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REVIEW ARTICLE

Hallmarks of cancer drug resistance and overcoming ways: a paradigm

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ABSTRACT

Over 100 types of cancers, affecting humans still remain most fearful disease in the world. To date, a number of anticancer therapies have been introduced. However, resistance in cancer is a running matter. This review focuses to seek out possible pathways of cancer resistance, ways of overcoming resistance and still remaining challenges to be resolved. The ways concerning cancer resistance are: cross resistance, resistance-promoting adaptive responses, tumor microenvironment, drug detoxification and inactivation, decreased drug accumulation, alterations in drug targets, drug efflux and compartmentalization, altered cell cycle events, alteration in apoptosis, autophagy, angiogenesis and proliferation, DNA damage repair, alterations in membrane lipids, resistance mutations, cancer stem cells and epigenetics. Along with host factors, some other factors such as p53, Pgp, MRP family, BCRP, LRP, sphingosine 1-phosphate, glucosylceramide, Bcl-2 family genes and PTEN also have contributions in anticancer drug resistance. MDR, MDR modulators, multifunctional nanoparticles, iRNA interference, targeted therapy, adaptive immunotherapy, or combination therapies are useful to overcome a number of cancer resistance. However, inevitable recurrences, cancer progression and metastasis along with the efficacy, safety, inherited/ acquired drug resistance, incomplete elucidation of anticancer drug resistance and the host factors are still-remained challenges in cancer therapy.

Keywords: cancer; challenges; resistance; overcome.

INTRODUCTION

Cancer is known as a severe health threat. Cancer causes 21% death in developed, while 9.5% in developing countries. Cancer cells have the ability to develop resistance to a number of therapies, including traditional therapies. The word 'resistance' comes when pharmaceutical treatments are not enough to combat diseases. Primary and acquired are the two main type resistances. Primary drug resistance exists prior to any given treatment, while acquiring after initial therapy. Targeted therapies have revolutionized cancer treatment; however, the development of drug resistance within the tumor limits their success in cancer patients.

Resistance becomes more dangerous when the resistant cells dominate the population of the tumor [1]. Cancers targeted to treat with combined drugs, better to be termed as 'multidrug' also undergoing to develop multi-drug resistance (MDR) due to cancer cells are structured and/or functionally different and may have different molecular targets. In intrinsic MDR, cancer cells exhibit resistance to chemotherapy at the initial anticancer drug exposure. On the other hand, acquired MDR develops resistance during the course of the treatment or upon recurrence of the disease after successful chemotherapy [2]. Several host factors are also involved in the development of both types of MDR, including those that impair the delivery of anticancer drugs and nullify their cytotoxic effects, and those that alter the genetic or epigenetic factors, leading to drug insensitivity.

In MDR, resistance to one drug is accompanied by resistance to other drugs having the structures and mechanisms of action similar or even completely different. The term 'MDR' was first applied to antibiotic-resistant infection [3] and now applied to cancer chemotherapy. Historically, the first significant advance of MDR came with the identification of the membrane transporter P-glycoprotein (Pgp), then followed by other transporters of the ATP-binding cassette (ABC) family, which is capable to catalyze the efflux of a range of structurally dissimilar anticancer drugs and helps to protect cells by ejecting a wide variety of toxins. Generally, a rapid resistance originates through multiple non-mutational and

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non-genetic mechanisms [4]. This paper discusses cancer drug resistance, challenges and overcome pathways.

Source of resistant cancer cells

The occurrence of resistant cells is a broad phenomenon. Sometimes, some factors also paly an important role to develop resistant cancer cells, such as hypoxia-inducible factor (HIF), that can cause a progression of renal cell carcinoma and acquired resistance to anti-angiogenic multi-kinase and mechanistic target of rapamycin (mTOR) inhibitors [5]. In general, factors relate genomic and epigenetic alterations, are the major source of resistant cancer cells, as the development of human cancers, a complex multistage process involving an accumulation of both of them [6].During the progress of the tumor, some cells undergo genetic alterations with a superior growth advantage in a given context. Cancer cell selection obeys the Darwinian law of evolution, hence, under therapeutic pressure; those populations that are most adaptive or resistant to treatment will be selected for. If we can treat them properly, others will be treated so [7]. The resistant cell also possesses some favorable characteristics such as a mutated drug binding site [8] and some stochastic alterations within the cancer cells [9]. Cell breathing time is another important factor in the growth and multiplication of resistant cancer cells. Vaccine therapy may broaden the antigenic breadth and induce the immune responses against autologous cancer cells in cancer stem cells (CSCs) [10]. Thus, cells will find more time to augment their population with a greater extent of the resistance.

