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Review

Mechanisms of acquired tumor drug resistance

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ABSTRACT

Systemic therapy often results in the reduction of tumor size but rarely succeeds in eradicating all cancer cells. Drug efflux, persistence of cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) and down-regulation of apoptosis are the most known general causes of therapy failure. Tumor escape from targeted compounds often involves pathway-specific mechanisms, which result in the restoration of the affected signaling cascade. The acquisition of drug resistance is mediated by mutations, changes in gene expression, alternative splicing, post-translational protein modifications, etc. Development of resistance to therapy may not necessary involve the emergence of new tumor clones: multiple studies demonstrate that even chemonaive neoplasms already have a small population of cells, which are capable of surviving therapeutic pressure and facilitating the disease progression. Use of combinations of cancer drugs, sequential therapy, adaptive therapy and topical ablation of drug-resistant malignant lumps may help to prolong the time to treatment failure. Many studies on mechanisms of drug resistance rely on the use of cell cultures and animal models. The development of approaches that allow efficient monitoring of the evolution of tumor phenotype in clinical setting presents a challenge.

1. Introduction

The development of cytotoxic and targeted therapies led to significant advances in cancer treatment. For the time being, the majority of tumor types can be successfully managed by various drugs. For some cancer diseases, e.g., high-grade serous ovarian cancer, EGFR-mutated lung cancer, BRAF-mutated melanoma, the disease controls rates approach close to 100%. However, in the metastatic setting, the duration of response to a given drug cocktail rarely exceeds 1 year, with even shorter progression-free survival (PFS) in subsequent treatment lines. As a result, metastatic cancer remains a largely incurable disease, with just a few exceptions including rare cancer entities (for example, testicular cancer) or anecdotal instances of unexpectedly long-term survival in patients with common malignancies [1–3].

Irrespective of cancer type or composition of systemic therapy, the acquisition of resistance is a highly complex process. Changes in the properties of cancer cells are almost always observed in drug-resistant tumors; these transitions may be attributed both to genetic and non-genetic events. The role of microenvironment and host factors attracted increasing attention in the past, owing to the development of new techniques for in vivo tissue analysis and landmark discoveries in the fields of cancer immunity, angiogenesis, stromal interactions, etc. The process of emergence of a drug resistant tumor lump may utilize either gain of molecular events or selection of pre-existing tumor clones, irrespective of whether genetic or non-genetic mechanisms are involved [4–6].

The escape of the tumor from the action of the therapy usually involves several layers of biological events. For example, the emergence of resistance may be attributed to the failure of drug delivery. Some tumors develop physical barriers to the drugs, which are composed of stromal components. Alternatively, there could be an activation of biochemical pathways facilitating drug efflux or decay. The most known mechanism of tumor escape from targeted therapy is the restoration of tumor-driving signaling either by the development of drug-resistant conformation of the target or by switching to collateral molecular cascades. Also, some tumors may undergo significant restructuring of molecular networks and lose addiction to the pathway, which orchestrated tumor growth before the onset of therapy [4,7–10].

2. Drug-specific and shared mechanisms of treatment resistance

Many targeted and cytotoxic drugs exert their action via a specific biological molecule or a well-defined cancer-driving signaling pathway. Accordingly, tumor escape from these drugs is usually related to reactivation of the involved biochemical cascade (Table 1; Fig. 1). For

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Table 1
Molecular events underlying cancer therapy failure.

Event	Examples	References
Pathway-specific mechanisms: reactivation of the same signaling cascade		
Modification of the target	New mutation in the target gene (EGFR T790M as well as various mutations in ABL, KIT, ALK ROS, etc. associated with TKI resistance); estrogen receptor mutations rendering resistance to aromatase inhibitors; androgen receptor mutations in castrate-resistant prostate cancer	[11–13,43,45,46]
	Splice-variant of the target gene (androgen receptor variant in castrate-resistant prostate cancer; BRCA1 exon skipping in platinum-resistant disease; BRAF splice-variant in vemurafenib-induced melanoma)	[52,55,56]
	Increased dosage of the target (e.g., target amplification): androgen receptor in prostate cancer; CYP19A1 in breast cancer; tyrosine kinases in TKI-treated cancers; BRAF in melanoma	[43,47,49,52]
Activation of downstream targets	Emergence of RAS mutations during anti-EGFR therapy; activation of MEK and ERK kinases in melanoma	[51,52]
Pathway-specific mechanisms: reprogramming of signaling network		
Activation of collateral signaling pathways	Amplification of neighbouring receptor tyrosine kinases in TKI-treated cancers; collateral signaling triggered by activation of the upstream members of the involved pathway, e.g. RAS mutations in vemurafenib-resistant melanoma	[43,46,52]
Emergence of tumor clone lacking the target	Open reading frame (ORF) restoring mutations in BRCA1/2 genes (failure of platinum or PARPi therapy); loss of estrogen receptor in breast cancer during endocrine therapy; loss of antigen or disrupted antigen presentation (resistance to immune checkpoint inhibitors)	[13,16,48]
General mechanisms		
Drug delivery failure	Activation of efflux pumps (MDR1 (P-glycoprotein, ABCB1), MRP (ABCC1), ABCG2 (BCRP)); stromal barriers; drug decay	[9,10,42]
Therapeutic resistance rendered by cancer stem cells	Enrichment of tumors by CSCs during therapy	[23]
Epithelial-mesenchymal transition	Switch to EMT phenotype upon treatment by kinase inhibitors, endocrine therapy, cytotoxic drugs	[23]
Evasion from apoptosis	Functional polymorphism of apoptosis-related gene BIM rendering resistance to EGFR TKI; JAK mutations in tumors resistant to pembrolizumab	[37,38]

