised cellular DDR and MDR (Bartkova et al., 2007; Buys et al., 2017; Network, 2011; Sakthivel and Hariharan, 2017; Song et al., 2015; Tung et al., 2016). An interesting study performed meta-analysis of gene expression data from multiple myeloma (MM) patients and compared the expression levels of DDR genes in primary cells from MM patients at diagnosis as compared to healthy donors (Cuce et al., 2019). The most upregulated genes were from the NER pathway, the main defensive barrier against DNA damage and a major repair system for DNA crosslinks. Specifically, 7 out of 31 genes involved in the NER pathway were significantly deregulated in 4 out of 5 datasets analysed, but almost none of the genes were deregulated in BER, MMR, HR, NHEJ or FA pathway. Another study (Sun et al., 2012a) explored mutations within the interacting domains of excision repair 1 endonuclease non-catalytic subunit (ERCC1) and Xeroderma pigmentosum complementation group F (XPF) proteins of NER, and showed that these mutated proteins were not able to restore complete DNA repair in bladder cancer. In addition, in breast cancer, ovarian cancer and CRC, several ERCC1 polymorphisms have been identified with significant association with OS and treatment response (Yang et al., 2019; Zhang et al., 2017b). ERCC1 plays a significant role in cisplatin DNA adducts repair in NSCLC (Wu et al., 2019a), esophageal cancer (Yao et al., 2018) or bladder cancer (Necchi et al., 2018; Urun et al., 2018). In testicular tumors, it was revealed that high cisplatin sensitivity correlates with deficiency in DNA crosslinks repair and low XPA and ERCC1-XPF expression (Usanova et al., 2010). In addition, cells with overexpressed NER proteins exerted very low sensitivity to cisplatin (Selvakumaran et al., 2003; Usanova et al., 2010). Another group demonstrated the relationship between increased NER gene expression and initial drug resistance with relapse in pediatric ALL patients (Al Omar et al., 2018). Functional variants in genes involved in DNA repair pathways are important determinants of cisplatin response in women with epithelial ovarian cancer (Ceccaldi et al., 2015). Mutations in the FA pathway were reported in 46.6% of ovarian cancer cases (Shen et al., 2015). In addition, impaired function of MMR genes (*hMLH1, hMSH2, hMSH3, hMSH6*) contributes to the development of microsatellite instability (MSI) in different malignancies, mostly endometrial and CRC, and their aberrant expression is associated with significantly longer OS, DFS and better prognosis of MMR-deficient patients (Baretti and Le, 2018; Hou et al., 2018). However, strong preclinical and clinical evidence suggests that MMR-deficient CRC tumors may be resistant to chemotherapy.

A panel of 62 cancer susceptibility genes were tested for mutations in over 15,000 breast cancer patients and healthy individuals (Chen et al., 2018). Results showed that 0.38% of wild type BRCA breast cancer patients had a loss of function mutation in the DDR gene *RAD51D*, whereas such mutations were detected in only 0.1% of the healthy population. BRCA1 and BRCA2 are key players in the error-free repair of DSBs by HR, the only error free repair mechanism. In HR-deficient cells due to loss of BRCA1 or BRCA2, alternative error-prone repair pathways repair DSBs, resulting in chromosome deletions, translocations, and subsequent cell death. BRCA1/2 deficiency causes HR impairment that was highly associated with breast, ovarian, pancreatic or prostate carcinogenesis (Narod and Foulkes, 2004; Pothuri, 2013; Roch et al., 2019). Such vulnerability of cancer cells can be exploited by treating HR-deficient tumors with Poly (ADP-ribose) Polymerase (PARP) inhibitors (PARPi). PARP is an enzyme involved in the repair of DNA damage of single-strand DNA, thus eliminating consequent accumulation of DSBs, leading to apoptosis. Blocking PARP enzymes with PARPi including olaparib, rucaparib, niraparib or talazoparib, has been appreciated in cancer treatment as an alternative for conventional chemotherapy, especially in cases of tumor chemoresistance (Pettitt and Lord, 2019). PARPi can target cancer cells with impaired DNA DSB repair related to HR (Anwar et al., 2015; Davar et al., 2012), by inhibition of DNA repair proteins, in combination with genotoxic chemotherapeutic agents. The PARPi olaparib is effective in ovarian, breast, prostate, or pancreatic cancers (Beaver et al., 2019; Curtin and Szabo, 2013; Jain and Patel, 2019; Lee et al., 2014a). Inhibition of PARP with PARPi could be further enhanced by applying a synthetic lethality concept (Ashworth and Lord, 2018; Yap et al., 2011). Several clinical studies have confirmed the principle of synthetic lethality induction by PARPi in BRCA-mutated cancers, resulting in approval of PARPis for advanced or relapsed ovarian cancer, chemoresistant ovarian cancer or metastatic breast cancer (Ledermann et al., 2014; Oza et al., 2017). Despite the promising preliminary results of clinical trials, prolonged treatment of cancer patients with a PARPi led to consequent MDR. The therapeutic effect of PAPRi can be abolished by the emergence of secondary mutations (e.g. in *BRCA1/2* or *RAD51C*, or *RAD51D* genes), resulting in drug resistance to both cisplatin and PARPi (Ang et al., 2013; Barber et al., 2013; Hollis et al., 2017; Kondrashova et al., 2017; Madariaga et al., 2019).

3.1.4. Epigenetic alterations

Epigenetic alterations are changes in DNA structure that do not involve sequence changes but are stably inherited from cell to cell. Epigenetic regulations including DNA methylation, histone, chromatin and microRNA (miRNAs) modifications, belong to additional regulatory mechanisms driving drug resistance in cancer (Kagohara et al., 2018; Nowacka-Zawisza and Wisnik, 2017; Shen et al., 2012; Wahid et al., 2017). Following chemotherapy, epigenetic events may occur and modify expression of numerous MDR genes, such as drug transporters (*ABCB1, MDR*) (Spitzwieser et al., 2016), pro-apoptotic genes (*DAPK and APAF-1*) (Wilting and Dannenberg, 2012), DNA-repair proteins (MLH1, MGMT) (Saghafinia et al., 2018) or histone modifiers (Ferraro, 2016).

DNA methylation is a major epigenetic alteration in various cancers. It is carried out by DNA methyltransferases (DNMT) (Giri and Aittokallio, 2019; Jeronimo and Henrique, 2014) that covalently attach a methyl group (CH_3) to cytosine residues in “CpG islands” in the genome (Goldberg et al., 2007; Zhang et al., 2019), thus contributing to inhibition of gene transcription resulting in gene silencing (Bird, 2002). Inhibition of DNMT activity can reverse DNA methylation and restore expression of important silenced genes (Berdasco and Esteller, 2010). Alterations in chromatin structure by histone modifications including acetylation, methylation, phosphorylation, ubiquitination, sumoylation, and ADP ribosylation of histone proteins represents another mechanism of transcriptional silencing of methylated genes (Liep et al., 2012).

Aberrant DNA methylation in cancer, is mostly associated with genes involved in cell differentiation and proliferation pathways, MAPK, WNT, VEGF and p53 signalling or expression of cell cycle inhibitors (Calvisi et al., 2007; Yuan et al., 2019). Promoter hypermethylation of tumor suppressor genes including *p15, p16, VHL, XAF1, IRF8, TP53, CDKN2A, CDKN2B, DAPK, SOCS1, CDH1, PTGS2, CCND2,* and *DCC* was shown in MM (de Carvalho et al., 2009) and B-cell lymphoma (Shawky et al., 2019), *BRCA1, E-cadherin, DAPK, MGMT, hMLH1, GSTP1, RARβ2, APC, ERβ, and CDH1, CDH13* in breast and ovarian cancer (Rodriguez-Balada et al., 2018; Shargh et al., 2014; Sun et al., 2017; Zhu et al., 2015a), *MAB21L1, CBLN2, NOVA1, GRIK1, RXRG, SORCS1, NBLA00301, PHOX2A, LONRF2, CHODL, ADHFE1, HAND2,* and *GNAO1* in colon cancer (Yang et al., 2017b), and *ABCD1, SLC5A10, SPIN3, ZNF69, ZNF608, CCDC8, FBXO17* in esophageal squamous cell carcinoma (Lu et al., 2019), etc.

In many cancers, hypermethylation is strongly correlated with drug resistance (Grasse et al., 2018; Li et al., 2019a; Ponnusamy et al., 2018; Shawky et al., 2019). In testicular carcinoma, different promoter methylation profiles can distinguish seminomas and non-seminomas, reflecting specific clinical features including drug resistance in patients (Costa et al., 2018; Lobo et al., 2019; Vladusic et al., 2014). Genes

encoding for pluripotency transcription factors such as POU5F1/OCT-3/4, NANOG, MYCL1, GDF3, LIN28-A, DPPA4, DPPA5, KIT, AP-2γ (Chieffi, 2017) and promoters of suppressor genes including *BRCA1, TP53, RASSF1A, CALCA* or *MGMT* are usually highly methylated (Martinelli et al., 2017; Takada et al., 2017). Similarly, in ovarian cancer hypermethylation of *BRCA1, hMLH1, MGMT, HOXA9, RASSF1A, OPCML* and *CCBE1*, displayed a correlation with chemotherapy resistance (Curry et al., 2018; Gloss and Samimi, 2014).

