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REVIEW

Mechanisms of tumor cell resistance to the current targeted-therapy agents

Gholamreza Khamisipour[1] · Farhad Jadidi-Niaragh[2,3,4] ·
Abdolreza Sotoodeh Jahromi[5] · Keivan zandi[6] · Mohammad Hojjat-Farsangi[7,8]

Abstract Resistance to chemotherapy agents is a major challenge infront of cancer patient treatment and researchers. It is known that several factors, such as multidrug resistance proteins and ATP-binding cassette families, are cell membrane transporters that can efflux several substrates such as chemotherapy agents from the cell cytoplasm. To reduce the adverse effects of chemotherapy agents, various targeted-based cancer therapy (TBCT) agents have been developed. TBCT has revolutionized cancer treatment, and several agents have shown more specific effects on tumor cells than chemotherapies. Small molecule inhibitors and monoclonal antibodies are specific agents that mostly target tumor cells but have low side effects on normal cells. Although these agents have been very useful for cancer treatment, however, the presence of natural and acquired resistance has blunted the advantages of targeted therapies. Therefore, development of new options might be necessary. A better understanding of tumor cell resistance mechanisms to current treatment agents may provide an appropriate platform for developing and improving new treatment modalities. Therefore, in this review, different mechanisms of tumor cell resistance to chemotherapy drugs and current targeted therapies have been described.

✉ Mohammad Hojjat-Farsangi
   mohammad.hojat-farsangi@Ki.se

[1] Department of Hematology, Faculty of Allied Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

[2] Department of Immunology, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran

[3] Immunology Research Center, Tabriz University of Medical Sciences, Tabriz, Iran

[4] Department of Immunology, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

[5] Research Center for Non-Communicable Diseases, Jahrom University of Medical Sciences, Jahrom, Iran

[6] Tropical Infectious Diseases Research and Education Center, Department of Medical Microbiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[7] Department of Oncology-Pathology, Immune and Gene therapy Lab, Cancer Center Karolinska (CCK), Karolinska University Hospital Solna and Karolinska Institutet, SE-171 76 Stockholm, Sweden

[8] Department of Immunology, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran

Introduction

After cardiovascular diseases, cancer is the second common cause of death, which is demonstrated by massive cell proliferation and cell death defects. Cancer is initiated by various factors, such as impairment and mutations of tumor suppressor genes and proteins [1].

For several years, chemotherapy has been one of the main anti-cancer treatments. Chemotherapy agents inhibit the rapidly dividing cancer and normal cells (e.g., hair follicles, bone marrow, and gastrointestinal cells). In addition to sever effects of chemotherapy agents, drug resistance develops after treatment regimens [2]. Therefore, development of new modalities such as targeted-based cancer therapy (TBCT) agents is necessary [3–5].

TBCT is a major and hot research topic in cancer treatment field and currently the US Food and Drug Administration (FDA), European Medical Agency (EMA) and other authorities in different countries are evaluating and approving various agents, including small molecule inhibitors (SMIs) and

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monoclonal antibodies (mAb) [6]. These agents target specific molecules and block biologic transduction pathways, which have been overexpressed or hyperactivated, respectively, by tumor cells. However, consistent findings have indicated that similar to chemotherapy, drug resistance to TBCT appeared in most patients [1, 7, 8].

Resistance to cancer target therapies is divided into intrinsic (primary, first-line, or natural) and acquired (secondary, second-line) resistances that are due to the natural factors exist before treatments or are secondary to drug treatments, respectively [9].

During and after treatment, tumorigenic cells exist, but they are not able to produce another tumor population due to the pressure of drugs [10]. However, acquisition of various mutations, such as single nucleotide polymorphisms (SNPs) in target molecule [11], crosstalk between signaling pathways, presence of tumor subpopulation cells, such as cancer stem cells (CSCs) [9, 10, 12], and dysregulation of DNA damage repair proteins that appear during or after treatment are the most important reasons for resistance to therapy (Tables 1 and 2) [13, 14].

Several studies suggested that using multi-targeted therapies, such as adenosine 3 phosphate (ATP)-competitive multi-targeted inhibitors (type I SMIs) or mAbs, as well as long-term therapy, may decrease the abundance of resistant tumor cells or prevent drug resistance [5, 9, 15]. Whether such approaches are applicable or not need a better understanding of tumor biology and the mechanisms underlying the tumor cell resistance to current cancer drugs.

In this review, the most important mechanisms of drug resistance in different tumors have been described. This article tried to provide a clear picture of drug resistance mechanisms for researchers and physicians to develop new treatment modalities or improve the treatment choices.

Types of drug resistance

Development of cancer drug resistance is the main reason for poor prognosis of cancer as an incurable disease. Resistance to the present therapies can be divided into two main categories, including the intrinsic and acquired resistances [9]. Intrinsic resistance exists naturally before any treatment; however, acquired resistance develops during or after the treatment process of malignant cells, which have been responsive to the former treatments (Table 1) [16].

Intrinsic and acquired resistances have been shown for most chemotherapy and targeted-therapy drugs in various malignancies. It should be noted that some mechanisms of drug resistance can be categorized in both natural and acquired resistance. In the following sections, different mechanisms of natural and acquired resistance have been described.

Natural resistance factors

Several factors have been noted to contribute to natural resistance. The presence of heterogeneous populations of tumor cells, such as CSCs, changes in drug metabolism, expression of drug resistance proteins in tumor cells, modified expression of target protein, dysregulation of apoptosis, high activity of DNA damage repair system, which is expressed by tumor cells, bone marrow microenvironment, and steric hindrance are among the most important factors that are involved in resistance of cancer cells to treatment agents (Tables 1 and 2).

Heterogeneity of tumor cells before treatment

One of the major reasons for intrinsic/acquired drug resistance is the presence of tumor subpopulation cells that are resistant to different types of drugs and may arise during treatment process (Fig. 1).

Previously, it was believed that tumors are the homogenous population of dividing cells. However, this theory has been replaced, and currently, it is known that cancers are consisting of the heterogenic population of cells with a great degree of genetic and phenotypic heterogeneity. In a given type of tumor, cancer cells are heterogeneous, and various populations of cells with several clonogenic potentials and capabilities exist [16, 17]. These populations are consisted of major and minor populations of tumor cells. During the treatment, the major populations are usually destroyed by cancer drugs and the minor resistant populations such as CSCs survive and remain quiescent due to drug pressure. Based on different conditions, such as the status of the immune system, age, and hormones, these minor populations may start to repopulate and establish another tumor, which is resistant to the first-line treatment [12].

Several kinds of research have shown that treatment failure in several tumors has been attributed to the presence of CSCs [16–19]. These cells are naturally extremely resistant to different therapeutic approaches (Fig. 1). Therefore, identification and characterization of normal and CSCs are major research areas of TBCT and have been described in the following section.

Stem cells are a minor population of cells and have the potential to differentiate into different types of cells. In several tissues, they function as a type of repair system, dividing without limit to repopulate other cells. Each new population of cells (originated from stem cells) has the capacity either to remain a stem cell or change to other types of more specialized cells with a define function, such as a brain and muscle cells [20, 21].

Two essential characteristics distinguished stem cells from other cell types. First, they are undifferentiated cells with renewing capacity (cell division) and might be inactive for a long period. Second, they can differentiate and become a

Table 1 Mechanisms of resistance to current targeted therapies

Type	Mechanism of resistance
Intrinsic resistance	
1	Heterogeneity of tumor cells before treatment
2	Cancer stem cells
3	Changes in drug metabolism (increased efflux of drugs from tumor cell membrane) and drug inactivation
4	Expression of drug resistance proteins
5	Extracellular vesicles
6	Low/overexpression of the target protein
7	Inefficient or dysregulation of apoptotic machinery
8	DNA damage repair
9	Bone marrow microenvironment
10	Steric hindrance
Acquired resistance	
1	Heterogeneity of tumor cells after treatment
2	Changes in drug targets: mutation and methylation
3	Mutations in the target gene after treatment
4	Hyperactivation of prosurvival signaling pathways
5	Up/downregulation of miRNAs
6	Crosstalk between intracellular signaling pathways
7	Chronopharmacology

tissue or an organ with specialized functions, when they activated under special conditions and environments. In several organs and tissues, such as bone marrow, these cells frequently divide to repair and substitute damaged cells or tissues. However, in other tissues, such as heart or pancreas, these cells only divide under special situations [20, 22, 23].