example, the acquired resistance to kinase inhibitors can be achieved by appropriate modification of the targeted enzyme or its downstream partners [11]. Similar mechanisms are involved in the cessation of effects of endocrine therapy for hormone-dependent tumors [12,13]. Tumor-specific DNA repair deficiency underlies therapeutic efficacy of platinum compounds or poly (ADP-ribose) polymerase inhibitors (PARPi); accordingly, acquired resistance to these drugs is often mediated by restoration of the affected DNA repair module [14,15]. Acquired resistance to immune therapy may be attributed to the loss of tumor-specific antigen expression [16].

In addition to pathways-specific events, there are several biological modules involved in the broad spectrum of drug resistance mechanisms (Table 1; Fig. 2). These modules are highly complementary to each other and are characterized by significant overlap. They include drug efflux resulting in so-called multidrug resistance, drug escape rendered by cancer stem cells (CSCs), epithelial-mesenchymal transition (EMT) and inhibition of apoptosis.

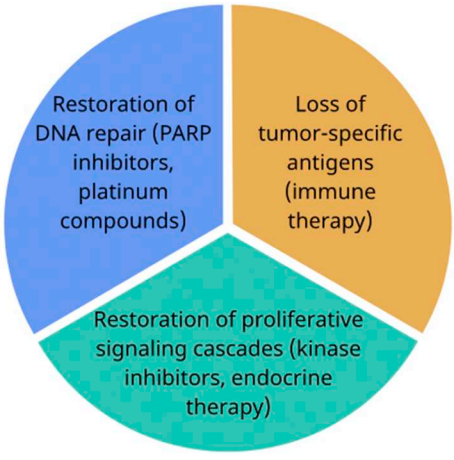

Fig. 1. Pathway-specific mechanisms of acquired drug resistance. Many targeted and cytotoxic drugs act via inactivation of a specific signaling cascade. Accordingly, loss of antitumor effect can be achieved by the functional restoration of the involved pathway.

Multidrug resistance is mediated by the activation of ATP-binding cassette (ABC) transporters. There are 48 members of ABC transporter family. The functions of these proteins often demonstrate a significant level of redundancy, however only 3 ABC transporters are usually discussed in the framework of drug resistance studies: ABCB1 (also known as multidrug resistance protein 1 (MDR1) or P-glycoprotein), ABCC1 (also known as multidrug resistance-associated protein 1 (MRP1)) and ABCG2 (also known as breast cancer resistance protein (BCRP)). Multiple investigations carried out on cell lines and animal models demonstrate that up-regulation of the expression of these proteins is involved in the acquired resistance to cytotoxic and targeted drugs. A high baseline level of ABC transporters often correlates with poor response to systemic therapy [9]. There is a limited number of human

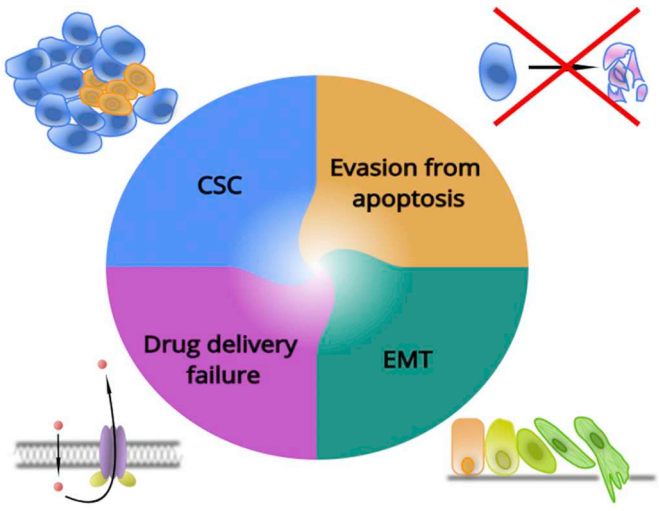

Fig. 2. Shared mechanisms of acquired drug resistance. There are some universal routes for tumor adaptation to the treatment, irrespective of whether cytotoxic or targeted therapy is applied. Therapy-resistant cancers are often characterized by altered drug delivery, epithelial mesenchymal transition (EMT), enrichment by cancer stem cells (CSCs) and down-regulation of apoptosis. Notably, these biological modules are characterized by significant overlap.

studies that compared expression of ABC transporters in paired pre- and post-treatment tumor samples. Some, although not all, of these reports demonstrated up-regulation of drug efflux pumps during cancer therapy [17–19].