Therefore, therapeutic targeting of epigenetic alterations becomes an important and promising strategy to augment efficacies of multiple treatment regimens and to overcome MDR (Ahuja et al., 2016). These therapies aim to reprogram cancer cells in order to reverse chemoresistance and restore drug sensitivity (Jubierre et al., 2018; Przybilla et al., 2017). Several therapeutic strategies with DNA methyltransferase inhibitors (DNMTi), hypomethylating agents (HMAs) such as 5-azacytidine (5-AC), decitabine, SGI-110, isocitrate dehydrogenase inhibitors (e.g. ivosidenib and enasidenib), or histone deacetylase (HDAC) inhibitors (HDACi, e.g. vorinostat, romidepsin, or belinostat) have been clinically tested and various drugs have already been approved for clinical practice (Ball et al., 2017; Bewersdorf and Zeidan, 2019). In some clinical trials in which decitabine was administered in cisplatin-resistant ovarian cancer patients, chemosensitivity was restored in refractory patients (Benson et al., 2015; Matei et al., 2012; Zhang et al., 2017c). Decitabine was more beneficial than 5-AC, attaining a better objective response rate and longer PFS, which correlated with the degree of demethylation of the tumor suppressor genes *MLH1, RASSF1A, HOXA10,* and *HOXA11* (Matei et al., 2012). However, most clinical trials employing a single inhibitor epigenetic therapy have not achieved significant results and showed severe adverse events such as neutropenia, thrombocytopenia, vomiting or severe hematological toxicities. This was observed for example after administration of belinostat or of the pan-HDACi vorinostat with carboplatin or gemcitabine in cisplatin-resistant ovarian cancer patients (Matulonis et al., 2015; Moufarrij et al., 2019). In order to obtain enhanced therapeutic effects, pre-clinical and clinical studies are focusing on the combination of DNMTi and HDACi epigenetic drugs.

Clinical trials employing combined epigenetic agents showed improved OS in subsets of cancer patients (Garcia-Dominguez et al., 2018; Valdespino and Valdespino, 2015). In NSCLC, combination of DNMTis and HDACis resulted in durable and robust clinical responses in several cancer patients (Schiffmann et al., 2016; Topper et al., 2017). In a phase I/II trial in NSCLC combining a regimen of 5-AC with entinostat, 21% of the patients responded and exhibited prolonged survival after subsequent treatment with cytotoxic chemotherapy (Juergens et al., 2011). In hematologic malignancies, combined epigenetic therapy was highly efficient (Blagitko-Dorfs et al., 2019). DNMTi's and HDACi's have become FDA approved for myelodysplasia/AML, T-cell cutaneous lymphoma (Kaminskas et al., 2005; Kantarjian et al., 2006; Mann et al., 2007) and relapsed peripheral T-cell lymphoma (Bertino and Otterson, 2011).

In CRC, clinical trials with epigenetic therapy have not shown a satisfactory response. A combination of 5-AC with entinostat was attempted in a phase II study of metastatic CRC patients who had previously failed two or more chemotherapeutic regimens (http://www.clinicaltrials.gov, NCT00942266). A Phase I/II study was performed in order to show that 5-AC can synergize with irinotecan and reverse chemoresistance to irinotecan in metastatic CRC patients (Sharma et al., 2017). This study also successfully used the hypomethylating agent, guadecitabine, shown to be clinically and biologically active in patients with myelodysplastic syndrome and AML (Issa et al., 2015; Wong et al., 2019b). Another promising result was obtained in a phase III, randomized, controlled trial with epigenetic chemosensitization, with valproic acid and the DNMTi hydralazine and cisplatin in metastatic cervical cancer, which resulted in greater rates of OS, objective response, and stable disease (Coronel et al., 2011). In a phase II trial in 17 heavily pre-treated and platinum-resistant ovarian cancer patients, resensitization to carboplatin was verified after treatment with HDACi. The number of demethylated genes from tumor biopsies was greater in patients with a PFS longer than 6 months than in those with less than 6 months PFS, and methylation of four genes correlated with survival (Matei et al., 2012).

Several clinical trials employing combination epigenetic therapy regimens in different cancers are ongoing or have been completed, including: oesophageal cancer, mainly employing HDACi (Schneider et al., 2017), (http://www.clinicaltrials.gov, NCT01045538), in a phase I clinical trial of combined therapy of folinic acid, 5-FU, irinotecan with vorinostat, which demonstrated stable disease, partial response, and no dose-limiting toxicity in patients (Abdelfatah et al., 2016); pancreatic cancer where ZEB1-associated drug resistant cells have been chemosensitized to gemcitabine with the HDACi mocetinostat (Chan et al., 2018; Meidhof et al., 2015); aggressive pancreatic cancer, where HDACi or DNMTi have been administered in combination with chemotherapeutic agents and surgery (http://www.clinicaltrials.gov, NCT01845805).

3.1.5. Deregulation of microRNAs (miRNAs)

Mostly found in non-coding intronic regions, this broadly conserved class of small RNAs, 20–25 nucleotides long, do not encode for any protein. Their main function is downregulation of gene expression at a post-transcriptional level, but in rare occasions they can also activate mRNA translation. The fact that each miRNA can regulate several mRNA targets, and that the same mRNA can be regulated by several different miRNAs, makes the whole network very complex (Gebert and MacRae, 2019). It is known that miRNAs have a role in cancer development, metastasis, angiogenesis and drug resistance (Peng and Croce, 2016). Most of the available data on deregulation of miRNAs and their impact on MDR has been obtained from *in vitro* studies (An et al., 2017). Here we focus only on deregulation of these molecules found in tumor samples (tissue or blood) derived from MDR patients, in order to obtain an overview on how miRNAs impact tumor therapy response in the clinical setting.

Expression of MDR efflux transporters of the ABC superfamily is regulated by miRNAs in a variety of tumors. It has been shown that downregulation of *ABCB1/MDR1* encoding for P-gp by different miRNAs, such as miR-331-5p and miR-27a in lymphocytic leukemia and myeloid leukemia (Feng et al., 2011), miR-let-7 in ovarian cancer (Boyerinas et al., 2012), miR-200c (Chen et al., 2012) and miR-195 (Yang et al., 2013) in breast cancer, miR-30a in advanced gastric cancer (Li et al., 2016a) and miR-9-3p in CML (Li et al., 2019b) reverses drug resistance. The miR-326 has been shown to regulate *ABCA2* in pediatric ALL and possibly has an impact on drug resistance (Ghodousi and Rahgozar, 2018). The first MDR transporter described to be regulated by miRNA (miR-519c), *ABCG2/BCRP* in S1 colon cancer cell line (To et al., 2008), was further shown to be also regulated by miR-519c in CRC and was suggested as one of the possible predictive biomarkers and potential drug target for modulating *ABCG2/BCRP* as a means to counteract drug resistance during chemotherapy (To et al., 2015). The drug efflux pumps belonging to the MRP subfamily are also regulated by different miRNAs. High expression of miR-145 in gallbladder cancer decreased the level of *ABCC1/MRP1* and increased cisplatin toxicity (Zhan et al., 2016). In SCLC, chemoresistance was mediated by miR-7 through repression of the same gene (Liu et al., 2015). It has been shown that miR-490-3p regulates *ABCC2/MRP2* in ovarian cancer and possibly increases response to cisplatin (Tian et al., 2017). Furthermore, the expression of *ABCC5* and its impact on drug resistance was shown to be regulated by miR-128 in breast cancer (Zhu et al., 2011) and by miR-101, miR-125a and miR-let-7a in hepatocellular carcinoma (HCC) (Borel et al., 2012). In addition, it is known that ATP7A is not only important for regulating copper Cu(I) in mammals, but is also involved in drug resistance (Li et al., 2018a). Interestingly, reversal of MDR is controlled by miR-495 mediated ATP7A regulation in NSCLC (Song et al., 2014).

Table 1
Clinical evidence for miRNAs regulating cancer MDR[#].