Currently, differentiating normal stem cells from CSCs is an important obstacle infront of researchers. Several investigations have shown that normal and CSCs might have similar differentiating marker profiles in the same tissues or organs. For example, normal mammary stem cells, as well as tumor cells in human breast cancer, have been shown to be CD24 negative [24, 25].

The presence of CSCs was initially described 20 years ago for acute myeloid leukemia (AML), and it was shown that these cells display the $CD34^+/CD38^-$ phenotype and following transplantation into severe combined immunodeficiency (SCID) mice rise into tumor cells. Moreover, it was demonstrated that a small population of breast CSCs has the phenotype of $CD44^+/CD24^{-/low}/Lin^-$ that were able to initiate tumor formation when transplanted into non-obese diabetic (NOD)/ SCID mice [26, 27].

Epidermal normal stem cells, as well as tumorigenic cells, are shown to be $CD34^+$ in the chemically induced tumor of the skin (squamous cell carcinomas) in the mouse [28]. Several studies have described markers that differentiate normal and CSCs in the same tissues [29, 30]. For example, CD26 has been demonstrated to be expressed by CSCs and is expressed in several types of cancer but not by normal stem cells. Moreover, its expression correlates with CSCs properties, such as the formation of new tumors, resistance to chemotherapy, and the formation of spheres in vitro [31]. Moreover, $CD34^+/CD38^-/CD13^-/CD33^+/CD90^+/CD123^{-/low}/CD117^+/$ $CD71^+$ phenotype has been described as the main phenotype of normal hematopoietic stem cells [32].

As described before, $CD34^+/CD38^-/Lin^-$ phenotype was the first that was described for leukemic stem cells in AML [33]. However, further studies have shown more complicated phenotype of CSCs. Several other markers, such as CD90, CD71, CD123, CD117, HLA-DR [34], and CD26 for chronic myeloid leukemia (CML) [35], CD33 for AML [36], and CD133 for acute lymphocytic leukemia (ALL) [37] have been suggested as CSC markers.

The presence of cisplatin-resistant cells ($CD133^+$) has been shown in non-small cell lung carcinoma (NSCLC) that also express CXC chemokine receptor (CXCR) 4 [38]. Moreover, several populations of highly quiescent cells that divide slowly have been noted. Treatment with all-trans retinoic acid and cisplatin has been effective on $CD133^+/CXCR4^+$ cells in NSCLC [38].

The expression of CD133 and CXCR4 on CSCs has been evaluated in ovarian cancer cell lines [39]. Several ovarian cancer cell lines, such as OVCAR-3, -4, and -5 and colon cancer cells, SW620 and HCT-116 express both markers.

Table 2 Mechanisms of drug resistance to the current targeted-therapy agents

Name	Trade name	Selective target	Resistant cancers	Mechanism of resistance (examples)
Afatinib	Gilotrif	HER2, EGFR, HER4	NSCLC, squamous cell carcinoma of the head and neck, breast cancer	Overexpression/mutation in targets
Canertinib	ND	EGFR, HER2, HER4	Head and neck, breast, and NSCLC, ovarian cancer	Overexpression/mutation in targets
Cediranib	Recentin	VEGFR	NSCLC, kidney and colorectal cancer	Overexpression/mutation in targets, CSCs
CP-673451	ND	PDGFR	NSCLC, colon carcinomas, glioblastoma	Upregulation of alternative pro-angiogenic signaling pathways, CSCs, overexpression of ABC family
Crizotinib	Xalkori	MET	NSCLC, anaplastic large cell lymphoma, neuroblastoma	Overexpression
Crenolanib	ND	FLT3, PDGFRα/β	AML, gastrointestinal stromal tumor, glioma	Mutation in targets
Cetuximab	Erbitux	EGFR	Head and neck squamous cell carcinoma, MCC	Mutation in targets
Dacomitinib	ND	EGFR	NSCLC, gastric, head and neck/glioma	Overexpression/mutation in targets
Erlotinib	Tarceva	EGFR	NSCLC, pancreatic cancer	Overexpression/mutation in targets, chronopharmacology
Gefitinib	Iressa	EGFR	NSCLC, AML	Overexpression/mutation in targets
Icotinib	Conmana	EGFR	NSCLC	Overexpression/mutation in targets
KW-2449	ND	FLT3	AML	Mutation in targets
Lapatinib	Tykerb	HER-2, EGFR	Breast cancer	Overexpression/mutation in targets, enhanced HER2 dimerization
Lenvatinib	ND	VEGFR2/3	Approved for thyroid cancer in Japan	ABC transporters, CSCs
LY2801653	ND	MET, RON	NSCLC	Activation of compensatory signaling pathways
Neratinib	HKI-272	EGFR, HER2	NSCLC, breast cancer	Overexpression/mutation in targets, enhanced HER2 dimerization
PD-173074	ND	FGFR	NSCLC, gastric carcinoma, breast cancer	Mutation in targets
Quizartinib	ND	FLT3	AML	Mutation in targets
R428 (BGB-324)	ND	AXL	AML, NSCLC, breast cancer	Reduced expression of miR-34a
Tandutinib	ND	FLT3	RCC, CML	Mutation in targets
Tivantinib	Arqule	MET	RCC, breast cancer	MET amplification
trastuzumab	Herceptin (Herclon)	HER2	Breast cancer, gastric adenocarcinoma, gastroesophageal junction adenocarcinoma	Mutations, steric hindrance
Tivozanib	AV-951	VEGFR1, 2, 3	RCC, breast cancer	ABC transporters, CSCs
Vatalanib	ND	VEGFR2	NSCLC, DLBCL, colorectal adenocarcinoma	CSCs
AZD8330	ND	MEK1, 2	Multiple myeloma	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
Binimetinib	ND	MEK1, 2	Metastatic melanoma	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
Bosutinib	Bosulif/SKI-606	SRC, BCR-ABL	Ph$^+$ CML	Mutation in targets

Table 2 (continued)

Name	Trade name	Selective target	Resistant cancers	Mechanism of resistance (examples)
Buparlisib	ND	PI3Kα, β, δ, γ	Multiple myeloma, head and neck cancer, glioblastoma, NSCLC	Activation of compensatory signaling pathways
Cobimetinib	ND	MEK1, 2	Metastatic melanoma	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
Dasatinib	Sprycel	ABL, SRC, cKIT	Ph$^+$ CML and ALL	Fixing the kinase domain in its active configuration
Defactinib	ND	FAK	Malignant pleural mesothelioma, NSCLC, ovarian cancer	ND
E6201	ND	MEK1, 2	Melanoma, fallopian tube, peritoneal cancer	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
Entospletinib	ND	SYK	AML, CLL	ND
Fostamatinib	ND	SYK, P-gp	T, B-cell lymphoma	ND
GNF-5	ND	BCR-ABL	CML	Mutation in target
Ibrutinib	Imbruvica	BTK	CLL, MCL, DLBCL, multiple myeloma	Mutation in target
Idelalisib	Zydelig	PI3Kδ	CLL, indolent NHL, FL, SLL	Upregulation or activation of other PI3K isoforms
Imatinib	Gleevec	SRC, BCR-ABL	ALL, CML, GIST	Mutation in target
Lestaurtinib	CEP-701	JAK2, FLT3, TrkAC, VEGFR2, PKC	AML	Mutation
Momelotinib	ND	JAK1–2	Multiple myeloma, metastatic pancreatic ductal adenocarcinoma, NSCLC	Activation of compensatory signaling pathways
NSC 74859	ND	STAT3	Breast, prostate cancers	ND
NVP-BYL719	ND	PI3Kα	Melanoma, head and neck cancer	Upregulation or activation of other PI3K isoforms
OPB-51602	ND	STAT3	NHL, AML, ALL, CML	ND
OPB-31121	ND	STAT3	Multiple myeloma, Burkitt lymphoma	ND
P505-15	ND	SYK	CLL	ND
Pacritinib	ND	JAK2	AML, refractory CRC, NSCLC, AML	ND
PD0325901	ND	MEK1, 2	NSCLC, CRC, melanoma	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
PF-00562271	ND	FAK	NSCLC, ovarian cancer	ND
Pictilisib	ND	PI3Kα, δ	Prostate, breast cancers, NSCLC	Upregulation or activation of other PI3K isoforms
Pilaralisib	ND	PI3Kα, β, δ, γ	Endometrial carcinoma, breast cancer	Activation of compensatory signaling pathways
Pimasertib	ND	MEK1, 2	Pancreatic, lung, ovarian cancers	BRAF amplification and new BRAF V600E splice isoforms, BRAF-independent MAPK activation
Ponatinib	Iclusig, Ariad	BCR-ABL, SRC	Ph$^+$ CML and ALL, hepatic biliary, small cell lung and thyroid cancers	Mutation in target
Refametinib	ND	MEK1, 2	Hepatocellular carcinoma	Activation of compensatory signaling pathways
Ruxolitinib	Jakafi and Jakavi	JAK1, 2	Breast cancer, CML, AML, NSCLC	Activation of compensatory signaling pathways
Saracatinib	ND	SRC		ND