Drug resistance in cancer

Resistance often follows initial responses to chemotherapy, although combinations of chemotherapeutic agents led to improved survival [11]. Both primary and acquired resistance can be caused by alterations in drug metabolism (sequestrations or enhanced detoxification) or modifications to the drug targets [12]. Resistance involves drug metabolism, including its uptake, efflux, and detoxification. It may result from the mutations that modify the activity or reduce the expression of surface receptors and transporters. A number of cytotoxic anti-cancer drugs need to undergo metabolic activation. Thus, resistance may develop by decreasing drug activation [13] *via* downregulation or mutation to the enzymes involving a metabolic pathway [14]. Furthermore, drug inactivation plays a major role in the development of anticancer drug resistance, through conjugation with reduced glutathione (GSH), which is a powerful anti-oxidant that protects the cells against the damaging effects of reactive oxygen species (ROS) [15].

Many cancer cells have an over reliance or dependency on an oncogene, better to be termed as 'oncogene addiction' [16]. The development of targeted therapies belongs to targeting such oncogenes. However, mutation of the targeted protein(s) may results drug resistance [17]. On the other hand, amplification of alternative oncogenes or inactivation of alternative survival pathways are two causes of drug resistance related to this phenomenon [18]. Thus, targeting of one protein alone is not sufficient due to other parallel pathways may support tumor growth and survival. This may link to a synthetic lethal relationship [19]. Targeting both pathways may be an effective treatment in this type of resistance [20]. It is evident that, mutation rate in cancer cells is higher than in normal (non-tumor) cells. In chronic cancers, as the tumor grows for years before it is treated, have ample time to develop resistant mutations to emerge and get fixed within the population of tumor cells before beginning of treatment. Although, an aggressive treatment may reduce the overall size of the tumor and population size of the tumor cells, but it can cause mutation and develop *de novo* resistance [1]. Primary mechanisms of anticancer drug resistance have been depicted in **Figure 1**.

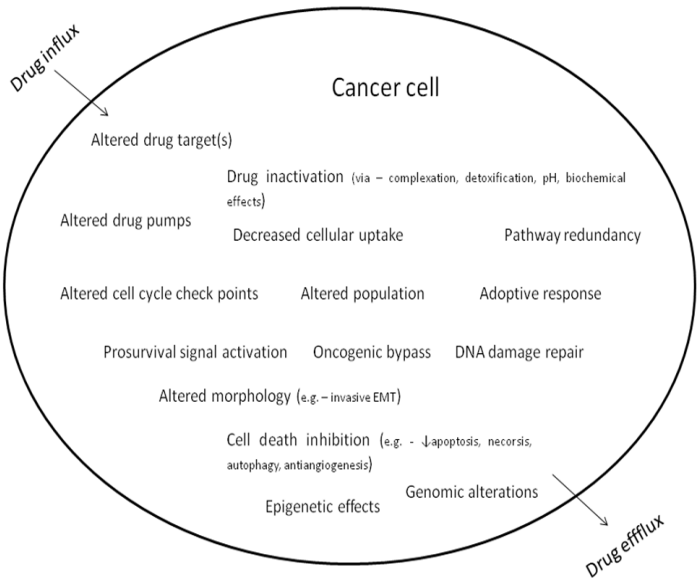

Figure 1. Primary mechanisms include anticancer drug resistance.

Cross resistance

By developing resistance to one drug, a cancer is capable to grow resistant to one or more anticancer drugs [12]. For an example, treatment of

advanced prostate cancer with gonadal testosterone-deprivation leads to the development of castration-resistant prostate cancer (CRPC) [21]. A high degree of cross-resistance was also observed between abiraterone and enzalutamide [22]. Loss of a drug transporter can lead to resistance to structurally diverse compounds [23]. MDR phenotype correlates with poor chemotherapy response to the drugs that are not recognized by transporters, thus evade efflux, efflux inhibitors, as well as drugs that are selectively lethal to Pgp expressing cells, and so on [24].

Resistance-promoting adaptive responses

Activation of prosurvival signalling: Numerous studies have reported for the activation of epidermal growth factor receptor (EGFR) as a resistance mechanism to various chemotherapies [25].

Oncogenic bypass and pathway redundancy: The molecular targeting agents, used to block prosurvival signals and tumor addiction helpful to specific gain-of-function mutations can develop various adaptive resistance mechanisms. For an example, ERBB3 (also known as HER3) and downstream signalling through the PI3K–AKT pathway, an important mechanism of adaptive resistance to EGFR-targeted therapies [26] termed as 'oncogenic bypass or 'kinome reprogramming'. In this case, the primary drug target remains unaltered and continues to be inhibited, but an alternative kinase becomes activated gives an adaptive feedback loop as well as a genetic mutation during treatment; emerging as a major mechanism of resistance.