miRNA function	miR regulation	miR-target	Effects(s)	Disease	Reference(s)
Regulation of MDR transporters	miR-331-5p ↓ miR-27a ↓	ABCB1/MDR1 ↑	doxorubicin resistance	Lymphocytic leukaemia and myeloid leukaemia (relapsed)	(Feng et al., 2011)
	let-7 ↓	ABCB1/MDR1 ↑	taxane resistance	Ovarian cancer	(Boyerinas et al., 2012)
	miR-200c ↓	ABCB1/MDR1 ↑	doxorubicin resistance	Breast cancer	(Chen et al., 2012)
	miR-30a ↓	ABCB1/MDR1 ↑	MDR and EMT	Advanced gastric cancer	(Li et al., 2016a)
	miR-9-3p ↓	ABCB1/MDR1 ↑	drug resistance	Chronic myelogenous leukaemia	(Li et al., 2019b)
	miR-326 ↓	ABCA2 ↑	drug resistance	Paediatric acute lymphoblastic leukaemia	(Ghodousi and Rahgozar, 2018)
	miR-519c ↓	ABCG2 ↑	no response to the therapy	Colorectal cancer	(To et al., 2015)
	miR-7 ↓	ABCC1/MRP1 ↑	drug resistance	Small cell lung cancer	(Liu et al., 2015)
	miR-145 ↓	ABCC1/MRP1 ↑	poor prognosis drug resistance	Gallbladder cancer	(Zhan et al., 2016)
	miR-490-3p ↓	ABCC2/MRP2 ↑	cisplatin resistance	Ovarian cancer	(Tian et al., 2017)
	miR-128 ↓	ABCC5/MRP5↑	doxorubicin resistance	Breast cancer	(Zhu et al., 2011)
	miR-101 ↓ miR-125a ↓ let-7a ↓	ABCC5/MRP5 ↑	reverses clinical MDR	Hepatocellular carcinoma	(Borel et al., 2012)
	miR-495 ↑	ATP7A ↑	MDR	Non-small cell lung cancer	(Song et al., 2014)
DNA repair	miR-9 ↑	BRCA1 ↓	platinum resistance	Ovarian cancer	(Sun et al., 2013a)
	miR-15a ↓ miR-16 ↓	BMI1 ↑	shorter OS	Ovarian cancer	(Dwivedi et al., 2016)
Cell death	miR-27a ↑	probably Bak ↓	resistance to cisplatin and probably some other drugs	Brest cancer	(Zhou et al., 2016a)
	miR-181a ↑	Bim ↓	promotes drug resistance	Breast cancer	(Zheng et al., 2016)
	miR-203 ↓	Survivin, Bmi-1 ↑	drug resistance	Leukaemia	(Zhang et al., 2016b)
	miR-33a ↑	BAK-SMAC/DIABLO/XIAP ↓	drug resistance	Osteosarcoma	(Zhou et al., 2016a)
	miR-374b-5p ↓	Bcl-2, BIRC3, XIAP ↑	drug resistance	Pancreatic cancer	(Sun et al., 2018)
	miR-17-5p ↑	PTEN ↓	drug resistance	Colorectal cancer	(Fang et al., 2014)
	miR-100 ↓	HOXA1 ↓	poor prognosis/drug resistance	Small cell lung cancer	(Xiao et al., 2014)
EMT	miR-106a ↓	Twist1 ↑	gemcitabine resistance	Hepatocellular carcinoma	(Wang et al., 2015)
	miR-203 ↓	SNAI2 ↑	poorer clinical outcome	Glioblastoma	(Liao et al., 2015)
Multiple targets	miR-195 ↓	Raf-1 ↓	doxorubicin resistance	Breast cancer	(Yang et al., 2013)
	miR-181b ↓	HMGB1 and Mcl-1 ↑	drug resistance	Acute myeloid leukemia	(Lu et al., 2014)
	miR-130a ↓	Bcl-2, Mcl-1, XIAP ↑	poor prognosis, shorter OS	Chronic myeloid leukemia	(Zhu et al., 2015b)
	miR-200c ↓	ABCB1/MDR1 and JNK2 ↑	drug resistance and metastasis	Colorectal cancer	(Sui et al., 2014)
	miR-647 ↓	Ankyrin-B, FAK, MMP2, MMP12, CD44, SNAI1 ↑	drug resistance and metastasis	Gastric cancer	(Cao et al., 2018)
	miR-100 ↑	PTEN ↓	poor response to chemotherapy	Pancreatic ductal adenocarcinoma	(Dhayat et al., 2015)
	miR-21 ↑	ABCB1/MDR1 ↑			
	miR-497 ↓	WEE1, CHEK1, AKT3, Bcl-2, VEGFA ↑	drug resistance	Neuroblastoma	(Soriano et al., 2016)
	miR-3142 ↑	PTEN↓ /PI3K/Akt pathway ↑	doxorubicin resistance	Chronic myeloid leukaemia	(Zhao et al., 2017a)
	miR-509-3p ↓	GOLPH3, WLS ↑	cisplatin resistance	Ovarian cancer	(Niu et al., 2019)
	miR-491-3p ↓	mTOR ↑	drug resistance	Tongue cancer	(Zheng et al., 2015)
	miR-20 ↓ miR-27a ↓ miR-181a ↓	ABCB1/MDR1, HIPK2, HIF1A ↓	drug resistance	Gastric cancer	(Danza et al., 2016)
	miR-15a ↓		poor prognosis and increased disease progression	Multiple myeloma	(Li et al., 2015)
Different molecular mechanisms	miR-27b ↑ miR-508-5p ↑	CCNG1 ↑	sensitive to chemotherapy	Gastric cancer	(Shang et al., 2016)
	miR-335 ↓	WBP5 ↑	MDR	Small cell lung cancer	(Tang et al., 2016)
	miR-518a-5p ↓	PIK3C2A ↑	imatinib resistance	Gastrointestinal stromal tumor	(Shi et al., 2016)
	miR-155 ↑	TP53 ↓	shorter survival, drug resistance	Lung cancer	(Van Roosbroeck et al., 2017)
	miR-21 ↑	nd.	shorter survival, drug resistance	Gastric cancer	(Qi et al., 2017)
	miR-137 ↓	AURKA ↑ p-ATM/Chk2 ↑	drug resistance	Multiple myeloma	(Qin et al., 2017)
	miR-105 ↑ miR-93-3p ↑	SFRP1 ↓	drug resistance and metastasis	Triple negative breast cancer	(Li et al., 2017)
	miR-21 ↓ miR-125b ↓ miR-224 ↓	nd.	chemotherapy sensitivity	Advanced lung adenocarcinoma	(Xu et al., 2018b)
	miR-708 ↑ miR-223 ↓ miR-27a ↓	FOXO3 ↓ E2F1 ↑ BMI1 ↑	platinum resistance, relapse	Childhood acute lymphoblastic leukemia	(Han et al., 2011)
	miR-181c ↓	ST8SIA4 ↑	drug resistance	Chronic myelocytic leukemia	(Zhao et al., 2016)

[#] The miRNAs were detected in clinical samples. The targets and regulation pathways were confirmed in *in vitro* studies.

The miRNAs may also interfere with cancer sensitivity to therapy by regulating genes involved in DNA repair. An interesting study showed that downregulation of *BRCA1* by miR-9 hampered DNA damage repair, consequently increasing the sensitivity of ovarian cancer to cisplatin and PARP inhibitors (Sun et al., 2013a). Significant correlations between low expression of miR-16 and high expression of BMI1 (a protein involved in DNA repair and cell cycle regulation) and shortened OS were noted, in high grade serous ovarian cancer patients (Dwivedi et al., 2016).

Induction of cell death is another molecular mechanism important for cancer therapy response, which can be modulated by miRNAs. A negative correlation between miR-27a and Bak was found in serum samples of breast cancer patients. Since it has been shown that the knockdown of miR-27a promotes apoptosis *via* the mitochondrial pathway in mammary gland T-47D cells treated with cisplatin, targeting miR-27a could provide a novel strategy for therapy (Zhou et al., 2016a). Furthermore, the miR-181b has been suggested to function as an oncogene during breast cancer development, and the miR-181b/Bim pathway may be a novel target to overcome chemoresistance (Zheng et al., 2016). Interestingly, miR-203 was found to directly target the 3′-UTRs of survivin and Bmi-1, affecting proliferation and self-renewal of leukemia stem cells, making this specific axis a valuable diagnostic and prognostic tool for leukemia treatment (Zhang et al., 2016b). Moreover, it has been demonstrated that miR-374b-5p targets several apoptotic proteins such as Bcl-2, BIRC3 or XIAP and attenuates chemoresistance in pancreatic cancer (Sun et al., 2018). In addition, PTEN is a target of miR-17-5p in CRC cells, and their context-specific interactions are responsible for MDR (Fang et al., 2014). Moreover, the highly conserved family of Hox genes plays a crucial role in cell death, receptor signalling and differentiation. It has been shown that chemoresistance of SCLC is *HOXA1*-mediated, which is further regulated by miR-100, making *HOXA1* a possible prognostic predictor and potential therapeutic target in human SCLC (Xiao et al., 2014).

A number of studies have shown the involvement of miRNAs in EMT and drug resistance (Brozovic, 2017). In fact, EMT and the expression of the cisplatin transporter ATP7B, were inhibited by miR-15a and miR-16, resulting in decreased degradation of the ECM and enhanced sensitization of ovarian cancer cells to cisplatin (Dwivedi et al., 2016). In addition, the expression of platelet-derived growth factor-D (PDGF-D), which plays a critical role in EMT and drug resistance in HC cells, was found to be associated with miR-106a and Twist1 levels in HC patients (Wang et al., 2015). Moreover, miR-203 expression in glioblastoma patients was inversely correlated to *SNAI2* expression, and tumors with low expression of miR-203 experienced poorer clinical outcomes. Re-expression of miR-203 or targeting *SNAI2* might serve as potential therapeutic approaches to overcome drug resistance (Liao et al., 2015).

MiRNAs have also been explored in the context of multiple targeting, thus having an impact on different signalling pathways such as proliferation, cell death, differentiation and metastasis. Interestingly, it was observed that expression of miR-195 reduced tumor cell survival and increased doxorubicin-induced apoptosis through downregulation of Raf-1, Bcl-2 and P-gp in breast cancer patients (Yang et al., 2013). Furthermore, miR-181b was found to be significantly decreased in relapsed/refractory AML patients and inhibited both *HMGB1* and *MCL1* expression. Curiously, *HMGB1* was expressed at high levels in relapsed/refractory AML patients and suppression of *HMGB1 via* RNA interference sensitized MDR leukemia cells to chemotherapy and induced apoptosis (Lu et al., 2014). Moreover, the expression of miR-130a was significantly associated with shorter OS and treatment-free survival in CML patients. This study also showed that miR-130a functions as a tumor suppressor by inhibiting multiple anti-apoptotic proteins, including Bcl-2, Mcl-1 and XIAP (Zhu et al., 2015b). Additionally, an inverse correlation between miR-200c and *JNK2*, *ABCB1* and *MMP9* expression was found in CRC. Restoration of miR-200c expression may serve as a promising therapeutic approach in MDR-induced metastasis (Sui et al., 2014). Furthermore, overexpression of miR-647 sensitized colon cancer to chemotherapy *in vivo* and reduced the expression levels of ankyrin-B, FAK, MMP2, MMP12, CD44 and SNAI1 in cultured colon cancer cells. These observations suggest that miR-647 may function as a novel target to overcome drug resistance and metastasis in CRC (Cao et al., 2018). In addition, upregulation of miR-21, miR-99a, miR-100 and miR-210 was associated with a significantly shorter OS and recurrence-free survival of PDAC patients. Interestingly, multivariate survival analyses identified miR-21 and miR-100 as unfavourable prognostic factors in resected and adjuvant treated PDAC stage II patients (Dhayat et al., 2015). Furthermore, low expression of miR-497 correlated with poor outcome of neuroblastoma patients. It is known that miR-497 targets multiple genes related to DNA damage response, cell cycle control, cell survival and angiogenesis, being a promising candidate for neuroblastoma therapy (Soriano et al., 2016). Also, it was confirmed that miR-3142-mediated doxorubicin resistance, occurs by targeting PTEN, which leads to downregulation and activation of the PI3K/Akt pathway. Inhibition of Akt using an Akt inhibitor or introduction of PTEN largely abrogated miR-3142-induced drug resistance. These findings indicate that miR-3142 induces cell proliferation and doxorubicin resistance, primarily through targeting the PTEN/PI3K/Akt pathway, hence suggesting the potential application of miR-3142 in cancer therapy (Zhao et al., 2017a). Moreover, one study found that miR-509-3p might be a potential therapeutic strategy for patients with platinum-resistant ovarian cancer since miR-509-3p was significantly down-regulated in cisplatin-resistant ovarian cancer tissues. Golgi phosphoprotein-3 (GOLPH3) and wntless Wnt ligand secretion mediator (WLS), as downstream targets of miR-509-3p, could be part of a future therapeutic strategy (Niu et al., 2019).