Table 2 (continued)

Name	Trade name	Selective target	Resistant cancers	Mechanism of resistance (examples)
			CRC, gastric, ovarian, small cell lung and prostate cancers, NSCLC	
Selumetinib	ND	MEK1, 2	NSCLC, DLBCL, AML, melanoma	Activation of compensatory signaling pathways
Tofacitinib	Xeljanz, Jakvinus	JAK1–3	Breast cancer	ND
Trametinib	Mekinist	MEK1, 2	Melanoma, CRC, NSCLC, gastrointestinal cancer	Activation of compensatory signaling pathways
ABT-199	Venetoclax	BCL-2	CLL	Mutations, impairment of apoptosis
Vemurafenib	Zelboraf	BRAF	Melanoma, thyroid cancer, CRC	BRAF amplification and new BRAF V600E splice isoforms 2. BRAF-independent MAPK activation

HER human epidermal receptor, *EGFR* epidermal growth factor receptor, *NSCLC* non-small cells lung carcinoma, *ND* not defined, *VEGFR* vascular endothelial growth factor receptor, *CSCs* cancer stem cells, *PDGFR* platelet-derived growth factor receptor, *ABC* ATP-binding cassette, *FLT3* FMS-like tyrosine kinase 3, *AML* acute myeloid leukemia, *FGFR* fibroblast growth factor receptor, *RCC* renal cell carcinoma, *CML* chronic myeloid leukemia, *DLBCL* diffused large B-cell lymphoma, *MAPK* mitogen-activated protein kinase, *BCR* B-cell receptor, *PI3K* phosphatidylinositol 3-kinase, *ALL* acute lymphoid leukemia, *FAK* focal adhesion kinase, *SYK* spleen tyrosine kinase, *CLL* chronic lymphocytic leukemia, *BTK* Bruton tyrosine kinase, *MCL* mantle cell lymphoma, *NHL* non-Hodgkin's lymphoma, *FL* follicular lymphoma, *SLL* small lymphocytic lymphoma, *GIST* gastrointestinal stromal tumors, *JAK* Janus kinase, *PKC* protein kinase C, *STAT* signal transducers and activators of transcription, *CRC* colorectal carcinoma, *Ph+* Philadelphia chromosome positive

Moreover, octamer-binding transcription factor (OCT) 4, SRY (sex determining region Y)-box (SOX) 2, kruppel-like factor (KLF) 4, and NANOG were highly expressed in CD133^{+}/CXCR4^{+} OVCAR-5 cells, and these cells were determined to be resistant to cisplatin in transplanted nude mice. Moreover, primary ovarian cancer cells have been shown to overexpress the ATP-binding cassette (ABC) sub-family G member (ABCG) 2 drug transporter protein, CXCR4 and CD133, and have been shown to have CSCs properties, including chemoresistance and tumor development [39].

It has been considered that embryonic stem cells (ESC) and CSCs have similar features, and it has been suggested that common molecules such as transcription factors may exist between ESCs and CSCs. SOX2 (SRY-related HMG-box gene 2) was originally described to be associated with the inhibition of neuronal cells differentiation and has been indicated to acts as an essential transcriptional factor to sustain the self-renewal ability of ESCs [40]. OCT4 (OCT3/4) is a member of the POU domain transcription factor family and has been shown to bind SOX2, which is the key regulator necessary for the self-renewal and pluripotency of ESCs [41].

NANGO transcription factor is another molecule that is expressed by CSCs and ESCs. It is a homeodomain protein that sustains the pluripotency of ESCs by preventing nuclear factor-κB (NF-κB) and collaborating with signal transducer and activator of transcription (STAT) 3 transcription factor [42]. It has been indicated that downregulation of these transcription factors decreases the formation of tumor sphere and

prevents tumor establishment in xenograft models [43]. In contrast, overexpression of these factors has been shown to be related with poor tumor prognosis and metastasis in different malignances, including gliomas, prostate and rectal cancers, gastric carcinoma, lung adenocarcinoma, and oral squamous cell carcinoma [44].

CD133 has been also described as a marker of tumorigenic cells in colon and brain tumors [20, 45, 46]. Although some studies have verified these results, however, other reports have suggested that this marker is not a common tumorigenic cells marker [47–49].

The OCT4 is expressed in aggressive human hepatocellular carcinoma and its expression associates with CSC markers [50]. Expression of SRY increased several stem cell factors, such as CD13 and OCT4. It has been shown that the promoter of OCT4 contained SRY-binding sites and was directly activated by SRY. In hepatocellular carcinoma cells, SRY knockdown reduced OCT4 expression and CSCs properties, such as chemoresistance, self-renewal, and tumorigenicity. However, overexpression of OCT4 and SRY has been noted to promote CSC phenotypes [50].

The expression of nestin (class VI intermediate filament) protein was initially detected in neural stem cells during ontogeny. Nestin expression has been reported in several tissues in pathological conditions [51]. It is overexpressed during the transformation of several human cancers, and the expression is correlated with disease progression. The expression of
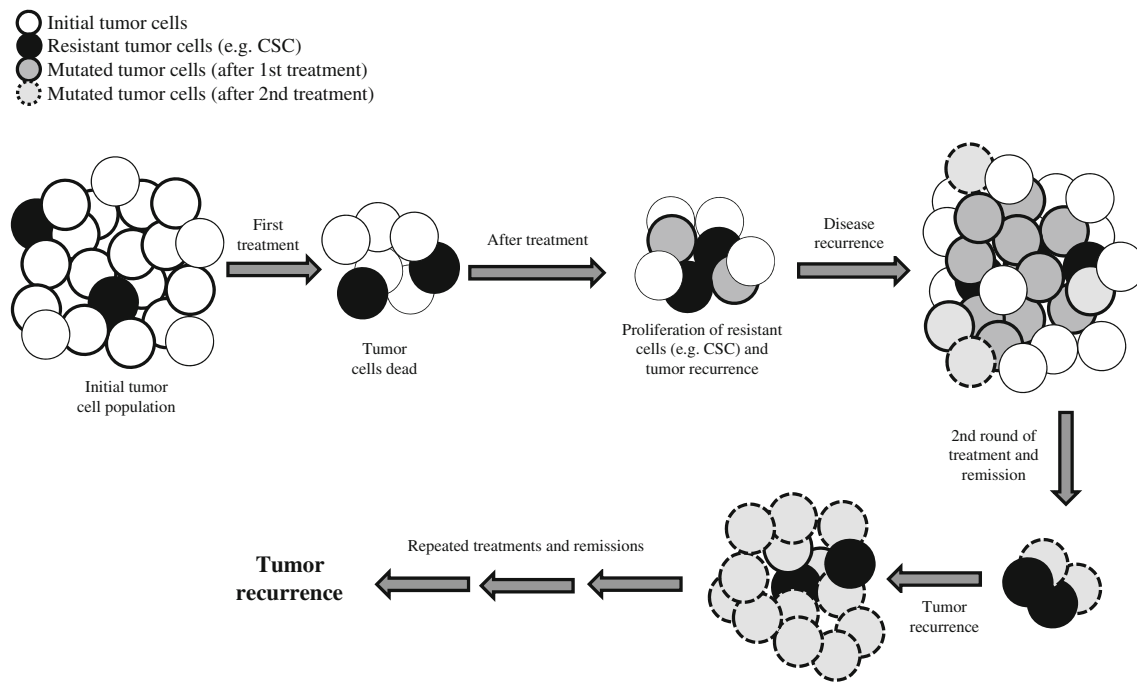
Fig. 1 Schematic cartoon showing the presence of several tumor cells populations. Each round of treatment destroys the sensitive cells; however, mutated cells due to the pressure of treatments as well as cancer stem cells (CSCs) survive and will start to grow in the proper time. CSCs are a minor population and are the main resistant population that will survive after treatments

nestin together with other CSC markers was described to be the phenotype of self-renewing cells in several cancers [51].