The CSC concept was initially developed to acknowledge intratumoral cellular heterogeneity. More than 80 years ago Furth et al. [20] observed for the first time that a single malignant cell could be sufficient to develop a malignancy in an experimental animal, however no more than 5% of cells forming a tumor had this capacity. A few decades later Kleinsmith and Pierce [21] showed the potential for some differentiation in embryonal carcinoma cells. A number of studies carried out on various tumor types in the beginning of 2000s demonstrated that a small fraction of tumor-initiating cells present in the cancer lump can be discriminated from the gross tumor bulk by the analysis of some expression markers. Furthermore, CSCs showed the ability to survive therapeutic intervention and to re-capitulate the original tumor expression phenotype during repopulation of the malignant mass [22–24].

Several features render resistance of CSCs to therapeutic interventions. CSCs usually have low rates of cell division. Given that the majority of cytotoxic drugs primarily affect proliferating cells, it is self-explanatory that CSCs may escape this treatment. CSCs are also characterized by increased activity of ABC transporters. Drug efflux is involved in the resistance mechanisms both for cytotoxic and targeted therapies; therefore, this property of CSCs is potentially applicable to all systemic treatment modalities. Some studies indicate that CSCs have increased DNA repair capacity, which explains limited efficacy of DNA damaging agents. Furthermore, CSCs often demonstrate down-regulation of apoptotic mechanisms [22–25]. Recent studies indicate that cancer stemness may be associated with intratumoral heterogeneity and immune suppression [26].

EMT is a transdifferentiation process in which epithelial cells lose their essential distinguishing properties, such as cellular polarity, cell-cell contacts and expression of some specific markers (E-cadherin, cytokeratin, etc.), and acquire instead mesenchymal features, such as increased cell motility, fibroblast-like morphology and expression of vimentin, N-cadherin, fibronectin, matrix metalloproteinases, etc. EMT is believed to be a cause of tumor invasion and metastases; however, some studies in mice show that the suppression of EMT does not necessarily prevent tumor spread. Instead, multiple reports convincingly demonstrated the involvement of EMT in the resistance to cytotoxic drugs, tyrosine kinase inhibitors, endocrine therapies, etc. Although the contribution of EMT in the escape from cancer therapy is well acknowledged, the mechanistic links to this phenomenon remain largely obscure. Most available studies refer to significant overlap between EMT and CSC, stating that EMT produces a CSC-like phenotype. In particular, EMT may result in activation of ABC transporters, decrease of cell proliferation rate and up-regulation of anti-apoptotic pathways [26–29].

Decreased ability to undergo apoptosis or other types of programmed cell death is a hallmark of cancer cell [30]. As most available cancer drugs eliminate malignant cells via apoptotic or related mechanisms, it is intuitively logical to connect treatment resistance to the down-regulation of cell death pathways. There are many arguments to support this notion [31–33]. For example, testicular tumors, which are exceptionally sensitive to chemotherapy, differ from the majority of other cancer types by preserved ability to undergo programmed cell death [34]. There are studies demonstrating relationships between the status of master regulators of apoptosis, such as p53 and bcl-2 proteins, and drug response [35,36]. The efficacy of tyrosine kinase inhibitors was shown to correlate with the functional polymorphism of apoptosis-related gene BIM [37]. The action of immune checkpoint inhibitors is mediated by T-cell induced apoptotic death of cancer cells, thus the interruption of the apoptotic pathway results in the cessation of therapeutic effect [16,38]. As stated above, loss of sensitivity to programmed cell death is particularly characteristic for CSC and EMT phenotype.

While the above mechanisms concern mainly properties of malignant cells, there is also the role of tumor microenvironment in determining drug resistance [39]. Cancer-associated fibroblasts (CAFs) and blood-derived cells may secrete substances, which protect tumor cells. For example, CAFs populating colorectal tumors secrete interleukin 17A (IL-17A) in response to cytotoxic treatment; this interleukin exerts stimulatory activity towards chemoresistant cancer-initiating cells [40]. Tumor-infiltrating myeloid-derived suppressor cells (MDSCs) produce interleukin 23 (IL-23), which activates an androgen receptor pathway in castration-resistant prostate cancer thus overriding the therapeutic effect of androgen deprivation [41]. Recent studies demonstrate that some tumors form symbiotic relationships with microorganisms, and these bacteria may mediate drug decay. In particular, the majority of pancreatic ductal adenocarcinomas (PDACs) contain Gammaproteobacteria, which express a long isoform of cytidine deaminase capable of destroying the PDAC-specific drug gemcitabine [42].