It is well known that mTOR functions as a serine/threonine protein kinase that regulates cell growth, cell proliferation, cell motility, cell survival, protein synthesis, autophagy, and transcription. Interestingly, the levels of miR-491-3 and of Rictor or mTORC2 activity were found to be negatively correlated in tongue cancer tissues. Low levels of miR-491-3p and a highly expressed Rictor, were associated with poor prognosis in tongue cancer patients, providing a rationale for targeting the miR-491-3p/mTORC2 axis to enhance the efficacy of chemotherapy against tongue cancer (Zheng et al., 2015).

Several studies investigated miRNA levels in correlation with patient response to therapy. One study analysed miR-20b, miR-27a and miR-181a expression with respect to epirubicin/oxaliplatin/capecitabine (EOX) chemotherapy regimen in a set of gastric cancer patients. It was observed that their aberrant expression was associated with chemotherapeutic response through modulation of *HIF1A*, *ABCB1/MDR1* and *HIPK2*, suggesting a possible novel therapeutic strategy (Danza et al., 2016). In Table 1, additional miRNAs affecting different signalling pathways, which are involved in MDR, are depicted as possible therapeutic targets (Han et al., 2011; Li et al., 2017; Qi et al., 2017; Qin et al., 2017; Shi et al., 2016; Van Roosbroeck et al., 2017; Xu et al., 2018b; Zhao et al., 2016).

The abovementioned data present evidence for the role of miRNAs in MDR, being a potential source of biomarkers and therapeutic targets to overcome MDR.

3.2. Intra-tumor heterogeneity (ITH) and dynamics

It is increasingly recognized that extensive genetic and phenotypic variation exists not only between tumors (inter-individual heterogeneity) but also within individual tumors (ITH) (Burrell et al., 2013). ITH is a key factor contributing to drug resistance as it provides genetic and epigenetic diversity, allowing therapy-induced expansion of pre-existing drug-resistant cancer cell clones (Gerlinger et al., 2012; Holohan et al., 2013a). ITH can be driven by tumor intrinsic mechanisms such as defects in DNA damage recognition and repair, telomere maintenance, chromosome segregation and alterations in epigenetic modifications (Burrell et al., 2013; Mazor et al., 2016; Yao and Dai, 2014), as well as microenvironmental selection pressures (McGranahan

and Swanton, 2017). Recent advances in next generation sequencing (NGS) technologies, in particular multiregional NGS and single-cell DNA/RNA sequencing, have provided valuable insights into the extent, spatial organization and temporal order of these events and the clinical implications of ITH.

An interesting study performed multiregional exome sequencing of primary and metastatic tumors in four patients with RCC (Gerlinger et al., 2012). This study provided evidence of ITH in every tumor, with spatially separated somatic mutations and chromosome aberration patterns. Strikingly, less than half of the identified mutations were found in every sequenced region – these mutations were considered to form the "trunk of the evolutionary tree", while the rest of mutations (63–69%) were found uniquely in one region or were shared among several regions, being considered as subclonal mutations that make up the "branches of the evolutionary tree" (Gerlinger et al., 2012). Subsequently, a number of multiregional or single-cell sequencing studies demonstrated the existence of ITH and branched evolutionary patterns in a variety of cancer types, including lung (Zhang et al., 2014), prostate (Boutros et al., 2015; Su et al., 2018a), breast (Martelotto et al., 2017; Ng et al., 2017), head and neck cancer (Zandberg et al., 2019), T-cell leukemia/lymphoma (Farmanbar et al., 2018), etc. However, the degree of ITH can be highly variable among patients with the same cancer type and differ between cancer types. For instance, melanoma and smoking-related lung cancer apparently have higher clonal mutation burden and lower ITH proportion, whereas glioma and neuroblastoma have low clonal and high subclonal mutational burden (McGranahan and Swanton, 2017).

ITH has profound implications for therapeutic decisions. Firstly, the multiregional NGS studies suggested that genomic analyses performed on single tissue samples would miss a large number of subclonal mutations and, importantly, would not allow discrimination between the common mutations located in the trunk and those in the branches (Gabusi et al., 2019; Gerlinger et al., 2012; Su et al., 2018a). Therefore, analysis of multiple biopsies from the same tumor is required for a comprehensive assessment of the genomic landscape. An attractive alternative to the collection of multiple tissue biopsies is" liquid biopsies" - blood-based analysis for the detection of circulating tumor cells (CTCs) or cancer cell products such as circulating tumor cell-free DNA or EVs that theoretically would allow assessment of molecular alterations present in tumor tissues without a tissue sampling bias. Moreover, the minimally invasive nature of liquid biopsies allows longitudinal sampling, thus enabling the assessment of solid tumor dynamics during the course of the disease (Babayan and Pantel, 2018). Currently however, the analytical sensitivity of liquid biopsies still lags behind that of conventional tissue biopsies (Chang et al., 2018; Namlos et al., 2018; Wu et al., 2019b). Secondly, ITH studies have revealed two major models of tumor dynamics leading to drug resistance: (i) adaptive model, which is based on the expansion of pre-existing, low-frequency subclones with a drug-resistant genotype during the course of therapy, and (ii) acquired resistance model, which is based on the acquisition of new genetic alterations or transcriptional profiles during the course of therapy and subsequent expansion of the drug resistant subclones (Fig. 3) (Ding et al., 2012; Kim et al., 2018).

A number of studies in various cancers support the adaptive model or a combination of both models. For example, the T790 M mutation in *EGFR* that confers resistance to EGFR TKIs was found in ~25% of lung cancer patients with activating EGFR mutations and was associated with shorter PFS (Lee et al., 2014b; Su et al., 2012). Similarly, high ITH for *HER2* copy number was associated with significantly shorter DFS in breast cancer patients receiving neoadjuvant chemotherapy plus HER2-targeted treatment (Rye et al., 2018). Interestingly, whole genome sequencing of primary and relapsed AML samples showed both evolution patterns during AML relapse (Ding et al., 2012). Single-cell DNA and RNA sequencing of longitudinal samples of TNBC patients undergoing neoadjuvant chemotherapy demonstrated that drug resistant genotypes were pre-existing at a low-frequency and were adaptively selected by

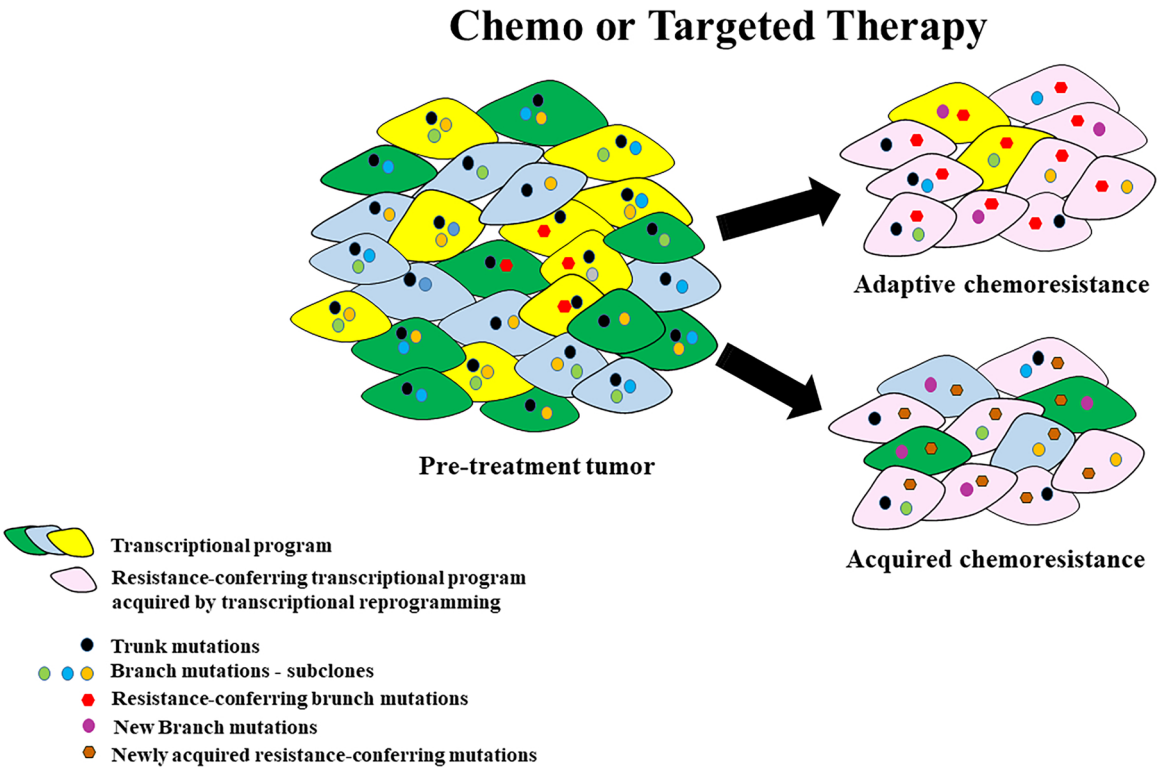

Fig. 3. Intra-tumor heterogeneity (ITH) and branch evolutionary pattern in a variety of cancer types. ITH studies have revealed two major models of tumor dynamics under chemotherapy or targeted therapy, leading to drug resistance: 1) Adaptive chemoresistance model, which is based on the expansion of pre-existing low-frequency subclones with a drug-resistant genotype during the course of therapy; and 2) Acquired chemoresistance model, which is based on the acquisition of *de novo* genetic alterations or transcriptional profiles during the course of therapy and subsequent expansion of the resistant subclones.

chemotherapy, whereas resistance-conferring gene expression profiles were acquired through transcriptional reprogramming during the course of therapy (Kim et al., 2018). Hence, according to this scenario, the detection of a putative drug resistant subclone in the pretreatment tumors, seems to be of paramount importance for therapeutic decision. On the contrary, a number of additional studies with RCC (Hamieh et al., 2018), soft tissue sarcoma (Hong et al., 2013), glioma (Johnson et al., 2014) and ovarian cancer (Patch et al., 2015), demonstrated an increase in mutation frequency in post-treatment samples and showed that the acquired resistance-conferring mutations were not detectable in the pre-treatment tumors. Conceivably, according to this scenario, monitoring treatment response by liquid biopsies would lead to early detection of acquired mutations, thus allowing for evidence-based clinical decisions before a clinically detectable relapse occurs.