Epithelial-mesenchymal transition (EMT): The epithelial to mesenchymal transition (EMT) causes solid tumors to metastatic. Epithelial cells from losing polarized organization and tight cell-cell junctions undergo changes in cell shape and develop a fibroblast-like morphology associated with increased motility and invasive capacity. There is a link between chemotherapy and targeted therapy resistance and the EMT phenotype [27]. Furthermore, angiogenesis, responsible to cause formation of new blood vessels around metastatic tumors [28] may result survival and resistance of cancer cells. The signaling processes of differentiation, essential for EMT also cause drug resistance in cancer cells [29].

Tumor microenvironment

Each tumor has a uniuqe microenvironment. For example, ECM, cancer-associated fibroblasts, immune and inflammatory cells and blood vessels are found in solid tumors [30], while bone marrow stromal cells, bone marrow endothelial cells, osteoclasts, osteoblasts, macrophages and T cells in haematological malignancies [31]. The protection provided by the microenvironment provides refuge for cancer cells from cytotoxic agents, thus allowing them to evade apoptosis and to develop acquired resistance.

Integrins: Integrins, the cell surface adhesion molecules that connect the cells with ECM [32]. Higher expression of integrins increases survival and drug resistance in cancer cells [33]. Inhibition of apoptosis and altered drug targets is evident in integrin-mediated adhesion to the ECM [34]. Moreover, they can modulate many signalling pathways, such as PI3K–AKT, ERK and NF-κB pathways that promote cell survival and drug resistance [35], especially to the kinase-targeted agents.

Cytokines and growth factors: The cytokines and growth factors through activation of autocrine, paracrine and endocrine oncogenic signalling play key roles anticancer drug resistance, as they can activate various survival signalling pathways.

Drug detoxification and inactivation

Drugs may show underlying pharmacokinetics due to the malmetabolism in cancer cells Molecules such as gluthathione (GSH), a crucial antioxidant, prevents oxidative stress, and keeps redox homeostasis stable in cells are known to cause conjugation with many drugs [36], which essentially detoxify and/or facilitate excretion of drugs, leading to not only escaping cancer cells but also grow resistance.

During drug activation in a host, it interacts with a number of proteins or enzymes. Driver mutations by making a protein constitutively active, in the presence of drug can modify, partially degrade, or complex the drug with other molecules or proteins, causes activation for other kind of activity. Cancer cells can develop resistance through drug inactivation [37]. Drug inactivation also occurs *via* cytochrome P450 (CYP) system and uridine diphospho-glucuronosyltransferase (UGT) super family [38].

Decreased drug accumulation in cancer cells

ATP-dependent efflux pumps, member of ATP-binding cassette (ABC) transporter family,

expression of them is one of the common consequences in the anticancer drug resistance development [39] *via* decreasing intracellular drug concentrations. A decreased drug uptake causes decrease in drug accumulation in cancer cells. Drugs are transported into the cells *via* several routes such as diffusion across the plasma membrane, loading of the drugs on specific receptors and either receptor mediated or non-specific endocytosis. The problems of these pathways lead to the development of drug resistance in cancer cells [40].

Alterations in drug targets

A drug's efficacy is influenced by its molecular target and alterations of this target. Alteration in the signal transduction process and modified enzyme expression levels can also cause drug resistance in cancer cells [41]. However, resistant cancer cells can produce mutated drug target(s) that retains its activity in the cell without being a target of that drug. Therefore, the target is not inhibited by it. Moreover, gene amplification via genomic instability in cancer cells may cause alterations in drug targets, which is one of the major causes of the development of acquired drug resistance.

Drug efflux

By reducing the drug accumulation through enhancing efflux, cancer cells can develop drug resistance. ATP-binding cassette (ABC) transporter family proteins, multidrug resistance protein 1 (MDR1), multidrug resistance-associated protein 1 (MRP1), and breast cancer resistance protein (BCRP) are known to cause many anticancer drug resistance [42]. The constitutive activation of signaling molecules such as kinases causes the cell cycle out of control and results in cancer. These proteins also regulate Pgp expression and are able to develop drug resistance [43].

Compartmentalization

Sequestration of the drugs in cellular compartments is an important reason to develop anticancer drug resistance. The physicochemical characteristics such as pH partition, generation of an electrical charge, membrane permeability, and so on also results in drug accumulation and anticancer drug resistance [44].

Altered cell cycle events

In cancer cells an uncontrolled cell proliferation arises from the defects throughout the cell cycle progression at G1, G2, S and mitotic phases. Cell cycle checkpoints, including a network of protein kinase signaling pathways, protect the cells from DNA damage induced by chemotherapeutic agents and provide the cells appropriate time to repair the damages [45]. Thus, defects in cell cycle checkpoints can cause not only carcinogenesis, but also drug resistance.