3. Resistance-associated mutations

The invention of targeted therapy has provided a straightforward framework for the discovery of treatment resistance mechanisms (Table 1; Fig. 3). The emergence of mutation in the target protein, which changes its conformation and makes it insensitive to the drug, has been initially demonstrated for ABL/KIT inhibitor imatinib and then reproduced for EGFR, ALK/ROS, MET and some other inhibitors [11,15,43–46]. EGFR-driven tumors often develop resistance to first-generation EGFR kinase inhibitors via acquisition of T790M mutation. The spectrum of drug-resistant mutations in other kinases is significantly more broad [43]. A somewhat different mechanism is utilized by breast cancer cells exposed to aromatase inhibitors. Breast carcinomas often retain normal activity of estrogen receptors (ER), and therefore the hormone ablation may result in the cessation of tumor growth. The development of resistance to endocrine therapy often involves a gain of mutation in the ER gene, which renders ligand-independent activity of this receptor [13]. Similarly, mutations in androgen receptor (AR) broaden the spectrum of its ligands, so the activation of AR is observed even in the absence of male steroid hormones [12,47].

There is an impressively elegant mechanism of acquired resistance

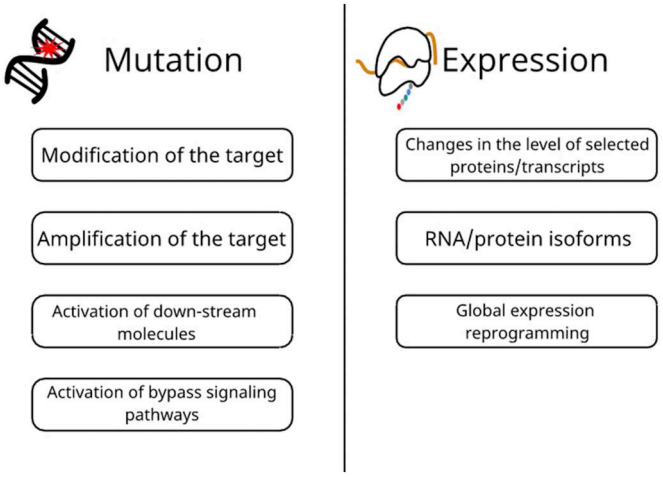

Fig. 3. Molecular events underlying acquired drug resistance. Some tumors develop therapeutic resistance by the gain of novel mutation. These mutations affect the conformation or amount of the target, re-activate the involved pathways by affecting down-stream molecules, or up-regulate collateral signaling cascades. Changes in the conformation or amount of the target can also be achieved through modifying the expression of the involved gene. Some tumors adapt to the drug exposure by global reprogramming of expression profiles.

to therapy for BRCA1/2- driven cancers. The development of tumors in BRCA1/2 germ-line mutation carriers almost always includes somatic inactivation of the remaining (wild-type) allele of the gene (so-called "loss of heterozygosity", LOH). As a result, tumor cells are selectively deficient in DNA double-strand break repair and therefore are highly sensitive to platinum drugs and PARP inhibitors. BRCA1/2 mutations cannot be categorized as a target per se, as BRCA1/2-specific treatments interact not with BRCA1/2 mutated proteins, but with the consequences of BRCA1/2 inactivation. Nevertheless, the process of acquiring resistance to cisplatin or PARP inhibitors is often based on the restoration of BRCA1/2 function. The most known route for the recovery of BRCA1/2 activity involves a second mutation in the pathogenic allele of BRCA1/2 gene, which is located in the vicinity of the germ-line mutation and restores the open reading frame (ORF) of the gene [14,48].

Amplification of a target-encoding gene is another mechanism of acquired drug resistance. Apparently, this leads to highly elevated level of corresponding protein, so the tolerable concentrations of the drug can no longer saturate the target. Gene amplifications have been demonstrated for the aromatase and several protein kinases [43,49]. The relationships between amplified genes and inhibitors of signal transduction cannot be described simply by the drug/target ratio. For example, treatment-induced EGFR amplification in EGFR-mutated lung cancer often involves a wild-type allele of the gene; this has to be perceived rather as initiation of bypass mechanisms than modification of the target per se [50]. An androgen receptor gene often becomes amplified upon hormone withdrawal as increased dosage of AR facilitates its ligand-independent activation [47].

Restoration of the signaling cascade may not necessarily involve the modification of a targeted protein. The same outcome can be achieved by mutation-driven activation of downstream molecules (Table 1). For example, the suppression of EGFR function in colorectal cancer by cetuximab or panitumumab can be abolished by mutation in RAS oncogenes [51]. Similarly, BRAF inhibition becomes biologically ineffective when tumor cells develop mutations in MEK or ERK kinases [52].

All described above examples refer to the recovery of the involved signaling pathway in its original form. However, cancer-related cascades are characterized by significant redundancy, therefore a transformed phenotype can be maintained by activation of collateral mechanisms (Table 1). For example, EGFR, HER2, ALK, ROS and MET kinases appear to be interchangeable in some circumstances. HER2 and MET amplification accompanied by gene overexpression is a well-established mechanism of lung cancer escape from EGFR inhibition [43,46]. Some breast cancers develop resistance to aromatase inhibitors via an activating mutation in HER2 oncogene [53,54]. Given that the down-regulation of receptor tyrosine kinases can be achieved by already available drugs, these data have immediate therapeutic implications. There are some other examples of involvement of collateral mechanisms. The emergence of vemurafenib-resistant melanoma clones often involves mutation-driven activation of the upstream regulator of BRAF, i.e. RAS protein. Mutated RAS molecules are capable of bypassing inactive RAF and can transduce proliferation signals via neighbouring pathways [52].