3.3. Cancer stem cell (CSC) MDR and enhanced plasticity capabilities

There is increasing evidence that CSCs, a subpopulation of cells within the heterogeneous tumor niche, with some phenotypic resemblances to adult tissue stem cells such as the ability to self-renew and differentiate, have the exclusive ability to regenerate tumors (Lobo et al., 2007) and might be responsible for the initiation of at least some primary tumors, as well as for the recurrence, metastasis and in some cases for MDR (Najafi et al., 2019; Turdo et al., 2019). For that reason, these cells are sometimes also called tumor initiating cells, tumor-propagating or tumor-precursor cells (Gupta et al., 2019; Najafi et al., 2019). Nevertheless, and most importantly, it is not clear yet whether or not cancer arises in normal stem cells or if some tumor cells acquire a CSC phenotype through clonal evolution (Badve and Nakshatri, 2012; Capp, 2019; Rycaj and Tang, 2015; Sanchez-Danes and Blanpain, 2018). Moreover, even if/when the cell of origin of a tumor is a stem cell, the stem cell program might not be intact following neoplastic transformation (Gupta et al., 2019).

CSCs were initially identified in AML (Bhatia et al., 1997; Lapidot et al., 1994) but have since been found in various solid tumors (Batlle and Clevers, 2017). The CSCs are MDR and escape various treatments such as chemotherapy or radiotherapy (Atashzar et al., 2019; Valent et al., 2012), given their enhanced capabilities such as DNA damage repair machinery, slower cell cycle kinetics, resistance to cell death mechanisms, overexpression of MDR efflux pumps, evasion from the immune response, adaptation to tumor microenvironment (TME) and greater cellular plasticity (Freitas et al., 2014; Turdo et al., 2019).

CSC plasticity increases ITH and ultimately also MDR, and may be induced by many factors (Najafi et al., 2019). These include extrinsic factors from the TME such as inflammation, hypoxia, acidity or metabolic plasticity (Kim et al., 2017) as well as intrinsic factors including the expression of EMT markers (Krebs et al., 2017). EMT-induced plasticity allows cells of some cancers to gain properties of stem cells and has a role in tumor progression, metastasis (Brooks et al., 2015) and drug resistance (Feng et al., 2014). In fact, in a study with 39 metastatic breast cancer patients, it was found that a major proportion of CTCs from these patients expressed EMT markers and presented tumor stem cell characteristics (Aktas et al., 2009). Data obtained from gene expression analysis of a cohort of primary human ovarian cancer showed that EMT genes are upregulated in chemonaïve drug resistant tumors (Haslehurst et al., 2012). Moreover, the overexpression of β1 integrin in HER-2-positive metastatic breast cancer patients treated with trastuzumab-based chemotherapy was considered an independent negative prognostic factor of tumor progression (Lesniak et al., 2009). In addition, integrin αvβ6 expression in aggressive colorectal carcinoma is a biomarker of cells that underwent EMT and a prognostic factor for tumors that will progress more rapidly (Bates and Mercurio, 2005).

Nevertheless, even though EMT is frequently observed in some cancers, it is rarely detected in others. However, recent evidence suggests that a full mesenchymal transition is not required for the metastatic process and the concept of hybrid EMT has been suggested. Indeed, there is some evidence that hybrid EMT is possible in human cancers (Gupta et al., 2019). For example, different degrees of EMT (passing through intermediate hybrid states) were found in skin and mammary primary tumors. These EMT subpopulations presented differences in cellular plasticity, invasiveness and metastatic potential (Pastushenko et al., 2018). Moreover, Lecharpentier *et al.*, demonstrated the presence of hybrid CTCs with an epithelial/mesenchymal phenotype in patients with NSCLC (Lecharpentier et al., 2011). In addition, tumor cells co-expressing both E-cadherin and vimentin were found in invasive breast cancer and were associated with the most aggressive phenotype and poor prognosis in breast cancer (Yamashita et al., 2015). Furthermore, an association was found between the presence of hybrid EMT or mesenchymal CTCs with clinical prognosis in patients with different types of cancers (Hyun et al., 2016; Satelli et al., 2015; Wu et al., 2015; Yu et al., 2013; Zhao et al., 2017b). Finally, breast cancer patients with brain metastasis presented CTCs with a generally higher EMT score (Boral et al., 2017).

4. Tumor/host interactions in MDR cancers

4.1. Role of tumor microenvironment (TME)

Tumors are highly complex ecosystems consisting not only of cancer cells but also of ECM and stromal cells – cancer-associated fibroblasts (CAFs), endothelial cells, pericytes, a variety of immune cells and in the case of hematological malignancies also bone marrow stromal cells - osteoclasts and osteoblasts. Moreover, the composition of the TME differs between the primary tumor and its metastases (Hanahan and Weinberg, 2011). The interactions between the components of TME are no less complex than in any normal tissue and involve soluble signaling molecules, EVs, cell-cell and cell-ECM interactions (Sadovska et al., 2015; Senthebane et al., 2017). The TME has a pivotal role in supporting the tumor phenotype and it is increasingly recognized that TME plays a crucial role in drug response in a variety of ways (Junttila and de Sauvage, 2013). In addition, the TME increases variability and complexity to the evolution of tumors, by promoting adaptation and heterogeneity of CSCs (Najafi et al., 2019).

Stromal cells can produce growth factors that shape gene expression programs and confer drug resistance upon tumor cells. For example, the abundance of CAFs was linked to AXL-high transcriptional program in melanoma cells that were associated with resistance to various targeted therapies (Tirosh et al., 2016). In fact, the presence of CAFs in TME-mediated drug resistance was also demonstrated in several other studies, such as in MDR esophageal squamous cell carcinoma patients (Qiao et al., 2018; Zhang et al., 2017a), ovarian cancer patients resistant to paclitaxel (Wang et al., 2018), pancreatic cancer patients resistant to gemcitabine (Zhang et al., 2018) and gastric cancer patients resistant to 5-FU (Ma et al., 2018). Furthermore, an expression of Snail in CAFs of human CRC tissues was observed, which was found to be crucial to 5-FU and paclitaxel chemoresistance *in vitro* (Li et al., 2018b). In addition, CAFs population isolated from stromal cells outgrown from follicular lymphoma patients protected follicular lymphoma tumor cells from apoptosis in response to several cytotoxic drugs (Staiger et al., 2017). Clinical data also demonstrated a strong association between the activation of the cAMP/PKA pathway of stromal fibroblasts and MDR in patients with breast cancer (Yu et al., 2017). Interestingly, a CAF subpopulation expressing high levels of CD10 and GPR77, two cell-surface molecules, correlated with chemoresistance and poor survival in multiple cohorts of breast and lung cancer patients (Su et al., 2018b). These studies highlight the impact of stromal cells, especially fibroblasts present in the TME, on therapy response. In addition, various tumor-infiltrating immune cells can interact with cancer cells and modify their response to chemotherapy (Sanchez et al., 2019). For instance, tumor-associated-macrophages (TAMs) may have an impact in cancer response to therapy. In the clinic, an increased presence of infiltrated macrophages was observed in patients with HCC whose tumors were

not reduced following chemotherapy with oxaliplatin, when compared with patients whose tumors were reduced, suggesting a strong influence of macrophages on drug response (Fu et al., 2019). Moreover, pancreatic cancer patients with low abundance of macrophages present in the primary human tumor also demonstrated superior response to gemcitabine treatment and better DFS when compared with those having high macrophage infiltration (Halbrook et al., 2019). In CRC patients undergoing surgery and standardized chemotherapy, a strong TAM infiltration was associated with resistance to therapy (Yin et al., 2017). The impact of other immune cells on drug resistance was also reported. Indeed, increased infiltration of tumor-associated neutrophils was associated with sorafenib resistance in HCC patients (Zhou et al., 2016b) and an infiltration of tumor-associated B cells was related to the development of resistance to BRAF and/or MEK inhibitors in melanoma patients (Somasundaram et al., 2017).

The organization, density, content and functional state of tumor vasculature have a crucial role in the distribution of drugs, nutrients and oxygen across the tumor and it has been correlated with clinical outcome in a variety of cancers. For example, BCRP overexpression in the microvasculature of the blood-brain barrier in brain tumors influenced the penetration of drugs into these tumors, which might contribute to the failure of antitumor therapy (Goncalves et al., 2018). Tumor endothelial cells were also shown to induce MDR in ovarian adenocarcinoma, which was suppressed by TKIs that increase intracellular drug accumulation (Bani et al., 2017).

The presence of several molecules capable of inducing therapy resistance in the TME has been reported. For example, a study demonstrated that leptin (an inflammation-regulating factor present around the tumor) in combination with CA125 (a diagnostic marker for ovarian cancer), allowed to clinically discriminate advanced epithelial ovarian cancer patients resistant to first-line therapy from sensitive patients (Lane et al., 2015). In addition, the presence of periostin (an osteoblast-specific factor-2), in the stroma of ovarian carcinoma patients was associated with platinum drug resistance (Sung et al., 2016). These studies highlight the relevance of an immunosuppressive TME in promoting drug resistance.