Apoptosis, autophagy, angiogenesis and host factors in drug resistance

Apoptosis is recognized as a unique form of cell death. In necroptosis, a caspase-independent cell death occurs through receptor-interacting protein kinases (RIP1 and RIP3) or mixed lineage kinase domain-like protein (MLKL). Although, its importance in cancer treatment is controversial, but it is evident to develop resistance to an altered apoptosis in cancer cells [46]. The Bcl-2, anti-apoptotic family of proteins elicits a broad cell survival program through promoting cell migration, invasion, and metastasis. In cancer cells, there is a higher expression level of these family proteins [47], which is responsible for the development of anticancer drug resistance [48]. Autophagy is a complex issue because it can play both a pro-death and a pro-survival role [49]. Autophagy can affect the sensitivity of tumor cells to the treatments [50]. In a study, cancer stem-like cells (CSCs) were found to develop resistance against photodynamic therapy (PDT) [51]. In another study, TXNDC17 (thioredoxin domain containing 17)-mediated taxol resistance was evident via enhancing autophagy in colorectal cancer cells [52]. Antiangiogenic therapy can also develop drug resistance, through multiple mechanisms [53], including VEGF and VEGF receptor (VEGF-R), FGF and FGF receptor (FGF-R), and PDGF and PDGF receptor (PDGF-R) pathways. It may select metastatic clones to avoid hypoxia, thus clonal evolution gradually leads to aggressiveness of the cancer situation and develop resistance to treatment. In a recent study, regorafenib was found to progress the malignancy *via* prevention of autocrine and paracrine VEGF signaling in colorectal cancer cells [54].

The 'host' can also play a major role in the development of cancer resistance. The tumor microenvironment is heterogeneous and can help to support a variety of resistance mechanisms. For example, cellular pathways affected by tumor hypoxia, can develop resistance [55]. CSCs by using some mechanisms such as expression of ABC transporters, aldehyde dehydrogenase system, prosurvival proteins altered DNA damage

response and altered signaling pathways can develop resistance [56]. Abdel-Hafiz suggested that CSCs plays an important role in driving metastasis and tamoxifen resistance in breast cancer cells [57].

MDR involving resistance to apoptosis

Suppression of pathways leading to apoptosis is thought to be an intrinsic feature of cancer cells [58]. Conversely, cytotoxic anticancer drugs commonly induce stress pathways such as p38 kinase [59] or suppress signalling pathways such as those coordinated by phosphatidyl-3-phosphate kinase (PI3K) and extracellular-regulated kinase-1 (ERK1) to reactivate pathways to apoptosis leading to pre-existing or acquired MDR, which increases suppression of apoptosis pathways. Inactivating mutations of the gene for p53 protein, activating mutations of the gene for PI3K, loss of expression of PTEN (a phosphatase controlling PI3K activity) and activating mutations of the genes for the RAS/RAF affect the balance of activity of the Bcl-2 family proteins and their relatives [60], which in turn control transition to apoptosis by modulating the stability of the outer mitochondrial membrane. Cytochrome *c* can induce a cascade of caspase enzymes that lead to convert the cell too small fragments, which can be recognized and ingested by nearby phagocytes. Loss of regulation of PI3K leads to increased activity of AKT (PKB), phosphorylation of bad, a member of the Bcl-2 family, results protection of mitochondria from the permeability transition and increased resistance to cell death. Similarly, activating mutations in the RAS or RAF genes lead to activation of the ERK1 enzyme, inactivated by phosphorylation of bid, another member of the Bcl-2 family and protection of mitochondria from the permeability transition. Phosphorylation of Bcl-2, following activation of the NF-jB transcription factor and its downstream target twist-1 by cytokines and other cellular stress, can lead to apoptosis resistance [61]. Induced overexpression of Bcl-2 itself can also provide a mechanism of apoptosis resistance [62].

Altered proliferation

Apoptosis is the normal response to DNA damage that cannot be repaired. But the threshold of death is much higher in cells that are not growing [63]. A part of a transient reduction in cell growth is mediated by p53, as the levels of this protein rise and reduces cell cycle by stimulating apoptosis at a certain threshold [64]. MicroRNAs regulate gene expression at the post-transcriptional level, and are involved in many different biological processes, including cell proliferation, differentiation, metabolism, stress response, and apoptosis. The aberrant expression of microRNAs plays a major pathogenic role in the carcinogenic process. MicroRNAs also play an important role in anticancer drug inducing resistance [65]. Thus, the mechanisms involving altered proliferation of cancer cells are linked to resistance directly or indirectly.