4. Changes in gene expression underlying drug resistance

The analysis of resistance-associated mutations is rewarding as genetic alterations represent discrete, stable and easily interpretable mechanism for tumor escape. The analysis of expression profiles linked to drug resistance is more complicated, taking into account a continuous nature of considered variables, potential plasticity of expression changes and, in many circumstances, a high number of involved genes and proteins.

The most convincing examples have been obtained in the studies of splicing variants of the targeted proteins (Table 1; Fig. 3). It has to be recognized, that alternative splicing can be mediated both by genetic mechanisms (e.g., mutations in the splice sites of the gene) and by changes in the regulation of the splicing. The expression of the ligand-independent splice isoform of an androgen receptor underlies the development of castration-resistant prostate cancer [12,55]. The consequences of some BRCA1 mutations can be overcome by skipping of the affected exon [55,56].

There is a myriad of changes in gene or protein expression observed upon emergence of drug resistance in cell culture experiments or in vivo. The resistance-driving changes include loss of the target (i.e., loss of addiction to particular protein), activation of drug removal mechanisms, initiation of bypass signaling pathways, emergence of compensatory routes (e.g., suppression of apoptotic cascades), phenotypic reprograming, etc. Probably, there are also some "passenger" alterations in molecular profiles, whose contribution in drug resistance phenotypes is less clear. For the time being, readjustment of expression portraits upon systemic therapy is studied mainly by rough quantitation of net amount of some RNA transcripts or proteins. It is beyond a doubt, that proteome-based analysis of protein isoforms will identify a huge number of post-translational modifications involved in acquired drug resistance [5,7,8,57–61].

5. Gain of new phenotype or selection of pre-existing clones?

There are two alternatives for the emergence of a drug-resistant phenotype, which are not mutually exclusive. Tumors exposed to systemic therapy usually contain at least 10^8–10^{10} cells [62]. The genome of transformed cells is highly instable, and many conventional cancer drugs act as mutagens. Therefore, it is highly likely that at least one cell within a tumor mass will gain a new molecular characteristic, either by mutation or by epigenetic event, which will render escape from therapy. In addition to this mechanism, there are multiple examples of persistence of isolated drug-resistant tumor cells in treatment-naïve tumors; these clones are expected to rapidly repopulate the tumor mass upon therapeutic intervention [4,63–65].

The biological reasons for persistence of drug-resistant cells in primary tumors represent an enigma, as the tumor obviously "does not know" how it will be treated. For example, cancers arising in BRCA1/2 germ-line mutation carriers usually demonstrate loss of BRCA1/2 heterozygosity in the gross tumor bulk, which underlies their sensitivity to platinum compounds. However, recent studies demonstrate that BRCA1-driven ovarian tumors usually contain a small fraction of cells with retained wild-type allele; these pre-existing BRCA1-proficient cells rapidly repopulate the tumor mass upon therapeutic pressure [66]. Furthermore, the relapses of these ovarian cancers, which occur after the therapy holiday, again demonstrate the loss of normal BRCA1 allele, i.e. they restore BRCA1 deficiency and become similar to primary tumors [67]. Therefore, two types of cells are present in BRCA1-driven tumors. BRCA1-deficient clones represent the majority of tumor bulk in the absence of therapeutic intervention; they obviously have a growth advantage, as cessation of the therapy leads to reappearance of the loss of BRCA1 heterozygosity. However, there is always a small admixture of BRCA1-proficient cells, which lose the competition to BRCA1-deficient clones in natural conditions but warrant tumor rescue upon start of therapeutic exposure. It is an enigma, what is the biological role of these persisting BRCA1-functional tumor cells in tumor housekeeping.

Treatment of colorectal carcinomas (CRCs) by anti-EGFR antibodies, cetuximab or panitumumab, often results in the emergence of clones bearing mutation in RAS oncogene. RAS proteins are downstream components of the EGFR signaling pathway. CRCs containing KRAS or NRAS mutation at diagnosis are not responsive to EGFR-targeted therapy, as this signaling pathway acts independently of the EGFR status. Therefore, it is not surprising that RAS-wild-type cancers utilize a similar mechanism while seeking for the escape from the therapy. Multiple studies show that some apparently RAS-wild-type CRCs may contain a minor fraction of RAS-mutated cells, and this pre-existing fraction undergoes expansion upon EGFR inhibition [68,69].