4.2. Selective pressures and tumor evolution

The TME imposes selective pressures that drive tumor evolution. Single-cell transcriptomic analyses demonstrated that each tumor contains clusters of cancer cells expressing diverse transcriptional programs related to proliferation/cell cycle, differentiation, stemness, immune response, hypoxia and stress response (Patel et al., 2014; Puram et al., 2017). Conceivably, these clusters are formed by spatially separated cells exposed to various selective pressures such as hypoxia, extracellular acidosis, nutrient deprivation, immune surveillance and chemotherapy. Arguably, hypoxia represents one of the most dominant selective pressures. Hypoxic areas are found in up to 50–60% of locally advanced solid cancers (Vaupel and Mayer, 2017). The majority of cells halt their proliferation or undergo apoptotic or necrotic cell death if exposed to acute hypoxia or anoxia, while a fraction of cancer cells survives and subsequently acquires an aggressive phenotype along with chemoresistance. Hypoxic signaling is mediated by the hypoxia-inducible transcription factors HIF-1 and HIF-2, that activate multiple gene expression programs leading to the induction of angiogenesis, enhanced cell survival, increased metastatic potential, acquisition of chemoresistance and expansion of cancer stem cell populations (Araos et al., 2018; Soeda et al., 2009; Sullivan et al., 2008). Among the direct HIF-1 target genes is the multidrug efflux pump *ABCB1*; indeed, exposure to hypoxia resulted in increased ABCB1 expression in various cancers and normal cell types (Chou et al., 2012; Comerford et al., 2002; Xie et al., 2013). Hypoxia-exposed cells developed ABCB1-dependent MDR (Li et al., 2016b), while HIF-1α inhibition reversed MDR via downregulation of ABCB1 (Chen et al., 2014). Moreover, exposure to intermittent levels of hypoxia resulted in higher ABCB1 expression and stronger MDR when compared with chronic hypoxia, in glioblastoma xenografts (Chou et al., 2012). However, it is yet unclear how persistent are the hypoxia-induced transcriptional programs after re-oxygenation.

The work performed by R. D. Schreiber's team over the last two decades has provided strong experimental evidence for cancer immunoediting - the process whereby the immune system controls tumor outgrowth and shapes tumor immunogenicity (Koebel et al., 2007; Matsushita et al., 2012; Shankaran et al., 2001). This concept predicts that the immune system not only eliminates cancer cells but also selects for non-immunogenic tumor cell variants, leading to the expansion of "immunologically sculpted" tumor cells (Dunn et al., 2002). However, so far, very few studies have provided experimental evidence in human tumors for the role of the active immune system in the "sculpting of tumor evolution". Interestingly, C. Swanton's team and the TRACERx consortium performed multiregional RNA and DNA sequencing analysis in 88 early-stage, untreated NSCLC cases and stratified the tumor regions as having either high or low levels of tumor-infiltrating lymphocytes (TILs). In lung adenocarcinoma but not in squamous cell carcinoma, regions with low TIL levels had greater subclonal diversity as compared to regions with high or heterogeneous levels of TILs. Moreover, in regions with low TIL levels, neoantigen editing was decreased for subclonal mutations as compared to clonal mutations, which may reflect a previous active immune attack or depletion of historically clonal neoantigens through copy-number loss. Regions with high TIL levels exhibited ongoing immunoediting either through defects in antigen presentation (such loss of heterozygosity in HLA) or by suppressing neoantigen expression via promoter hypermethylation. Furthermore, this study demonstrated that high immune-evasion capacity was associated with poorer clinical outcome (Rosenthal et al., 2019). Likewise, the expression of highly immunogenic neoantigens was significantly decreased at recurrence in a fraction of glioma patients, thus supporting the concept of tumor evolution under persistent immune selective pressure (Nejo et al., 2019).

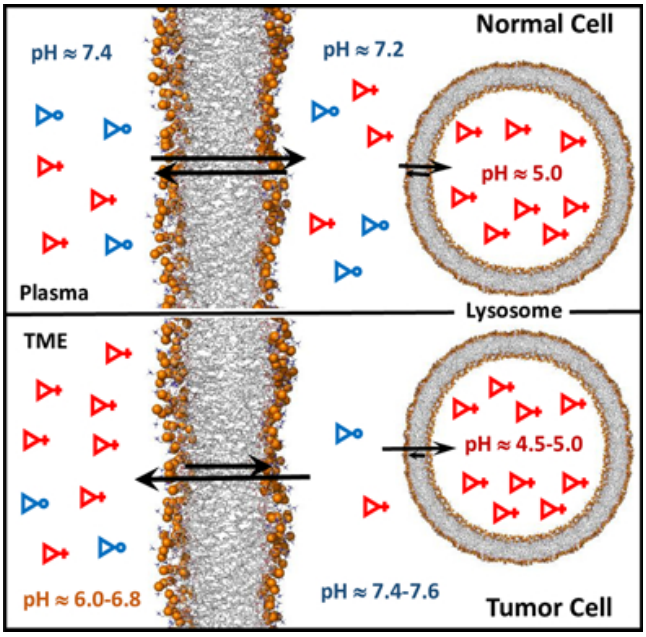

Fig. 4. Schematic representation of the impact of the pH gradient on antitumor drugs distribution in normal (top) and tumor cells (bottom). Drugs with a Lewis base group are represented in their positive (red plus sign) and neutral (blue zero sign) protonation states. The relative size of the arrows represents the membrane diffusion, which is proportional to the available neutral species at a given pH value. TME stands for the acidic tumor microenvironment (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

4.3. MDR mediated by the acidic tumor microenvironment and sequestration of anticancer drugs in acidic lysosomes

Rapidly proliferating malignant cells display an enhanced glucose consumption, which promotes anaerobic glycolysis even under aerobic conditions (Gatenby and Gillies, 2004; Ji et al., 2019; Kroemer and Pouyssegur, 2008; Lu, 2019; Pillai et al., 2019; Taylor et al., 2015; Warburg, 1956). In order to eliminate the excess acidity generated by the intense cellular metabolism, malignant cells upregulate the expression and activity of several transporters which extrude protons (Izumi et al., 2003; Spugnini et al., 2014, 2015; Taylor et al., 2015). When coupled to poor tumor perfusion, these proton efflux transporters lead to an acidification of the pericellular microenvironment known as the TME (Ji et al., 2019). The pH values in the extracellular milieu of the TME range from 6.0 to 6.8 (Fig. 4), with the level of acidity being positively correlated with the tumor grade (Logozzi et al., 2019). Acidic pH also induces the activity of proteolytic enzymes such as matrix metalloproteinases (MMPs) and cathepsins, which can be toxic to the surrounding stromal cells, leading to tissue remodelling and local invasion (Conlon and Murray, 2019; Kessenbrock et al., 2010). Another effect of the acidic TME is the selection of tumor cells which are adapted to withstand these acidic conditions, leading to a more aggressive cancer phenotype (Taylor et al., 2015). In contrast to the extracellular environment, the intracellular tumor milieu is slightly or strongly alkaline (Persi et al., 2018; Webb et al., 2011; White et al., 2019), which is presumably associated with the upregulation of the proton efflux transporters. Furthermore, retention of alkaline cytoplasmic environment generates a large pH gradient relative to the acidic lumen of lysosomes (pH ~ 4.5-5). This large pH differential allows for the efficient entrapment of hydrophobic weak base drugs within lysosomes and acidic organelles including endosomes, via protonation in the acidic lumen of these compartments (Gotink et al., 2011; Zhitomirsky and Assaraf, 2017, 2015a; Zhitomirsky and Assaraf, 2016, 2015b; Zhitomirsky et al., 2018). Thus, the acidity of the TME along with the large differential of nearly 3 logs between the acidic lysosome and the alkaline cytoplasm is correlated not only with increased tumor metastasis, but also with anticancer drug resistance. As such, strategies aimed at alkalization of both the TME as well as the lysosomes, may block tumor metastasis and overcome chemoresistance (Taylor et al., 2015; Zhitomirsky and Assaraf, 2017; Zhitomirsky and Assaraf, 2016). Furthermore, tumor cells take advantage of this alkaline cytoplasm since it also leads to histone acetylation, which facilitates increased gene expression and consequently increased protein synthesis (McBrian et al., 2013). The reverse pH gradient has been associated with tumor cell proliferation, invasion, metastasis, aggressiveness, and resistance to therapy (McCarty and Whitaker, 2010; Taylor et al., 2015; Webb et al., 2011). Strategies aimed at increasing the extracellular pH and/or decrease the cytoplasmic pH, have already been exploited in cancer therapy (McCarty and Whitaker, 2010; Neri and Supuran, 2011; Persi et al., 2018). In particular, PPIs can decrease intracellular pH, while also increasing the extracellular pH and have been shown to enhance the activity of chemotherapeutic agents in MDR tumors (Lee et al., 2015; Spugnini et al., 2011; Taylor et al., 2015).