DNA damage repair

Cancers must acquire permanent genomic mutations. Once a mutation is acquired cancers become addicted to a different DNA repair pathway. Therefore, the repair of damaged DNA permits anticancer drug resistance via directly or indirectly reversing damaged DNA, and even DNA damage response (DDR) mechanisms [66].

Alterations in membrane lipids

Cancer cells are different from the differences in lipid profiles from their healthy forms (Leach, 1996). Alterations in membrane lipids are important factors for acquiring resistance and even MDR. Cieślik-Boczula et al stated that the formation of domains with different content of pyrimidine analog (FPh-prm)/dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) can be responsible for the membrane-related mechanism of chemoprevention of pyrimidine analogs [67]. It was also demonstrated that an inhibition of the outward transport of anticancer drugs by the Pgp in cancer cells may be the core mechanism in that case.

p53 in anticancer drug resistance

The protein 53 (p53) is an important transcription factor with tumor suppressor functions [68]. Except, of the stress conditions, cells have inactive p53 protein with a short half-life at low levels. In cellular stressful conditions such as DNA damage, hypoxia, nitric oxide exposure, decrease in ribonucleotides and oncogenic signaling, p53 becomes activated and intracellular levels of p53 proteins are increased [69]. Activation of p53 prevents cellular proliferation *via* arresting cell cycle at G1 or G2 phase or *via* triggering apoptotic signals. In case of any damage of DNA, p53 induces cell cycle arrest and provides the cell an appropriate time needed for repairing the DNA [70]. When the damage is serious that cannot be repaired, p53, in turn, makes the cells undergo apoptosis [68]. Activation and inactivation of p53 is regulated by the phosphorylation, ubiquitinylation, acetylation and interactions with

other proteins [71]. Murine double minute 2 (Mdm2) is the protein that majorly regulates p53 activity *via* protecting it from interacting with the transcription proteins through binding to the transcriptional activation domain of p53, and also *via* providing the ubiquitin ligase-mediated degradation of p53 [72]. To date, abnormalities in p53 function have been reported in more than 60% of cancers [73]. These abnormalities lead to uncontrolled cell proliferation as DNA cannot be repaired and cell cycle cannot be arrested in the cells having mutated p53, leading to development of anticancer drug resistance [74].

Pgp in anticancer drug resistance

Among the ABC transporters involved in MDR, Pgp is the most common efflux pump in the plasma membrane [75]. Structurally, Pgp is a single polypeptide including two homologous parts, each having a hydrophobic transmembrane domain (TMD) and a nucleotide- binding domain (NBD); those are separated by an intracellular linker region. Each TMD consists of six membrane spanning helices. Transmembrane domains are responsible for the specificity of substrate drugs by forming channels, whereas nucleotide-binding domains participate in ATP binding and hydrolysis [76]. Pgp is able to bind a large variety of hydrophobic drugs, especially the conjugated anticancer drugs [77].

MRP family in anticancer drug resistance

Not only Pgp over expression but also MDR associated protein 1 (MRP1/ABCC1) was found to be amplified in anticancer drug resistance [78], as they also pump toxic substances out of the cell in an ATP-dependent manner [79]. The drugs transported by ABCC1 are similar to Pgp substrates (except taxanes). Unlike ABCB1, ABCC1 can also export drugs modified by glycosylation, sulfation and glutathione [80, 81]. The other members of MRP family, MRP2/ABCC2, MRP3/ABCC3, MRP6/ABCC6 and MRP7/ABCC10 have been also evident to develop resistance to anticancer agents [82].

BCRP in anticancer drug resistance

The other ABC transporter involved in MDR is breast cancer resistance protein (BCRP/ABCG2). In contrast to Pgp and MRP1, it contains only one NBD precedes one TMD with six membranes spanning helices [83]. BCRP has a potential role in drug resistance in hematologic malignancies like AML and CML due to its frequent expression on malignant hematopoietic and lymphoid cells [84]. Some BCRP inhibitors, transported out of the cell at low concentrations, at high concentrations are capable to inhibit ABC transporters.

LRP in anticancer drug resistance

Lung resistance related protein or major vault protein (LRP/MVP) is not localized to the cell membrane like MDR1 and MRP1. LRP, found in the cytoplasm is a main component of multimeric vaults and associated with cytoskeletal elements as well as nuclear membrane that help to transport drugs from the nucleus to the cytoplasm *via* vesicular trafficking [79]. LRP can cause anticancer drug resistance in some cancer cells [85]. For an example, Zhang et al stated that LRP-1 as well as MRP-1 were increased in NDRG1 over expressing cells, implying NDRG1-mediated pathways in multidrug resistance of neuroblastoma [86].