It has been shown that neural SCs and glioma SCs express similar markers. Glioma SC markers are nestin^{+}, CD15^{+}, and CD133^{+} [52]. Nestin is expressed during brain development in glioma tissue. It is also expressed in 95.8 % of glioma tumor cells and is correlated with disease prognosis. The expression of the nestin has been noted to be associated with poor disease prognosis in malignant pleural mesothelioma [53]. Therefore, it is mainly expressed in the invasive tumor cells that are located at the peripheral side of tumor rather than tumor center [54].

The surface receptor of hyaluronic acid, CD44, has been suggested as a CSC marker in gastric cancer. Its expression has been described to be associated with disease stage, tumor size, lymph node metastasis, venous invasion, and lymphatic invasion of gastric cancer cells [55].

Overall, while some studies have described similar stem cell phenotype for both normal and CSCs, however, other reports have suggested a few markers that differentiate CSCs from normal stem cells. More investigation is necessary to find specific surface or intracellular molecules (such as transcription factors) to differentiate CSCs from their normal counterparts.

On the other hand, current data strongly support the notion that CSCs might be considered as the major players of drug resistance, both to traditional chemotherapies and current targeted-therapy agents and the specific targeting of these cells might be a great step forward for cancer treatment.

Expression of drug resistance proteins and changes in drug metabolism

Drug metabolism is one of the main reasons for drug resistance. These factors include drug inactivation, absorption, distribution, and excretion. Tumor cell membrane and special membrane-bound proteins are responsible for drug efflux from the cells. Of several transporters, the ABC and the solute carrier (SLC) as well as xenobiotic metabolizing enzyme (XME) families are the most important transmembrane proteins that drive the transportation of many chemicals and drugs across the cell membrane [9]. Most of these proteins eliminate lipids from several kinds of hydrophobic drugs, including alkylating agents (cyclophosphamide, chlorambucil, lomustine, procarbazine), tyrosine kinase inhibitors (TKIs) (moceranib, masitinib, imatinib, genistein), platinum compounds (cisplatin, carboplatin), antimetabolites (gemcitabine, cytarabine, 5-fluorouracil, methotrexate), topoisomerase I and II inhibitors (camptothecins, indenoisoquinoline, mitoxantrone, doxorubicin), and microtubule inhibitors (vincristine, vinblastine, vinorelbine, paclitaxel) [9, 56, 57].

Different phases of drug metabolism in the body can change the efficacy of therapy on tumor cell growth. Several types of intracellular enzymes, such as the (glutathione-S-transferase(, (GST) family, cytochrome P450 (CYP) system, and uridine diphospho-glucuronosyltransferase (UGT) family are involved in drug metabolism inside the cells [58, 59].

Several tumor types or specific populations within a tumor overexpress specific glycoproteins in which they excrete drugs from the cells and in a way, they neutralize the effects of drugs [60, 61].

As described, among different proteins, ABC, SLC, and XME molecules are the major types of drug transporters that induce drug resistance. ABC transporters are divided into three subtypes, including importers, exporters, and those which are involved in DNA repair and translocation process [62, 63].

Currently, more than 49 genes have been detected to encode the members of ABC transporter family, which are categorized into 7 sub-families (A to G). Several studies have described the effects of gene polymorphisms on drug transporters [64] and in ABC transporter family, more than 50 SNPs have been detected [65]. ABC sub-family B member 1 (ABCB1) and sub-family G member 2 (ABCG2), P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance protein 1 (MDR1), and multidrug resistance-associated protein 1 (MRP1) are among the most involved proteins in drug resistance [64]. Polymorphisms may change clinical outcomes through several mechanisms. The effectiveness of ABCB1 or ABCG2 function may increase through the decrease of binding to SMIs. Moreover, transporters with dysfunctions may result in increased toxicity due to changed transport of drugs from normal cells such as bone marrow cells. It has been shown that synonymous SNPs in the ABCB1 change the reaction of the drug with the transporter, due to changes in protein folding [63].

SLC transporter system has 52 families and 362 different genes [66]. Three families are the major players for cancer drug efflux, including the organic anion transporting family the SLC21 (SLCO), the SLC22 (the organic cation/anion/zwitterion transporter family), and the SLC15 (the proton oligopeptide cotransporter family).

XME enzymes are another family of enzymes involved in biotransformation of anti-cancer drugs [60]. Cytochrome P-450 isoform families (18 families with 57 different isozymes), UDP glucuronosyltransferase families (2 families with 16 isozymes) [67], and glutathione S-transferases (6 families with 16 isozymes) [68] are among the most prominent families. Other members of this big family are aldo-keto reductases [69], short chain dehydrogenase or reductase [70], carbonylreductase [71], alcohol dehydrogenase [72], aldehyde dehydrogenase [73], xanthine/aldehyde oxidase [74], nicotinamide adenine dinucleotide phosphate (NADPH)-quinone oxidoreductase [], flavin-containing monooxygenase [75], sulfotransferase [76], arylamine N-acetyltransferase [], and epoxide hydrolase [77]. Activation of these proteins induces drug resistance in tumor cells.

Due to the high number of the members in ABC, SLC, and XME enzymes, these enzymes can specifically be involved in the metabolism and inactivation of a broad range of cancer drugs. For example, resistance to methotrexate in various leukemias has been shown to be due to the decreased influx of this drug that is mediated by the SLC19A1 enzyme, a member of SLC family. Several genetic alterations such as point mutations led to downregulation of SLC19A1 protein expression and decreased the influx of anti-cancer drugs [61].

Extracellular vesicles and drug resistance

Extracellular vesicles (EVs) (such as exosomes and microvesicles) are known as small particles (100–1000 nm) that are surrounded by phospholipid bilayer similar to the cell membrane. These vehicles are important organelles, involved in various intercellular transportations (Fig. 2) [78]. One of the major roles of these microvesicles is disseminating cancer drug resistance to other non-resistant cancer cells. Specifically, these organelles transfer different molecules involved in resistance to other cells by shedding from resistant cells and consequently induce drug resistance to non-resistant cells. Several mediators, such as microRNAs (miRNAs) (miR-100, miR-222, miR-30a, miR-34a, miR-145, miR-485-3p, miR-1228, miR-1246, miR-1308, miR-149, miR-455-3p, miR-638, miR-923, miR-1246, miR-23a, miR-1469, miR-638, miR-1915, miR-2861) and drug efflux pumps (P-gp, ABCG2, MRP1, ABCA3) are transported by these exosomes or microvesicles and when they reached the recipient non-resistant cell, they are fused and internalized by cells via endocytic pathway [78].

In addition to the transfer of drug-resistant phenotype to non-resistant cells, these organelles are directly involved in the removal of cancer drugs from treated cells [79, 80].