The acidity of the TME can also alter the transmembrane uptake of various anticancer drugs. Some of these lipophilic cytotoxic agents diffuse passively across lipid bilayers most efficiently in their uncharged form (Trédan et al., 2007). Many compounds selected from drug design and screening studies, that successfully underwent PK and PD evaluation, exhibit high hydrophobicity and one or more Lewis base groups with pK_a values typically ranging from 7.5 to 9.5 (Gotink et al., 2011; Zhitomirsky and Assaraf, 2017, 2015a; Zhitomirsky and Assaraf, 2016, 2015b; Zhitomirsky et al., 2018). At physiological pH, these acid dissociation constants lead to mostly protonated (i.e. charged) compounds in solution, which improve considerably their water solubility (Sieger et al., 2017). Furthermore, pK_a values are strongly influenced by the level of the site solvent exposure and by the electrostatic interactions with neighbour polar groups. This effect has been shown for amino acids inserting into a lipid bilayer, where their neutral forms are stabilized due to desolvation (Teixeira et al., 2016). Therefore, it is expected that anticancer drugs, many of which are lipophilic weak bases,

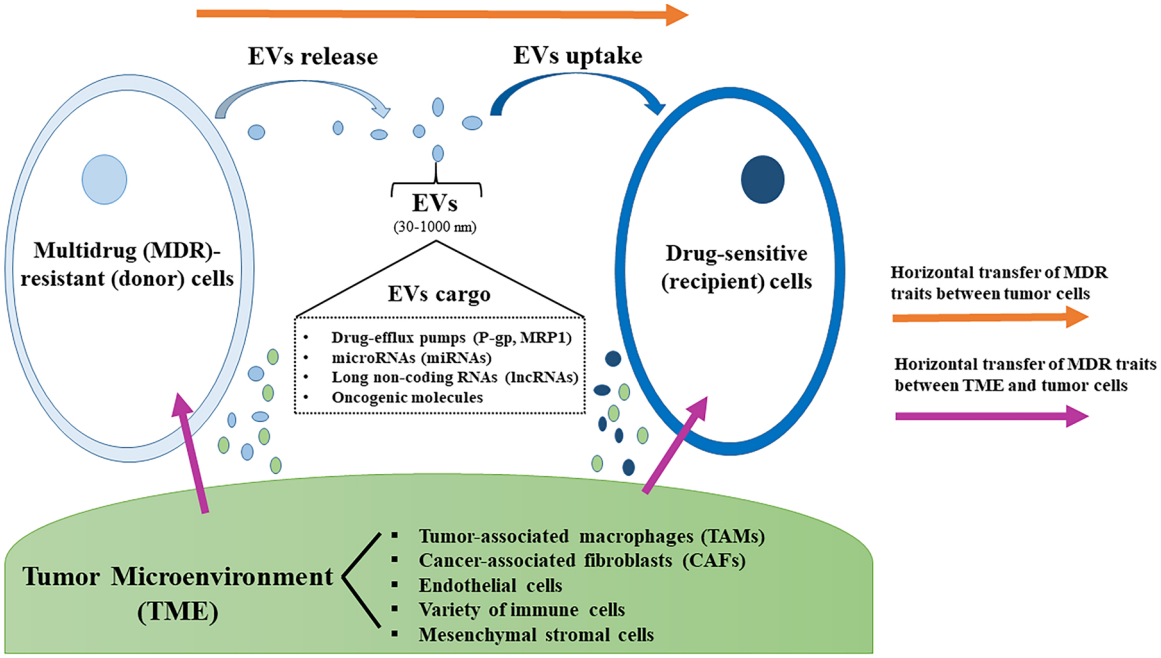

Fig. 5. EV-mediated horizontal transfer of MDR traits, between tumor cells or between stromal cells present in the tumor microenvironment and tumor cells. EVs ranging from 30 to 1000 nm carry in their cargo, different molecules involved in MDR, such as drug efflux pumps, microRNAs, long non-coding RNAs and oncogenic molecules, contributing to the dissemination of drug resistance. EVs released by MDR (donor) cells can transfer MDR-associated proteins and other MDR-associated molecules to drug-sensitive (recipient) cells. In addition, EVs-mediated bidirectional interaction between tumor cells and different stromal cells present in the tumor microenvironment (TME), such as tumor-associated macrophages (TAMs), cancer-associated fibroblasts (CAFs), endothelial cells, a variety of immune cells and mesenchymal stromal cells, can have an impact on the dissemination of MDR.

have their pK_a values strongly decreased when inserting into lipid bilayers, transiently deprotonate and passively diffuse across cell membranes. Hence, the acidic TME presents itself as an important barrier to passive diffusion, since at a lower pH value, anticancer agents, such as doxorubicin, mitoxantrone, vincristine, and vinblastine, will accumulate outside tumor cells in their protonated forms (Gerweck et al., 2006). This is probably one of the simplest drug resistance mechanisms that have been successfully adopted by tumor cells.

As mentioned above, the cytotoxic activity of hydrophobic weakly basic anticancer drugs is markedly hindered by lysosomal sequestration in MDR cancer cells with increased lysosome number per cell (Adar et al., 2012; Duvvuri et al., 2004; Gotink et al., 2011; Kaufmann and Krise, 2007; Kazmi et al., 2013; Zhitomirsky and Assaraf, 2017, 2015a; Zhitomirsky and Assaraf, 2016, 2015b; Zhitomirsky et al., 2018). These antitumor agents including for example daunorubicin, doxorubicin, sunitinib and nintedanib, are targeted towards the cell nucleus (Binaschi et al., 2001) or vital cellular kinases, hence their marked sequestration within lysosomes retains them away from their cellular target sites. These intracellular organelles have a highly acidic pH (pH ~4.5- 5) and become efficient pharmacological sinks for weakly basic lipophilic anticancer drugs. The ability to transiently deprotonate, and cross cellular lipid bilayer membranes via passive diffusion, becomes severely compromised once these compounds reach the internal water/lipid interface of lysosomes. In this respect, the highly acidic pH sets a very strong energetic barrier to deprotonation, thereby leading to the dramatic accumulation of anticancer agents in these organelles (Kaufmann and Krise, 2007; Zhitomirsky and Assaraf, 2016, 2015b; Zhitomirsky et al., 2018). Furthermore, lysosomal sequestration of anticancer drugs has been shown to trigger both lysosomal biogenesis and exocytosis (Medina et al., 2011; Sardiello et al., 2009; Zhitomirsky and Assaraf, 2015b), leading to tumor cells with increased number of lysosomes which can efficiently sequester lysosomotropic chemotherapeutics and prevent them from reaching their cellular targets, followed by their extrusion via lysosomal exocytosis (Zhitomirsky and Assaraf, 2015a; Zhitomirsky et al., 2018). This mechanism has been proposed as a novel modality of drug-induced, lysosome-mediated, drug resistance, hence acquiring MDR to multiple anticancer drugs with lysosomotropic properties (Zhitomirsky et al., 2018). Moreover, as detailed below, lysosomal sequestration of these anticancer drugs not only enhances lysosomal biogenesis and drug sequestration but also provokes exocytosis of drug-loaded lysosomes, hence expelling the cytotoxic drug cargo to the extracellular milieu.

4.4. Intercellular transfer of traits by extracellular vesicles (EVs)

EVs are considered important mediators of intercellular or horizontal communication between cells, strictly influencing the malignant potential of cancer cells. Importantly, EVs may contribute to the dissemination of drug resistance since EVs released by MDR tumor (donor) cells can transfer MDR-associated proteins and other MDR-associated molecules to drug-sensitive tumor (recipient) cells (Fig. 5), which may then acquire the MDR phenotype (Lopes-Rodrigues et al., 2017; Tkach and Thery, 2016; Xu et al., 2018a). Indeed, several studies in different types of cancer cell lines have described the selective packaging of molecules involved in drug resistance into EVs, such as drug-efflux pumps, miRNAs or long non-coding RNAs (lncRNAs) (Maacha et al., 2019; Sousa et al., 2015; Xu et al., 2018a). Moreover, the modulation of the TME mediated by tumor-derived EVs and the EVs-mediated bidirectional interaction between tumor and tumor-associated cells contributing to drug resistance, have also been addressed in several studies involving cancer cell lines (Maacha et al., 2019; Namee and O'Driscoll, 2018; Sullivan et al., 2017). Furthermore, *in vivo* studies supported the *in vitro* evidence for the involvement of EVs in drug resistance via numerous mechanisms, depending on the type of cancer and cancer treatment (Maacha et al., 2019; Namee and O'Driscoll, 2018; Sullivan et al., 2017). Nevertheless, to the best of our knowledge, to date, there is no evidence that this intercellular transfer of MDR traits occurs in patients.

Since EVs and their cargo may be found in biological fluids, their potential as a source of biomarkers of drug resistance has been suggested (Xu et al., 2018a). Indeed, following the research lines based on *in vitro* and in *vivo* data, some studies have confirmed the clinical potential of EVs present in the circulating blood of cancer patients as predictive biomarkers of drug resistance. For instance, the detection of higher levels of P-gp in EVs isolated from the blood of docetaxel-resistant prostate cancer patients (but not in patients undergoing cabazitaxel treatment), suggested that P-gp could be a potential biomarker to diagnose docetaxel resistance in prostate cancer patients and to select an appropriate taxane-based treatment (docetaxel or cabazitaxel) (Kato et al., 2015). It should be noted that the absence of P-gp in EVs from prostate cancer patients treated with cabazitaxel is in accord with the recent finding that cabazitaxel is more active than first-generation taxanes in P-gp-overexpressing tumor cell models due to its reduced affinity for P-gp (Duran et al., 2018, 2015).

An upregulation of TrpC5 (a transient receptor potential channel 5), which is known to regulate P-gp through the TRPC5–NFATc3–P-gp signaling cascade [since NFATc3 stimulates the transcriptional activity of the MDR1 promoter (Ma et al., 2012)] was found in circulating EVs from breast cancer patients that did not respond to chemotherapy with anthracycline/taxane, indicating the possible role of P-gp in mediating chemoresistance (Ma et al., 2014b). In another study, high expression levels of TRPC5 in EVs isolated from the plasma of metastatic breast cancer patients were significantly correlated with poor patient response to chemotherapy containing anthracycline and/or taxane (Wang et al., 2017b). In addition, UCH-L1 (ubiquitin carboxyl terminal hydrolase-L1), previously described to upregulate P-gp expression and enhance MDR (Wang et al., 2016), was found at high levels on circulating EVs isolated from the serum of advanced breast cancer patients with poorer response to adjuvant anthracycline/taxane chemotherapy (Ning et al., 2017). Regarding other drug efflux pumps, an upregulation of BCRP in the cargo of circulating EVs isolated from plasma of breast cancer patients was associated with poor response to anthracycline-taxane based neoadjuvant chemotherapy (Chen et al., 2015). Although with a smaller cohort of patients, another study identified the presence of MDR efflux proteins, such as MDR-1/3, enriched in EVs isolated from the serum of docetaxel-resistant prostate cancer patients (Kharaziha et al., 2015).