Sphingosine 1-phosphate in anticancer drug resistance

Sphingosine 1- phosphate (S1P) is another important factor for developing anticancer drug resistance. Generally, S1P favors proliferation, angiogenesis and cell survival. A shift in the balance toward S1P was seen in glioblastoma (GBM) and other cancers, and resulted in tumor cell survival and resistance to anticancer chemotherapy [87]. Sphingosine kinase-1 (SK1-1), which is responsible for the synthesis of S1P, was reported to decrease the apoptotic effects of anticancer drugs [88].

Glucosylceramide in anticancer drug resistance

Glucosylceramide (GC) is also found to be increased in drug resistant cancer cells [89]. Suppression of glucosylceramide synthase (GCS) activity results in a decrease in MDR1 expression levels, and this reverses anticancer drug resistance [90]. The glycosylation by GCS is a critical step regulating the modulation of cellular activities by controlling ceramide and glycosphingolipids (GSLs). Chemotherapy or other stresses can increase in ceramide, which drives cells to proliferation arrest and apoptosis or autophagy. Furtermore, ceramide glycosylation promptly eliminates ceramide and its induced processes, leads protecting cancer cells. An enhanced ceramide glycosylation can increase GSLs, participating in selecting cancer cells to drug resistance. Ceramide glycosylation by GCS is a rate-limiting step in GSL synthesis, thus inhibition of GCS sensitizes cancer cells to anticancer drugs and eradicates CSCs. If ceramide glycosylation

remains uncontrolled it can modulate gene expression and decrease MDR1 through the cSrc/β-catenin pathway and restoring p53 expression *via* RNA splicing [91]. GCS is also known to de-activate in the regulation of apoptosis progression in a number of cancer cells [92], it may be due to the regulation of apoptosis-related proteins such as Bcl-xL [93].

Bcl-2 family genes in anticancer drug resistance

Bcl-2 is an oncogene, which enhances cancer cell proliferation and suppresses apoptosis. Bcl-2 is evident to express in an uncontrolled manner in various cancer cells. The family of Bcl-2 also comprises the genes encoding proapoptotic Bax, Bad, Bim and antiapoptotic Bcl-xL and Bcl-2 proteins [94]. The presence of CSCs is important in the prevention of therapy failure and tumor recurrence. Upregulation of Nrf2 leads to the overexpression of drug efflux proteins such as ABCG2 in CSCs, resulting in cancer treatment failure and cancer relapse. In cervical CSCs, an aberrant upregulation of Nrf2 along with an elevated transcriptional regulation of ABCG2, Bcl-2 and Bmi-1 was seen, that resulted prolonged cell survival, infinite cell proliferation and highly resistant apoptosis [95].

PTEN in anticancer drug resistance

The phosphatase and tensin homolog, PTEN, is a tumor suppressor which has phosphatase activity, preventing PI3K/Akt signaling pathway, known as an important cancer promoting pathway [96], as it plays a key role in cancer development and maintenance of CSCs [97], thus results development of drug resistant cancer cells.

Resistance mutations

Resistance mutations are of two types (a) mutations that interfere binding of the drug and (b) mutations that make the drug target perform their biological function more efficiently. In the first case, it occurs by altering the active domain of the protein (e.g.- the catalytic domain of an enzyme) directly or indirectly. Direct interference happens by altering residues at the binding site, while indirect interactions modify the dynamics of the protein, such as by destabilizing an inactive state that binds to the drug, and hence efficiency of the whole protein [98].

Epigenetics-mediated cancer drug resistance

The two main types of epigenetic changes are DNA methylation and histone modification *via* acetylation or methylation [99]. Epigenetic mechanisms can also influence DNA damage repair. DNA mismatch repair processes can be lost due to hypermethylation of the human mutL homolog 1 (hMLH1) gene promoter, and this can lead to cancer development [100]. The DNA repair enzyme MGMT inhibits the killing of tumor cells by alkylating chemotherapy agents. Methylation of *MGMT* causes gene silencing and decreased MGMT production. Epigenetic alteration of *MGMT* expression has been associated with a modified chromatin configuration [101].

Cancer stem cell and drug resistance

The cancer cell population is very heterogeneous, as the cells within a tumor are not equivalent, neither structurally nor genetically, which is an obstacle to targeted treatment. Heterogeneous populations have stem cell properties and are usually drug resistant. However, another small fraction of adult cancer cells also possesses drug resistance capabilities [102,103]. The bulk tumor cells lack the capacity for self-renew. Only the CSCs are capable of self reproduction, which are insensitive to chemotherapy and even to radiation therapy. CSCs can reside in a dormant state for a long duration and have metastatic property [104], supporting the three hallmarks of cancer [58] such as evading apoptosis, limitless replicative potential and tissue invasion as well as metastasis. If all cells within a tumor are able to divide and inherit genetic changes to the next generation, there is a strong selection pressure of cancer therapy, thus leading to develop resistance [105]. Source of cancer stem cells and possible control by the tumor microenvironment of them have been shown in **Figure 2**.