For example, doxorubicin and several SMIs have been collected in these vesicles and are shed by tumor cells after treatment [79]. It is suggested that the hydrophobic characteristics of some drugs may enhance their interaction with lipid layer of vesicles and finally result in drug elimination from the cells. Moreover, the presence of several drug transporters in these vesicles, such as ATP7A/B and MRP2, increases the efflux of drugs from cancer cells [78, 80]. The presence of drug-resistant proteins has been shown in several malignancies, such as P-gp in docetaxel-resistant prostate cancer cells [81] and paclitaxel-resistant ovarian cancer cell line [82], MRP1 transporter in ALL [83], ABCG2 in doxorubicin-resistant breast cancer cells [84], and ABCA3 in rituximab-resistant B-cell lymphoma cells [85], which are responsible for induction of drug resistance in these tumors [78].
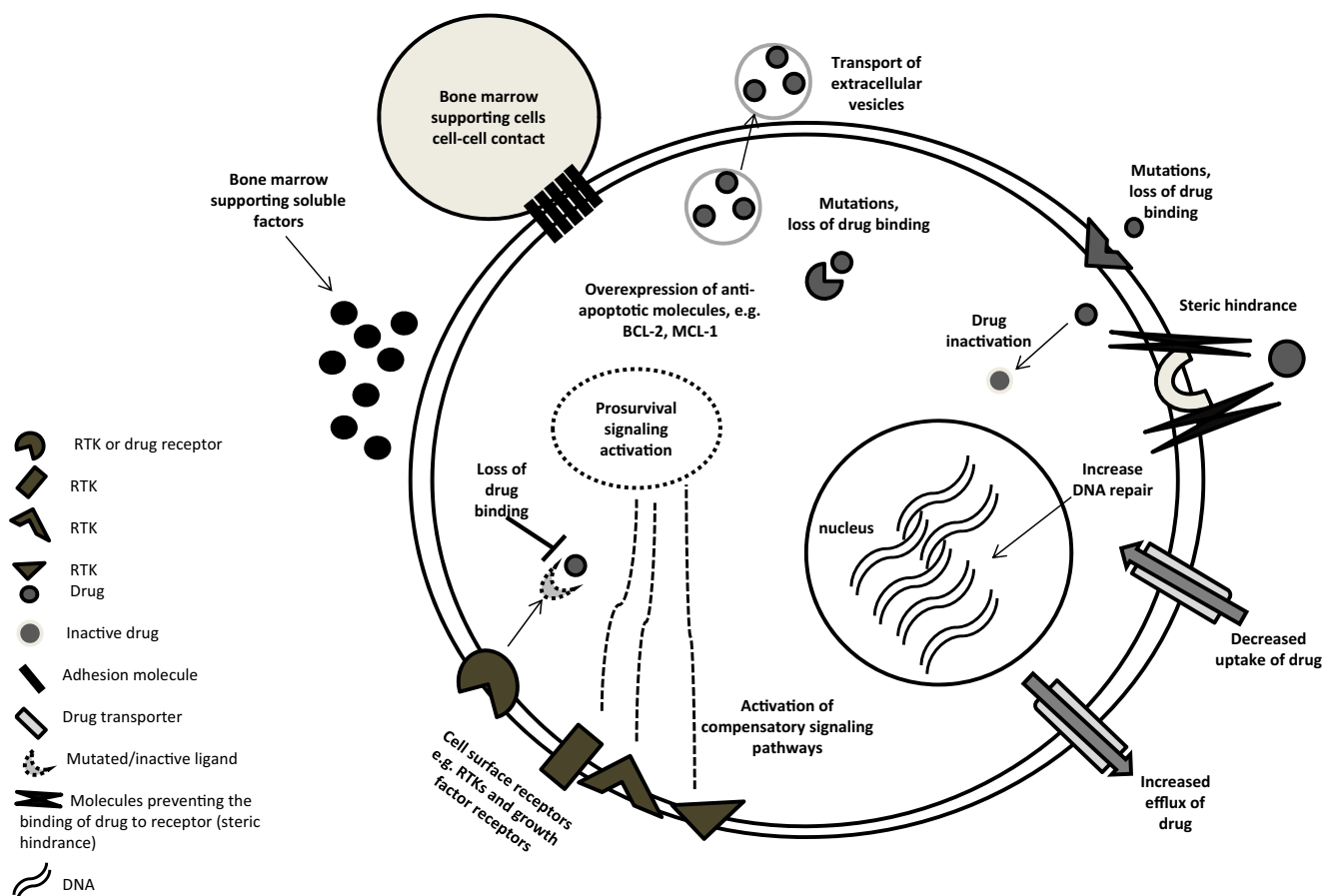
Fig. 2 A summary of various mechanisms of anti-cancer drug resistance. Mutations in drug target, activation of compensatory signaling pathways, increase in DNA repair system, and overexpression of anti-apoptotic proteins are the major mechanisms of resistance

Modified expression of target protein

Several studies have noted the development of resistance to cancer drugs due to over or low expression of target proteins [86].

Post-treatment overexpression of the androgen receptor gene has been described in around 30 % of recurrent prostate cancer patients that were treated by castration; however, untreated prostate cancer patients did not show amplification of androgen receptor [87].

It has been shown that the activity of B-cell receptor (BCR)-ABL is required for development and transformation of CML. Various inhibitors have been produced to target BCR-ABL oncoprotein and have been tested in clinical trials (herbimycin A and 2-phenylaminopyrimidine ST1571). However, later researches showed the development of drug resistance due to overexpression of BCR-ABL oncoprotein [86].

Overexpression of IGF-1R has been shown to reduce the inhibitory effects of trastuzumab on human epidermal receptor (HER) 2-overexpressing breast cancer cells and induce resistance of tumor cells to trastuzumab [88]. Blocking IGF-1 by

IGF-binding protein 3 (that inhibits the activation of IGF-1R) restored the sensitivity of tumor cells to trastuzumab.

Moreover, in patients with lung cancer, amplification of MET oncogene is one of the main mechanisms that lead to acquired resistance to gefitinib and erlotinib [89].

Data show that decrease or increase expression of target proteins by tumor cells, in several cases is associated with tumor cells resistance, especially to targeted-therapy agents.

Dysregulation of apoptosis

Various cancer drugs may induce DNA impairment and induce apoptosis and necrosis of tumor cells following the activation of the downstream apoptosis pathways (Fig. 2). However, apoptosis deregulation of tumor cells has been ascribed as a major hallmark of cancer cells that failed the effects of chemotherapeutic and targeted-therapy agents [90]. The anti-apoptotic property of tumor cells is usually based on the dysregulation (usually overexpression) of a few genes, such as B-cell lymphoma (BCL)-2, myeloid cell leukemia (MCL)-1, and tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL). Overexpression of the anti-apoptotic BCL-

2 protein has been shown to prevent mitochondria-associated apoptosis pathway and prompts resistance to cancer agents [91, 92]. Therefore, targeting upregulated molecules by TBCT agents such as SMIs is an interesting approach to sensitize tumor cells to targeted therapies (e.g., in combination with other treatments). Targeting BCL-2 by SMIs is under intensive investigation, and currently, FDA is evaluating BCL-2 SMI, venetoclax (RG7601, GDC-0199/ABT-199) for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL) patients with 17p deletion.

TRAIL molecule has been known as an important factor in apoptosis pathway and behaves as a ligand that induces the process of apoptosis. Downregulation of TRAIL has been shown to be associated with drug resistance in several malignancies and to overcome drug resistance, induction of TRAIL expression is a proper strategy [93–95]. Currently, three therapeutic strategies have been described for activation of TRAIL pathway, including the administration of TRAIL (recombinant form) (known as Apo2L/AMG951), using activating human anti-death receptor 4 (mapatumumab) or DR5 (lexatumumab) antibodies and delivery of the TRAIL coding sequence in adenoviral (Ad) format into cancer cells (Ad5-TRAIL). These methods are under investigation for inducing apoptosis in tumor cells [56, 96].

Current data on targeting and activating apoptosis-inducing proteins in tumor cells with dysregulated apoptotic proteins are useful, and the combination of these agents with other cytotoxic agents are promising and might confer a higher survival rate for cancer patients.

Repair of DNA damage

DNA damage repair is another mechanism that contributes to induction of cancer drug resistance (Fig. 2). Many chemotherapeutic agents, such as platinum drugs, topoisomerase inhibitors, and alkylating agents, induce DNA damage; however, DNA damage repair machinery of tumor cells effectively influences the effects of DNA-damaging drugs [13].

A proper therapeutic approach is to inhibit DNA damage repair system of malignant cells and thus different agents that inhibit components of the DNA repair machinery have been developed [14]. The most noticeable example of targeting DNA damage repair is inhibitors of the DNA repair enzyme poly-ADP-ribose polymerase (PARP). Several PARP inhibitors have been produced and have shown promising effects. Olaparib induces cell death in cancer cells with mutations in the BRCA1 (breast cancer 1) and BRCA2 (breast cancer 2) tumor suppressor genes. These genes are crucial for repair of DNA double-strand breaks (homologous recombination). Lack of repair of DNA double-strand breaks is usually compensated by single-strand repair mechanisms that are dependent on the function of PARP. Therefore, PARP inhibition

induces cell death due to the genetic instability in dividing tumor cells [56].