Furthermore, discontinuation of anti-EGFR therapy results in the fading of RAS-mutated clones and gradual re-sensitization of the tumor to EGFR antibodies [51]. These observations do not entirely fit into orthodox perceptions of the nature of tumor progression. Classical studies performed in late 1980s convincingly demonstrated that gain of a KRAS mutation provides some advantage to the tumor clone during CRC progression [70]. This is supported by observations on more aggressive phenotypes of CRCs carrying RAS mutation [71]. In theory, single cells bearing activated KRAS within a KRAS-wild-type background should immediately replace the remaining tumor mass, or, if activation of KRAS is incompatible with the status of other signaling cascades, should lose the competition to their neighbours. However, none of these scenarios holds true, as some tumors demonstrate some balance between KRAS-mutated and KRAS-wild-type cells.

Similar instances of persisting drug-resistant cells have been demonstrated for many treatment modalities. Some of these examples are justified by sound biological arguments. For instance, the capability of cells to efficiently efflux foreign compounds is supported by their high energy consumption. This is a disadvantageous property in the absence of drug exposure, therefore these cells constitute the minority of tumor mass in the chemonaive tumor. However, they rapidly repopulate the tumor volume upon treatment pressure, but then decline again after the cessation of therapy [72]. It is essential to comment that the presence of small amounts of drug-resistant cells within a gross tumor mass is not necessarily mutation-driven, but can be attributed to intratumoral variability of expression profiles [73].

It is important to realize that many experiments with persisting resistant cells have been carried out at the limit of available technologies. Therefore, caution must be taken while interpreting the data. The best example of controversies in this field is related to the analysis of mechanisms of acquired resistance to EGFR inhibitors. EGFR T790M mutation was identified as the main cause of resistance to gefitinib or erlotinib soon after the invention of these drugs. There are series of subsequent studies suggesting that isolated EGFR T790M-mutated cells often persist in treatment-naïve tumors and that their presence and proportion within tumor mass correlates with reduced time-to-progression. However, the detection of low-abundance EGFR T790M mutation is particularly prone to artifacts. For instance, archival formalin fixed paraffin-embedded samples, which are the only tissue source for clinical studies, produce significantly more T790M-specific signals than corresponding “fresh” tissues when high-precision molecular analysis is applied [74]. Furthermore, ultra-sensitive methods of the T790M testing usually detect high background noise for this allele, suggesting either that a small amount of T790M-mutated copies is present in every DNA sample, including normal DNA, or, alternatively, that many available studies failed to consider technical limitations related to T790M detection. Even more surprisingly, presence of a relatively high proportion of EGFR T790M-mutated cells in the treatment-naïve samples, which is observed in approximately 3% of patients with tyrosine kinase inhibitor (TKI) sensitizing EGFR mutation, does not preclude durable and pronounced response to gefitinib [74]. Interestingly, while in the case of a BRCA1-driven drug-resistant phenotype the tumor clone with a retained BRCA1 allele emerges first, and only afterwards it is getting replaced by BRCA1-deficient cells carrying additional mutation (loss of the normal BRCA1 allele) [66], the opposite sequence of events is observed for the T790M. Lung cancer cells carrying TKI-sensitizing mutations appear first, and, at some point, even without drug pressure, some clones acquire additional T790M substitution affecting the same allele of the gene [75]. Several issues related to the persistence of EGFR T790M clones in treatment-naïve tumors remain to be resolved. How addition of the T790M mutation to the TKI-sensitizing EGFR mutation affects biological properties of the cells? What is the role of equilibrium between T790M-mutated and T790M-wild-type clones? Why the presence of visible amounts of EGFR T790M-positive cells is still compatible with prolonged clinical response to gefitinib, despite laboratory data claiming the opposite?

The examples of ecosystems presented above, where the majority of cells in the tumor are sensitive to a given drug, but the persistence of small amounts of cells with drug-resistant mutations is an intrinsic characteristic of tumor being, cannot be easily explained by available biological knowledge. The programme of tumor development does not need to include back-up mechanisms to combat drug exposure, as the latter is an unnatural event. Apparently, co-existence of mutation-positive and mutation-negative cells reflects another intrinsic feature of the tumor biology. One can speculate that there are some mechanisms supporting phenotypic diversity of tumor cells, where even disadvantageous clones are not entirely eliminated by more successful competitors. The maintenance of a broad repertoire of cell phenotypes can be costly, but warrant some plasticity upon unfavourable circumstances. Alternatively, persisting drug-resistant cells have some discrete physiological role, which is not directly related to the defence from therapeutic interventions and remains to be determined.