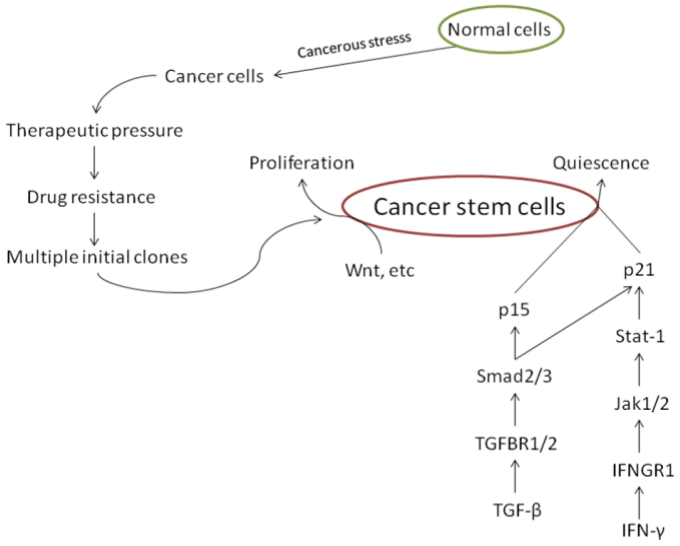

Figure 2. Occurrence of tumor stem cells and hypothetical control by the microenvironment.

Tumour heterogeneity in resistance

Tumor heterogeneity having stem cell property can arise resistance and even MDR in a number of cancer cells. The generation heterogeneity through mutations or epigenetic changes, affect not only cell cycle entry, but also centrosome replication [106], and centrosome defects lead during mitosis to chromosome instability, tetraploidy and aneuploidy. Moreover, microsatellite instability and defective DNA repair can also contribute to a so-called mutator phenotype, while tumor cells may develop large numbers of genetic changes [107].

Drug resistance is a consequence of endogenous defense mechanisms

Drug resistance can be seen as a necessary evolutionary consequence of the body's need to get rid of toxins [108] or xenobiotics. Protection mechanisms involving proteins that pump the drugs out of the cells (e.g.- Pgp), mutation of the target of a particular toxin, and activation of alternate biological pathways instead of the one hit by a toxin. Host defense peptides have been demonstrated to exhibit prominent advantages in cancer therapy that can overcome the limitations of traditional chemotherapy agents, such as toxicity on non-malignant cells and the emergence of drug resistance [109].

Evolutionary ways of overcoming anticancer drug resistance

MDR mechanisms controlling drug efflux from cells

At least, 48 structurally related transporters, known collectively as the ABC family, are known [110], and the three subfamilies concerned with drug transport are the 'B' subfamily that includes Pgp, the 'C' subfamily that includes MRP-related (multi-resistance protein related) transporters and the 'G' subfamily that includes the ABCG2, MXR and ABCP proteins. Some of these transporters act directly on the drug while others act on conjugates concerting with the cellular conjugating enzymes that first link the drug to glutathione, glucuronide or sulphate. Expression of ABCG2 and MRP1 has been reported inside populations of tumor cells lines with some of the characteristics of stem cells [111], consistent with the hypothesis that CSCs commonly express these drug efflux proteins [112]. To overcome this type of resistance, GST inhibitors and substrates for GSH conjugation are used.

Overcoming of transport MDR

There are two main approaches to overcoming transport MDR [80]. The first is to co-administer a drug that inhibits the action of the transporter [113] and the second is to design or utilize anticancer drugs whose activity is not significantly altered by the presence of transporters [114]. First, second and third generation inhibitors are the best choices to overcome this kid to resistance. Drugs that are insensitive to transport resistance mechanisms, requires they should be taken up efficiently into the cells and is relatively resistant to conjugation with glutathione, glucuronide or sulphate. In this way, the rate of uptake rate greatly exceeds the potential rate of transporter-mediated efflux. Cellular uptake of drugs by diffusion is generally controlled by diffusion; lipophilic drugs can enter into the cells rapidly by diffusion. In a recent study, Jin et al suggested that MUC1 has an important role in the induction of drug resistance [23]. Through stimulation of EGFR activation and nuclear translocation, MUC1 increased the expression of ATP-binding cassette transporter B1 (ABCB1). Thus, a targeted suppression of EGFR or ABCB1 may effectively reverse chemoresistance.