The same as targeting anti-apoptosis proteins, the combination of drugs that target DNA repair machinery of tumor cells with other cytotoxic agents may be useful to prevent anti-cancer drug resistance.

Bone marrow microenvironment and drug resistance

Tumor cells located in bone marrow are usually more resistant to cancer drugs than cells in peripheral blood (Fig. 2). Several studies have described that the protection is afforded by secreted chemokines and expression of their ligands, such as CXCL12 and CXCR4 in bone marrow environment and by stromal cells that support tumor cells through cell to cell contacts with tumor cells [97, 98] (Fig. 2).

For instance, inhibition of FMS-like tyrosine kinase-3 (FLT3) by inhibitors (e.g., FI-700) has shown good clinical results in AML patients with FLT3 mutations; however, the bone marrow tumor cell responses are frequently less than the peripheral blood tumor cells. It has been shown by Kojima et al. that protection is mediated via CXCL12/CXCR4 signaling in the bone marrow [99].

To overcome the resistance of AML cells (with FLT3-mutations) to SMIs, a combination of different types of SMIs such as JAK inhibitors with FLT3 inhibitors has been shown to override the effects of bone marrow stromal cell-mediated resistance of AML cells [100].

In addition to bone marrow microenvironment, other factors such as cytokine/chemokine milieu might affect the sensitivity of tumor cells to drugs. For example, exposure to platinum doublets (cisplatin plus vinorelbine) has been described to change the cytokine/chemokine microenvironment and the phenotype of lung tumor cells, rendering them more sensitive to cytotoxic T lymphocyte (CTL)-mediated lysis [101]. It has been noted that exposure to platinum doublets significantly reduced the protein secretion ratio of transforming growth factor-β (TGF-β) to interleukin (IL)-8. Moreover, gene expression studies of two lung tumor cells in response to sublethal chemotherapy has shown the expression of 16 genes, including those related to cytokine/chemokine and apoptotic proteins as tumor necrosis factor-α (TNF-α), CXCL5, IL-8, and B-cell lymphoma-2 (BCL-2) genes. These data may indicate that sublethal doses of cisplatin/vinorelbine enhances the sensitivity of tumor cells to perforin/granzyme-mediated CTL killing thought modulation of tumor cells phenotype, cytokine/chemokine milieu, and the ratio of pro-apoptotic to anti-apoptotic proteins [101].

Steric hindrance and drug resistance

Steric hindrance is another mechanism of drug resistance. It is demonstrated that overexpression of other molecules that

surround the target protein inhibits the interaction of cancer drugs with targeted protein [102]. For example, resistance of tumor cells to trastuzumab has been described to be related to high expression of MUC4 (a membrane-associated glycoprotein) in HER2-overexpressing cells. MUC4 has been shown to bind to HER2 and inhibits binding of trastuzumab to HER2 through steric hindrance [103]. It is suggested that MUC4 may be associated with cancer development due to the ability to inhibit the recognition of tumor cells by the immune system and prompt the metastasis and progression of cancer cells via activation of HER2 and prevention of tumor cell apoptosis [104]. Moreover, the mucinous subunit of MUC4 (ASGP-2) binds to HER2 through the EGF-like region of HER2 [103]. It has been proposed that MUC4 may increase the phosphorylation of HER2 on tyrosine residue 1248 [103], which increase the transforming ability of HER2 [105]. Decreasing the expression of MUC4 gene has been shown to increase the effects of trastuzumab on MUC4 knockdown cells [106]. It is suggested that MUC4 might hide epitopes of HER2 that bind to trastuzumab and inhibits the binding of HER2 to antibody and prevents the heterodimerization of HER2 with other epithelial growth factor receptor (EGFR) members, such as HER3 and EGFR, via steric hindrance that results in resistance of cells to drug [106].

Therefore, downregulation or blocking the expression of molecules involved in steric hindrance might be considered as a proper strategy to overcome this type of resistance in tumor cells.

Acquired resistance

Several factors, including tumor cell heterogeneity, changes in drug targets, mutations after treatments, hyperactivation of prosurvival signaling pathways, up/downregulation of specific microRNAs, crosstalk between survival signaling pathways, and chronopharmacology factors contribute to the development of acquired resistance following tumor treatments (Table 1, Figs. 1 and 2).

Tumor cell heterogeneity after treatment

As described in natural resistance factors, a tumor is typically originated from a normal or non-cancerous cell, which undergoes through several processes that are called tumorigenic transformation. This transition is the result of different mutations in the genome, which converted the origin normal cell to an unusual tumor cell. Moreover, an established tumor is persistent by several subpopulations of cells that are self-renewing (CSC) and can generate tumorigenic cells [107, 108]. The heterogeneity of tumor cells has been described in natural resistance section.

Changes in drug target in tumor cells: methylation and mutations

Qualitative and quantitative modifications in drug targets are critical mechanisms of drug resistance. These changes may be quantitative, such as reduced or lost the expression of the drug target, or may be induced by factors as inhibition of drug binding to the targets by other proteins. These changes contribute to both natural and acquired resistance. Induction of mutation that modifies the structure of drug targets (genetic alteration) is a qualitative factor that may change the affinity of the drugs for their targets. Several types of these mutations have been described in next section.

In addition to genetic alterations, other factors such as epigenetic factors might contribute to drug resistance. Epigenetic modifications usually change the expression of target genes. These alterations mostly comprise of covalent modifications of DNA sequence and histone modifications that change gene expression levels by methylation of gene promoter (at cytosine residues by methyltransferase enzymes in the CpG islands of gene promoter regions) or indirectly by changes in chromatin packaging that regulate the availability of DNA to special transcription factors. These modifications that induce drug resistance are associated with dysregulation of apoptotic factors and DNA repair enzymes as well as abnormal expression of drug efflux transporters [56].

Several studies have shown the association of these changes with drug resistance. In DU145 prostate cancer cells, docetaxel and cabaxitaxel resistance (DU145 10DRCR) has been described to be associated with DNA methylation of cell-cycle regulatory and pro-apoptotic genes [109]. Hypermethylation of CpG island that silences DNA/RNA helicase Schlafen-11 (SLFN11) enzyme has been noted to be related to resistance to chemotherapeutic agents such as platinum compounds [110]. Inhibition of DNA methylation using methylation inhibitor decitabine (5-aza-2′-deoxycytidine or DAC) has been shown to sensitize AML cells to the chemotherapy agent. Decitabine is a DNA hypomethylating agent and induces differentiation and apoptosis of AML leukemic cells to aclacinomycin (ACLA) and cytarabine. Decitabine has described to decrease the expression of DNA methyltransferase 1 (DNMT1) in AML patients [111].

Several types of acquired mutations have been described during the treatment of malignancies (Table 2).

Point mutations are very common and occur in dividing tumor cells and are the most frequent mechanism of acquired TKI resistance [112–114]. The most frequent type of point mutations reduces the affinity of the target for the drug while the enzyme catalytic activity may not change. The changes in the amino acids near the enzyme binding site for the drug are another type of mutations and reduce the accessibility of the target region for the inhibitor binding [115]. Other point mutations increase the affinity of the enzyme for ATP and

decrease the effectiveness of the type I inhibitors (ATP competitors) (Tables 1 and 2).

The best example of acquired resistance, due to mutations, is CML patients, resistant to imatinib TKI that targets BCL-ABL oncoprotein. CML patients constitutively express active BCR-ABL. Imatinib prevents the activity of BCR-ABL by binding to the inactive protein and inhibits autophosphorylation and activation of downstream signaling proteins [116]. However, the majority of patients in advanced or chronic stages develop imatinib resistance [117]. More than 30 % of the relapsed CML patients gain point mutations that are near 100 different point mutations. These mutations change the 3-dimensional structure of the ABL kinase and abrogate the ability of the imatinib to bind the ABL kinase [116, 118]. To target the ABL mutants in imatinib-resistant patients, the second generation of TKIs, such as nilotinib, dasatinib, bosutinib, and sunitinib, were developed [119, 120]. These TKIs recognize a distinct conformation of BCR-ABL and are proper for imatinib-resistant patients. Dasatinib and nilotinib interact with several mutants of ABL (imatinib-resistant); however, these SMIs are not suitable for T315I (threonine to isoleucine substitution at position 315) mutant form that modifies the kinase and different contact points between the SMIs and the protein kinase [121]. KW-2449 inhibitor has been developed to inhibit T315I mutant form [122].