Overall, the development of a drug resistant phenotype may combine both linear and non-linear trajectories. If the tumor mass already contains a fraction of cells that are fully fit to survive and proliferate upon drug exposure, the linear model of tumor repopulation appears to be true. For example, this is likely to be observed in case of selection of pre-existing BRCA1-proficient clones during platinum therapy or expansion of cells with activated drug efflux. However, drug-resistant clones may not always be present in the treatment-naïve tumor, so the gain of protective molecular events may take some time. For instance, the emergence of second ORF-restoring BRCA1/2 mutation is well documented mainly for heavily pre-treated patients. The delay in progression of a EGFR T790M-mutated clone, which is observed in a subset of gefitinib-treated patients, may indicate, that the presence of the T790M allele is not always sufficient to resist TKI exposure in vivo, so perhaps additional events are needed to overcome the treatment pressure. Some studies demonstrate that, in the absence of pre-existing defensive mechanisms, cancer cells may elicit non-specific “stress response” to anticancer drugs. This response involves expression reprogramming of a small subset of cells, which become capable of tolerating drug exposure and forming the reservoir for the preservation of the tumor entity. These “persister” cells continue to generate diverse genetic and expression variants until one of these newly evolved clones turns out to be fully fit for expansion upon drug exposure [76–78]. Studies on breast cancer revealed that expression reprogramming is responsible for the preservation of the residual tumor mass after neoadjuvant therapy [79]. The phenomenon of “persister” cells is well known from microbiological studies on antibiotic resistance [80]. It is essential to comment that the use of the term “persister cells” applies here to a subset of cells, which quickly undergo reversible expression reprogramming, but not to the isolated persisting cells with distinct mutational characteristics, which were described in previous paragraphs.

Isolated drug-resistant cells support tumor survival upon therapeutic exposure. However, the repopulation of tumor mass is not necessarily a simple process involving mechanistic expansion of drug-resistant clones. Obenauf et al. [81] demonstrated interaction between drug-sensitive and drug-resistant cells during therapy by kinase inhibitors. In particular, treatment of drug-sensitive cells by a therapeutic compound induced secretion of some substances, which actively stimulated the growth of drug-resistant clones. This observation appears to be a general phenomenon, as experiments with BRAF, EGFR and ALK inhibitors rendered similar results.

6. Therapeutic implications

There are three main avenues that consider prevention or overcoming drug resistance by modification of treatment strategies. The first one is the sequential therapy, where drug-resistant clones are treated with another therapeutic compound, ideally with the reference to newly acquired tumor characteristics. The second strategy is based

on the use of combination of therapeutic compounds. The third approach remains in an experimental phase and relies on so-called adaptive therapy.

Sequential therapy is empirically used in the majority of cancer patients. For example, guidelines for endocrine therapy in hormone receptor positive breast cancer suggest to switch to another type of antiestrogen drug upon failure of first ER-targeted treatment, as mechanisms of resistance to these drugs do not necessarily overlap. Gain of mutation in the ESR1 gene during therapy by aromatase inhibitor (AI) indicates that the use of another variety of AI is not feasible. Instead, the degrader of the estrogen receptor, fulvestrant, is equally efficient both for mutated and wild-type ER [82]. However, ESR1 genetic testing is unlikely to enter clinical routine, as the switch from AI to fulvestrant is effective irrespective of the ESR1 mutation status. The situation is different for prostate cancer. Emergence of AR-V7 splice isoform predicts limited impact from continuation of endocrine therapy, but provides a rationale for the switch to cytotoxic treatment [83]. The discovery of gefitinib-resistant mutation EGFR T790 M led to the development and approval of the so-called third-generation EGFR inhibitor, osimertinib, which specifically targets both T790 M and EGFR-activating (ex19del and L858R) mutations [84]. There are clinical algorithms guiding the choice of ALK inhibitor depending on the type of acquired ALK mutation [45]. Overall, sequential therapy may have limited perspectives given the diversity of drug resistance mechanisms and relatively short duration of tumor response to second-line therapy.

Combination treatment is aimed to either prevent the emergence of resistance or overcome the cessation of tumor response. It may address an intrinsic heterogeneity of tumor cells and target intratumoral clones with distinct pathological characteristics as well as delay the evolution of drug-resistant phenotypes by interfering with complementary molecular cascades. The examples of combined inhibition of several signaling pathways or concurrent targeting of several members of the same signaling cascade include the use of estrogen antagonists together with mTOR or CDK inhibitors in breast cancer, simultaneous administration of BRAF and MEK inhibitors for patients with melanoma or lung cancer, combined blockade of BRAF and EGFR in gastrointestinal malignancies, etc. [13,52,85]. High-dose chemotherapy may be regarded as an extreme example of combination therapy; interestingly, this approach resulted in cure from metastatic BRCA1/2-driven cancer in some patients [86]. Somewhat alarmingly, recent studies suggest that many clinically approved drug combinations are not sufficiently justified by clinical or biological evidence, so the improved response rates to some therapeutic cocktails simply reflect the summation of the probabilities of response to separate drugs but not the synergistic effect of the utilized compounds [87].

The described above examples refer mainly to mutation-driven pathway-specific drug resistance. There are attempts to interfere with general mechanisms of tumor escape. Some experimental approaches rely on the pharmacological targeting of drug efflux pumps, cancer stem cells, epithelial mesenchymal transition, etc. However, clinical application of these concepts remains complicated, as the relevant signaling cascades are characterized by a high level of redundancy and similar biological processes are involved in functioning of normal tissues [9,23,24,28,88].