The possibility of using EVs-associated miRNAs as biomarkers of drug resistance has been investigated in clinical studies. For instance, EVs containing the miRNAs let-7g-5p and miR-497-59 were identified as potential biomarkers of treatment outcome in metastatic cutaneous malignant melanoma patients receiving the MAPK inhibitors vemurafenib and dabrafenib (Svedman et al., 2018). In NSCLC patients, the presence of miR-146a-5p in EVs isolated from patients' serum was suggested as a predictive biomarker of the efficacy of cisplatin treatment, useful for real-time monitoring of drug resistance (Yuwen et al., 2017). In addition, several miRNAs, such as miR-16-5p, miR-15a-5p, miR-20a-5p and miR-17-5p were present at low levels in the cargo of EVs isolated from blood samples of MM patients resistant to bortezomib (Velcade) when compared with a group of patients that responded to bortezomib treatment, suggesting a potential role for these miRNAs in predicting resistance to bortezomib (Zhang et al., 2016a). Moreover, low levels of miR-301a in the cargo of EVs from serum of glioma patients were found after surgical resection of the primary tumor but increased at recurrence, suggesting a possible role of the miR-301a in EVs as a diagnostic tool to predict drug response (Lan et al., 2018).

Other modulators of drug resistance have been described in clinical studies of EVs cargo. For instance, higher expression levels of TAG72 were detected in EVs isolated from the plasma of colon cancer patients displaying a poor response to 5-FU treatment, suggesting an association between TAG72-rich EVs and resistance to 5-FU (Xiao et al., 2019). High levels of GSTP-1 (glutathione S-transferase P1) were detected in EVs from the serum of breast cancer patients in progressive/stable

disease when compared with a partial/complete response group, indicating that GSTP-1 could become a predictive biomarker of chemoresistance to anthracycline-taxane treatment (Yang et al., 2017a). Furthermore, the levels of UCH-L1 in EVs isolated from the serum of breast cancer patients were negatively correlated with anthracycline-taxane therapy outcome (Ning et al., 2017). In gastrointestinal stromal tumor patients treated with imatinib therapy, a significant expression of SPRY4 (Sprouty homolog 4 protein) was found in circulating EVs from patients with metastatic tumors when compared to patients with resected primary tumors, suggesting that SPRY4 may serve as a reliable biomarker to predict imatinib response (Atay et al., 2018). In addition, Hur et al., demonstrated that EGFR mutations, such as the p.T790 M mutation, were detected in EVs present in the plasma of NSCLC patients, suggesting the use of EVs to identify patients who develop resistance to EGFR-TKIs (Hur et al., 2018).

These clinical studies suggest the potential clinical impact of EVs-mediated drug resistance and the potential of EVs as a source of biomarkers of drug resistance in general, MDR in particular.

5. A burning need for precision medicine and real-time personalized treatments

Historically, cancer therapy was mainly based on tumor's location, cancer stage and histopathological features (Heymach et al., 2018). However, clinical oncology practice has dramatically changed in the past 20–30 years. Since 1992, there have been declines in overall incidence and mortality rates for many types of cancer. In addition, in less than a decade, cancer survivor's increased by more than four million in the US (Pal et al., 2019). This is partly related to the development of molecular targeted therapies, which interfere with specific target molecules associated with cancer cell proliferation, progression, and metastasis. Indeed, the Food and Drug Administration (FDA) has approved various molecular targeted therapies that have demonstrated remarkable clinical success in the treatment of several cancer types including leukemia, breast, colorectal, lung, and ovarian cancer (Lee et al., 2018b), among others.

It is finally accepted that historical "golden rule" protocols of treatment or "one size fits all" chemotherapy, used previously for multiple decades, is not the proper approach we have to hold on. During the past decade the term personalized medicine (or currently precision medicine) from getting tight between lines of scientific discussions finally became the term increasingly used as a novel clinical approach to treat patients. Tumor heterogeneity, which increases upon each therapeutic manoeuvre and concomitant drug resistance, decreases tremendously the success of therapy. It is currently known that each tumor, despite the same pathophysiological origin, is distinct and requires a tailored therapy approach (Savoia et al., 2017).

There was concern that the term "personalized" could be misinterpreted to imply that treatments and preventions are being developed uniquely for each individual. In fact, personalized medicine usually refers to medical decisions, practices, and/or products being tailored to the individual patient. Precision medicine relies on individual molecular profiles using genomic, transcriptomic, proteomic, metabolomic and bioinformatic approaches to obtain a correlation between the regulation of gene(s) (functional protein) and disease status. In this context, the goal of precision medicine is to select the "right treatments" to the "right patients" at the "right time". Thus, the focus of precision medicine is to identify which approaches, based on genetic, environmental, and lifestyle factors, will be the most effective for each patient (Chae et al., 2017).

At the time precision medicine is mainly based on: (i) detection of known biomarkers and tailoring therapy according to them and, in a near future perhaps through the possible clinical use of (ii) *ex vivo* models such as patient derived xenografts (PDXs) and patient derived organoids (3D) and/or (iii) real-time monitoring of treatment responses and *ex vivo* guided therapy.

Regarding (i), lately there is an increasing number of companies, which are offering molecular profiling of tumor tissue (from paraffin block or biopsy) or blood samples. The output of these analyses could help oncologists to tailor the most efficacious therapeutic regimen. However, the obtained report needs to be the result of a multiplex analysis of biomarkers. That means that depending on the current knowledge about a specific tumor type, analyses need to be performed on DNA, RNA, protein and metabolite levels. Also, the algorithms used to create the report need to retrieve data obtained in the clinic and/or collected from clinical samples. It is important to emphasize that currently the results based on blood samples and plasma-derived circulating tumor DNA and circulating free-cell DNA as well as in circulating tumor cell-derived xenografts are still not sensitive enough to allow for their applicability in clinical practice and it will still take time for their possible application in clinical practice (Matchett et al., 2017). Recently, a very promising platform has been developed by Spetzler et al. (2017, 2018), based on unique profiling of the molecular composition of cells, tissues and circulating microvesicles/exosomes. The technology is able to simultaneously measure millions of molecular interactions within complex biological systems in their natural state(s) and reveal a unique disease associated biosignature (Domenyuk et al., 2018, 2017). This could be a valuable tool for precise blood sample analysis.

Regarding (ii), since we still do not know all biomarkers for disease outcome, it is necessary to combine biomarker analysis with *ex vivo* tests in the form of patient-derived cell cultures (PDCs). Lee et al. (2018a), provided evidence that PDCs may provide a useful model for individualized cancer therapy (Lee et al., 2018a). Further, growing number of evidence is showing possible use of patient-derived organoids (Clevers, 2016; Weeber et al., 2017) and multi-organs on a chip as possible models for testing drugs and identifying the treatment of choice (Sontheimer-Phelps et al., 2019; Zhao et al., 2019). One of the obstacles is that the time needed to grow this 3D organoid is still too long, even though shorter than growing the PDX. Lack of microenvironment as well as immunological system is often emphasized as disadvantages of this approach. However, the combination of biomarker testing using this 3D approach should be more beneficial than their separate use.

Regarding (iii), drug resistance and particularly MDR remains a primary hindrance towards successful chemotherapy. Circulating biomarkers and their proper detection either by real-time PCR, NGS or any other method, will allow predicting the patient risk, heterogeneity of tumor mass and predicting and/or monitoring the treatment outcome. On May 2017, a landmark in the history of precision cancer medicine and cancer drug approvals occurred, as FDA approved the first treatment based exclusively on the genetic make-up of a certain tumor in an individual cancer patient, rather than the type of cancer or its location in the body. Pembrolizumab, a programmed death-1/programmed death ligand-1 immune checkpoint inhibitor, was approved for the treatment of adults or children with advanced solid tumors that show specific genomic alterations as MMR deficiency or high MSI (MSI-H). Another promising treatment, larotrectinib, that targets the tropomyosin receptor kinase fusion gene, a rare genomic abnormality in tumors, also appears to be active across several adults and children cancer types (Heymach et al., 2018).

Although significant advances in targeted therapeutics had been observed in some medical oncology areas, as in late stage melanoma and NSCLC, limitations in other cancers also exist with respect to the lack of biomarker driven clinical trials design, availability of biomarker data, and challenges in understanding how to translate these multiplex data in clinical practice. These obstacles have limited the application of targeted therapies and highlight the need for validated bioinformatic tools and data platforms that can contribute to guide clinicians in patient management (Chae et al., 2017).

Another way to bypass these obstacles is the application of flexible trial designs, including "umbrella", "basket" and "hybrid" trials, respectively, based on genomic profiling, aberrant molecular pathways,

independent of cancer origin and on different molecular drivers within the same histology or the same molecular driver across different histologies. The Beat AML Core Study, developed by the Leukemia & Lymphoma Society's, seems to be the first precision oncology trial for a blood cancer (NCT02927106) (Chae et al., 2017).

In addition, the impact of genetic variants on treatment response and the risk of severe adverse reactions to drugs (pharmacogenetics) has been widely recognized as a fundamental step towards the development of precision medicine. The SNVs, structural variants such as inversions and copy number variations (deletions and amplifications) in genes related to drug action, metabolism, absorption and elimination are known contributors to individual's drug response (Motavaf and Bahrami, 2016). Furthermore, the development of artificial intelligence approaches must be considered, and their integration in clinical practice could be the main driver to healthcare transformation towards precision medicine. However, these extraordinary challenges should be carefully considered to ensure the safety and beneficial impact to healthcare (Xu et al., 2019). Lastly, tailoring personalized treatment for metastatic, drug resistant and recurrent tumors must rely on the in-depth understanding of molecular mechanisms of drug resistance. Combining the abovementioned approaches, understanding the mechanisms underlying cancer survival and recognizing that each tumor is specific, will allow the impact of real time monitoring on patient outcomes, thereby hopefully leading to more efficacious or even curative cancer treatments.

Declaration of Competing Interest

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Appendix A. Supplementary data

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