As a multi-targeted TKI, imatinib binds to the cKIT and platelet-derived growth factor receptor (PDGFR). The kinase is highly active in gastrointestinal stromal tumors (GIST) [123]. However, the same as AML patients, more than 50 % of GIST patients have been noted to develop mutation within KIT gene that confers decreased affinity of imatinib to the kinase [124]. To inhibit the activity of the mutants cKIT, sunitinib was produced; however, imatinib-resistant GIST patients developed resistance to this TKI [125].

Activating FLT3 mutations frequently happen in AML. Treatment of AML patients with PKC412 (staurosporine derivative) prevent FLT3 activity; however, several patients developed mutations in the FLT3 kinase region [126].

As previously described, sorafenib (multi-kinase inhibitor) targets vascular endothelial growth factor receptor (VEGFR) 1-2, BRAF, PDGFR, cKIT, and FLT3 [4]. This TKI has shown broad anti-tumoral activity. The combination of sorafenib with other TKIs has induced a variety of point mutations in FLT3 [127], PDGFR [128], and BRAF [129] that confer tumor resistance.

For the treatment of breast cancer patients, lapatinib is a proper TKI and is approved by the FDA as an EGFR inhibitor. It has been developed to suppress phosphorylation and downstream signaling of EGFR and HER2 [130]. Twelve mutations in the kinase region of HER2 have been shown to confer resistance to lapatinib [131]. In contrast to lapatinib, EXEL-7647 is active on all mutant forms.

Other EGFR-TKIs, such as erlotinib and gefitinib, are among the most widely investigated SMIs in NSCLC and were approved by the FDA for the treatment of this cancer. These SMIs are ATP-competitor TKIs and belong to the first generation of selective EGFR-TKIs [4]. These TKIs are used as the front-line targeted therapy for NSCLC patients with EGFR mutations. However, the efficacy of these TKIs is shown to be impeded by different mutations of EGFR members. Mutations that activate the EGFR members, as the deletion in exon 19 and L858R (leucine to arginine substitution at position 858) point mutation, are the most frequent mutations, and patients show good response to these two TKIs that increase the kinase activity of EGFR members [3, 4]. However, T790M missense mutation and insertions in exon 20 are early genetic events that confer resistance to EGFR-TKIs in NSCLCs. It has been shown that T790M-EGFR point mutation increases steric hindrance at the ATP-binding region of EGFR and inhibits the binding of EGFR-TKIs such as gefitinib to EGFR members [3, 4].

Afatinib (irreversible EGFR-TKI) is useful in combination with cetuximab (anti-EGFR mAb) on T790M-EGFR mutants which can overcome acquired resistance induced by reversible EGFR-TKIs. Afatinib plus cetuximab has been indicated to induce significant regression in erlotinib-resistant NSCLC cells with T790M in vitro. Moreover, the combination of afatinib (40 mg/day) plus cetuximab (500 mg/m^2 every 14 days) has shown good effects in a cohort of 22 NSCLC patients with acquired resistance to gefitinib and erlotinib [132]. In a phase I and II cohorts, 100 pretreated EGFR-mutant patients were treated with afatinib in combination with cetuximab. Data showed 38 and 47 % overall response rate (ORR) in T790M mutation positive- and negative-treated patients, respectively, as well as 4.6 months of median progression-free survival (PFS) in spite of confirmed T790M. Currently, other trials, such as ECOG and SWOG, are testing the efficacy of afatinib with or without cetuximab as salvage or first-line treatment for EGFR-mutant patients [133].

Several point mutations in HER2, such as V777L (valine to leucine substitution at position 777), L866M (leucine to methionine substitution at position 866), V842I (valine to isoleucine substitution at position 842), L755S (leucine to serine substitution at position 755), G309A/E (glycine to alanine/glutamic acid substitution at position 309), and S310F (serine to phenylalanine substitution at position 310), have been described in colon and breast cancer cells. These mutations have shown to increase the activity of signaling pathways and cell growth. Several studies have noted that these activating mutations induced resistance to anti-EGFR treatments, such as cetuximab and panitumumab, by increasing mitogen-activated protein kinases (MAPK)/ERK phosphorylation. However, neratinib and afatinib (irreversible EGFR-TKIs) inhibit HER2 mutants in low nanomolar doses [134].

Crizotinib, an ALK-TKI, has showed high efficacy in a subgroup of NSCLC patients with EML4-anaplastic lymphoma kinase (ALK) gene rearrangement [135]. However, most of these patients have developed acquired resistance to crizotinib in 1 to 2 years after treatment. Several mechanisms have been described to be responsible for acquired resistance to crizntinib. Alteration of the *EGFR* gene, EGFR-T790M mutation, *ALK* gene mutations, such as F1174L (phenylalanine to leucine substitution at position 1174), L1196M (leucine to methionine substitution at position 1196), G1202R (glycine to arginine substitution at position 1202), C1156Y (cysteine-to-tyrosine substitution at position 1156), G1269A (glycine to alanine substitution at position 1269), and S1206Y (serine to tyrosine substitution at position 1206), are the main mutations. Other mechanisms are bypass intracellular signaling pathway via fibroblast growth factor receptor-1 (FGFR1), AXL, and MET overexpression [136]. Alectinib (a selective ALK-TKI) has been used for the treatment of crizotinib-resistant patients; however, several treated patients have developed acquired resistance due to two novel ALK mutations (V1180L/valine to leucine substitution at position 1180 and I1171T/isoleucine to threonine substitution at position 1171) [137].

Ibrutinib is a TKI of Bruton tyrosine kinase (BTK) that binds covalently to cysteine 481. This inhibits the SYK and LYN autophosphorylation of the SRC homology (SH) 3 domain and prevents downstream activation of BCR signaling and phospholipase Cγ2 (PLCγ2). However, acquired ibrutinib resistance due to mutations in BTK and PLCγ2 has been described [138]. Recently, a cysteine-to-serine mutation in BTK (C481S) has been shown that converts ibrutinib covalent binding to reversible binding with the lower effect of ibrutinib [138]. Moreover, two mutations in PLCγ2 (R665W/ arginine to tryptophan substitution at position 665 and L845F/ leucine to phenylalanine substitution at position 845) that are gain-of-function mutations have been described to be involved in ibrutinib resistance in CLL patients [138, 139].

Recently, Acalabrutinib or ACP-196 that is an irreversible BTK inhibitor with more selectivity has been designed to decrease the side effects of first-generation BTK inhibitors [140]. The anti-tumor impact of this inhibitor has not been tested in ibrutinib-resistant patients.

Hyperactivation of prosurvival signaling pathways

Hyperactivation of intracellular signaling pathways is an important mechanism of cancer drug resistance. Several pathways including phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR), ERK/MEK, NOTCH, WNT, forkhead box O3 (FOXO3) A, and STAT pathway hyperactivation have been described for several tumors, such as AML and multiple myeloma [141–147].

It has been noted that the inhibition of FLT3 by TKIs would not inhibit the downstream signaling molecules, such as AKT, ERK, S6K, and STAT in sorafenib-resistant AML cells with mutations in the tyrosine kinase domain of the FLT3 [142]. In these cells, it has been described that activation of MEK/ERK or PI3K/AKT pathways in resistant cell lines is the main reason for tolerance to sorafenib. Blocking MEK, AKT, and mTOR by SMIs induced apoptosis of resistant cells to sorafenib [142, 148].

In breast cancer, it has been demonstrated that overexpression of glutathione and activation of WNT signaling pathway are the main reasons for radio-resistance of tumor cells [149]. The synergistic effects of entinostat/lapatinib combination were described to overcome cancer resistance to lapatinib in HER2-overexpressing tumor cells. The promising effects were due to downregulation of AKT/FOXO3 pathway that results in activation of Bim1 (pro-apoptotic protein) [148].

Hyperactivation of NOTCH signaling pathway has been described in breast CSCs. Inhibition of NOTCH signaling has been shown to increase the sensitivity of the cells to cancer drugs [149].

Hyperactivation of other signaling molecules as STAT3 and NF-κB in glioblastoma [141] and WNT/β-catenin signaling pathway have been described in different cancers that are resistant to cancer drugs [143, 144, 150].