While sequential and combination therapy fit well into the current medical attitudes towards cancer management, the concept of adaptive therapy contradicts established treatment guidelines. Standard regimens for targeted or cytotoxic drugs are aimed to achieve maximal reduction of tumor size by complete elimination of a drug-sensitive cell population. There is experimental evidence from agricultural entomology, microbiology and cancer biology indicating that drug-sensitive populations of living beings may suppress the expansion of their drug-resistant counterparts. As result, massive killing of drug-sensitive cells within the tumors releases resources for an otherwise poorly competitive drug-resistant cell population, that negatively affects long-term disease outcome. Animal studies demonstrate that the use of low-dose or intermittent drug regimens, which result in only partial elimination of drug-sensitive cells, may render longer control of cancer spread [4,72,89–91]. Some clinical data support the feasibility of this concept [92,93].

The approaches described above concern mainly systemic treatment. However, it is also essential to recognize the potential of topical surgical or radiological ablation in the treatment of tumor recurrences. Indeed, the invention of highly efficient systemic treatments significantly changed the anatomic pattern of disease relapses. For example, use of trastuzumab in HER2-positive breast cancer (BC) patients resulted in an increased proportion of women with isolated brain metastases. It appears that HER2-targeted antibodies, being capable of controlling metastases in the visceral organs, have limited penetration to the brain. Therefore, HER2-positive BC patients previously dying from liver or lung metastases now have improved life expectancy and therefore have good chances to survive until the manifestation of brain disease. Accordingly, the local control of oligometastatic lesions in the brain results in significant improvement of the disease outcomes [94]. Similar observations were obtained for EGFR-mutated lung cancers treated with EGFR tyrosine kinase inhibitors. These tumors are also frequently characterized by oligometastatic progression; therefore, intelligent combination of systemic therapy and topical ablative intervention may result in improved disease outcomes in at least a subset of patients [95]. A recent study suggests that BRCA1-driven ovarian cancers can be viewed in a similar way. Platinum-based therapy, which is the standard systemic treatment for ovarian malignancies, is particularly efficient in BRCA1 mutation carriers; as result, a high proportion of disease relapses observed in this category of patients is represented by single tumor lumps and is potentially amenable to local treatment [96].

7. Outstanding issues and perspectives

Most of the studies related to cancer drug resistance mechanisms have been accomplished using cultured cells or tumors growing in experimental animals. Some of the obtained data are highly relevant to cancer treatment in humans: for example, second BRCA1/2 mutations restoring open reading frame of the involved gene were initially discovered in platinum- or PARPi-resistant cell lines, and then identified in patients experiencing failure of BRCA1/2-specific therapy [48,97,98]. On the other hand, there are laboratory observations, which have so far not received firm clinical confirmation. For instance, the development of cell lines resistant to microtubule interfering agents is associated with the gain of mutations in tubulin genes [99]. However, actual clinical significance of this mechanism remains unclear [100].

Human studies on acquired cancer drug resistance require access to treatment-exposed tumor tissues. It is self-explanatory that the use of repeated biopsies of multiple tumor lumps is complicated due to technical limitations, potential harm to the patients and ethical issues. The analysis of residual tumor fragments in body fluids (so-called “liquid biopsies”) is now routinely utilized as a substitute for conventional tissue excision. However, it is essential to recognize that liquid biopsies have a number of critical limitations [101]. The development of in vivo imaging technologies, which allow evaluation of the status of selected biological molecules, is vitally important for the clinical studies on cancer resistance. Some tumors, e.g., breast and ovarian neoplasms, are often subjected to a few weeks of systemic therapy before the surgery in order to reduce tumor volume. Recent studies demonstrate that malignant tissues, which are excised after neoadjuvant therapy, are almost entirely represented by drug-resistant clones [66,79]. Therefore, systematic comparison of therapy-naïve tumor samples and residual cancer masses removed during the surgery may provide important information [102].

It is common to draw parallels between cancer research and studies on infectious diseases. In particular, the analysis of the balance between drug-resistant and drug-sensitive clones during treatment has

similarities for antibiotic and targeted therapies [76–78,80]. All infections are characterized by a specific interaction between the host, the pathogen and the affected tissue; these relationships deserve to be considered while searching for an optimal strategy to control cancer spread [103]. Both malignant transformation and the development of drug-resistant clones are believed to resemble Darwinian evolutionary processes, where random gain of mutations is followed by selection of the best adapted clones [63,65,104]. Intriguingly, there is evidence obtained from bacterial genetics, which indicate that the rate of emergence of advantageous mutations may somehow exceed the one for neutral genetic events [105,106]. In other words, the mutagenesis occurring during various external challenges is not a truly random event, but, according to Cairns et al. [104] "cells may have mechanisms for choosing which mutations will occur". It is of interest whether similar relationships are involved in the development of cancer and its acquired resistance to drug exposure.

Recent years are characterized by dramatic advances in the development of high-throughput technologies for biomedical research. Use of high-precision techniques, which allow comprehensive analysis of tumor molecular portraits on the single-cell level, are likely to result in significant breakthrough in understanding of drug resistance mechanisms and, hopefully, in the development of new approaches to cancer management.

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Declaration of Competing Interest

None.

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