MicroRNAs and acquired cancer drugs resistance

miRNAs/miRs are non-coding, single-stranded RNAs that contain 19–22 nucleotides. These short RNAs behave as regulators of signaling pathways and are important key regulators in tumor progression [151].

Several studies have shown links between the altered expression of miRNAs and acquisition of drug resistance [152]. MiRNA deregulation in cancers has been indicated to be involved in defective miRNA biogenesis pathways, deregulation of gene transcription, epigenetic modifications, such as methylation of the CpG islands, induction of mutations, and alteration of DNA copy numbers. One or more factors may contribute to miRNA deregulation in human cancer [153]. These molecules have dual function in cancer drug resistance and overexpression, or downregulation is associated with both sensitivity and resistance to cancer therapeutic drugs.

Drug resistance due to miRNA expression has been described for several malignancies. miR-7, miR-10, miR-15a, and miR-16 have been described to target *MDR1*, homeobox D10 (HOXD10), BCL-2, and cyclin-D1 (CCND1) genes, respectively, and induce resistance to cisplatin, taxol, tamoxifen, and docetaxel in breast cancer [151]. Altered expression of miRNA has been noted to induce chemotherapy resistance by targeting vital signaling molecules, such as phosphatase and tensin homolog (PTEN) and estrogen receptor (ESR) 1 in AKT, K-RAS and MAPK in PI3K/AKT signaling

pathways, and BCL-6 and BCL-2 molecules. Moreover, MDR1 protein, which is involved in drug resistance, has been indicated to be deregulated by the expression of miRNAs. Also, modification of the levels of miRNAs that target zinc finger E-box-binding homeobox (ZEB) 1 and C-MYC molecules (involved in epithelial mesenchymal transition; EMT) have been noted in resistance of breast cancer cells to chemotherapies.

Overexpression of miR-210 was described to be related to the sensitivity of breast cancer cells to trastuzumab in patients with the minimal residual disease compared to patients that have a complete response and in patients with metastasis of tumor cells to lymph nodes [154].

Expression of miR-34a has been indicated to sensitize gefitinib-resistant NSCLC and HCC 827 cell lines [155].

Microarray studies demonstrated that chronic exposure of A549 cell line with gefitinib increases the expression of 25 miRNAs and suppresses the expression of 18 others. This difference in the expression of miRNAs has been noted to be related to a 3-fold increase in IC50 of gefitinib. In this study, the expression of miR-7 has been observed to abolish the overexpression of EGFR and restored the sensitivity of A549 cells to gefitinib [156].

Overall, current studies strongly suggest the critical role of miRNA expression in cancer drug resistance. While some miRNA expression is associated with drug resistance, the expression of several others has been shown to be associated with sensitivity of tumor cells to cancer drugs. Currently, several studies are investigating the role of miRNAs in cancer drug resistance.

Crosstalk between intracellular signaling pathways

Crosstalk between several intracellular signaling pathways is one of the major reasons for acquired resistance to targeted-therapy agents [139]. BCR and receptor tyrosine kinase-like orphan receptor 1 (ROR1) [157–163] signaling pathway cross-communication is an example that has been recently reported [164]. It has been noted that BCR and ROR1 control each other expression in a manner that is vital for tumor cell survival in ALL patients [164]. Downregulation of BCR by the BCR-ABL TKI dasatinib (inhibits the Philadelphia chromosome), as well as inactivation of AKT, inhibition of Igα and Igβ, induced upregulation of ROR1 in leukemic cells. On the other hand, downregulation of both ROR1 and BCR dephosphorylated AKT prevented cell growth and increased cell killing. However, downregulation of ROR1 or BCR did not induce the same effects, suggesting complementary effects. The data also indicated an intracellular link (PI3K/AKT) between the BCR and ROR1 signaling pathways [139, 164].

Crosstalk between RTKs, such as EGFR family members, insulin-like growth factor-I receptor (IGF-1R), VEGFR, and MET, are known to enhance cancer progression and induction

of drug resistance [165]. The anti-HER2 mAb trastuzumab has improved outcomes in HER2-positive breast cancer patients. However, many patients develop resistance within the first year of treatment [166]. Activation of multiple-receptor tyrosine kinase (RTK) signaling pathways has been indicated to contribute to trastuzumab resistance. Similarly, a considerable percentage of lung or colon cancer patients do not respond to anti-EGFR treatments and acquired resistance after primary treatments [167].

Resistance of HER2-overexpressing tumors to trastuzumab has been shown to be associated with signaling from IGF-1R in breast cancer. Crosstalk between IGF-1R and HER2 through physical interaction of IGF1R with phosphorylates HER2 induced acquired resistance in trastuzumab-resistant cells; however, this interaction does not happen in trastuzumab-sensitive tumor cells [102].

Alectinib is a selective ALK-TKI, and several studies have indicated promising efficacy in NSCLC with EML4-ALK gene rearrangement. However, several treated patients have shown acquired resistance to this second generation of ALK-TKI [137]. In addition to point mutations, other mechanisms have been described for acquired resistance. By using alectinib-resistant H3122 NSCLC cell line (H3122-AR) with the EML4-ALK gene rearrangement, it has been described that there is increased phosphorylation level of EGFR in H3122-AR cells compared with H3122 [137]. Increased secretion of transforming growth factor (TGF) α (EGFR ligand) has been shown to be the reason for the hyperactivation of EGFR. Blocking TGFα expression has been indicated to restore the sensitivity of H3122-AR cells to alectinib. Dual targeting of ALK and EGFR by alectinib and afatinib has showed to restore the sensitivity of H3122-AR cells to treatment both in vitro and in a mouse xenograft model [137].

Overall, the complication of tumor cells signaling suggests the requirement of targeting several RTKs for efficient cancer therapeutics.

Chronopharmacology and resistance to targeted therapies

Chronopharmacology is the study of the effects and behavior of therapeutic agents during the biological timing and endogenous factors. The goal of chronopharmacology is to increase the understanding of periodic and predictable changes in the effects and tolerance of drugs in tumor patients (in the field of tumor treatment) [168, 169]. Several studies have described that anti-tumor effect of cancer drugs differs at the time of day of administration, and it might be a clinically important factor in cancer-treated patients that may prevent drug resistance [170].

The impacts of timing on the anti-tumor effects of erlotinib have been investigated in the mouse model of Lewis lung cancer xenografts [170]. Results proposed that anti-tumor efficacy and toxicity of erlotinib on xenografts of NSCLC mice model is

dependent on the time of day of administration. The effects may be associated with the EGFR-AKT/cyclin D1/cyclin-dependent kinase (CDK) 4 signaling pathway and might be a clinically important variable [170]. The association of chronopharmacology factors with cancer drug resistance has not been well studied, and more investigations are necessary to explore the effects for prevention of drug resistance.

Conclusions and future prospective

Current data indicate that most or all patients with cancer develop resistance to different types of treatments, including chemotherapy and targeted-therapy regimens. The resistance to cancer drugs is due to the combination of several complicated factors, including pharmacokinetic and pharmacodynamic mechanisms. These factors that are involved in drug resistance might be due to primary reasons that developed in the absence of drugs or are secondary due to the drug effects. Therefore, a better understanding of tumor cell biology and mechanism of tumor cell resistance to therapies is necessary to define proper strategies and avoid drug resistance. To prevent drug resistance, several strategies, such as targeting various molecules that are expressed by tumors (multiple-targeted therapy) using SMIs and mAbs and combination therapy, such as SMI combination with immunotherapy methods, and targeting CSCs or optimizing the methods of intra-tumoral drug delivery as well as a defined treatment guideline for each cancer, might be necessary to prevent drug resistance and cancer recurrence. CSCs are highly resistant to cancer drugs and very likely cause disease relapse. Specific targeting of these cells is a major obstacle to cancer treatment. Overwhelming this problem in different cancers is important; however, difficult-to-achieve. Moreover, a better understanding of bone marrow microenvironment, mechanisms of overactivation of survival signaling pathways by tumor cells and CSCs, and cell-to-cell interaction of tumor cells with supporting cells are important factors for defeating cancer. On the other hand, current drugs might not be effective in cancer treatment and new modalities with more potential effects on both CSCs and tumor cells are essential.

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