MDR involving host immune responses

Interleukins (e.g.- IL-6 and -8) induce senescence of tumor cells [115]. As a consequence of cell turnover, tumor apoptotic is released continuously from the tumor and taken up by tumor macrophages and dendritic cells with a resultant immunosuppressive response [116]. T-cell mediated release of interferon-gamma (IFN-γ) potentially prevent the proliferation of CSCs, and therapy reduces interferon release could allow the continuation and even with stimulation of tumor growth. HMGB1, a high mobility group protein associated with chromatin, and calreticulin [117], a protein associated with the endoplasmic reticulum. Substances that facilitate the production or effects of such proteins can be used to augment responses of tumor cells to anticancer drugs. Release of chemokines within the tumor leads to the recruitment of immature macrophages to tumor tissue, but until they are appropriately activated these may lead cancer resistance to immunotherapy. Adoptive transfer of NK cells may be helpful in cancer therapy, as they have natural cytotoxicity against tumor cells and safety upon adoptive transfer of patients [118]. Partial or complete loss of HLA class I expression is evident in a wide spectrum of human tumor types, which may result from immune selection of escape variants by tumor-specific CD8 T cells, that

generally links to acquired resistance to checkpoint inhibition therapy [119].

MDR modulators

Numerous therapeutic agents, classified as first, second and third generation are MDR modulators. Pgp and LRP-mediated drug resistance is vastly studied in MDR modulatory resistance. Moreover, the membrane transporter proteins ABCG2 (BCRP) and ABCC1 (MRP1) are also involved in the formation of MDR in cancer chemotherapy [120]. Recently, many promising strategies have emerged using natural resources such as plants, fungi, and even marine organisms to overcome MDR. These modulators are low in toxicity and are well tolerated in the human body. One of the approaches to reverse MDR in cancer treatment is the inhibition of Pgp, while LRP-mediated drug resistance could be reversed by a pyrimidine analog.

Multifunctional nanoparticles for targeted chemotherapy

The rapid growth of solid tumor results in the altered physiology of the tumor leads to leaky and defective vasculatures. The increased vascular permeability coupled with impaired lymphatic drainage in the tumor produces an enhanced permeability and retention (EPR) effect, which is often referred to as passive targeting [121]. Targeted nanomedicines can overcome various limitations of conventional chemotherapy; enhance selectivity, early and more precise cancer diagnosis, individualized treatment as well as overcoming drug resistance [122,123].

RNA interference (iRNA) therapy

RNA interference (RNAi) therapeutics (e.g.- siRNA, miRNA, etc.) is going to be a popular medicinal remedy for a variety of ailments, including cancer [124]. iRNA, a biological process in which cells use to inhibit or silence specific gene expression through the destruction of specific messenger RNA (mRNA) molecules triggered by RNA molecules. Typically, iRNA can be achieved through two different pathways: (a) an RNA-based approach where effector small interfering RNA (siRNAs) is delivered to the target cells, and (b) a DNA-based approach in which effective siRNAs are generated by the intracellular processing of RNA hairpin transcripts [125]. However, delivering siRNAs to targeted tumor sites still a challenge. Naked siRNAs can be rapidly degraded by serum ribonucleases and can hardly cross the cell membrane due to their polyanionic nature and relatively large molecular weight [126]. Nanocarriers designed for iRNA therapy can be synthesized from a variety of materials, including polymers (e.g. - biodegradable polymers), metal oxides, carbon nanotubes, and modified nanoparticles (e.g. - lipid-modified dextran nanoparticles) are helpful to manage MDR cancers [127,128].

Combinatorial nanoparticles loaded with both anticancer drugs and MDR modulators/siRNAs

Combinatorial nanoparticles, formulated with both MDR modulators and chemotherapeutic agents, have been used successfully to restore the sensitivity of tumor cells and to enhance the therapeutic efficacy of cancer treatment. Co-administration of anticancer drugs and siRNAs is also another effective strategy to enhance the therapeutic efficacy of cancer treatment [129]. Moreover, a combination of epigenetic drugs with conventional chemotherapy should be more effective in treating tumors and drug resistant cancers.

Miscellaneous

Membrane lipids-mediated MDR can be overcome by using lipophilic cationic agents. Drug resistance, including MDR arisen from p53 function can be overcome by targeting p53 expression, while drug resistance arising from the over expression of GCS can be reversed by inhibiting GCS activity [130]. In order to overcome Bcl-2-related resistance, agents targeting Bcl-2 family members can be used, while resistance arisen by PTEN mutation could be overcome *via* targeting PI3K/Akt signaling, and also *via* increasing intracellular levels of PTEN [131].

Major obstacles to success in reversing clinical MDR

Early termination or clinical failure of MDR modulators are two major problems in mutli-drug therapy in cancer patients. Unexpected and undesired pharmacokinetic interactions between the modulators and the anti-cancer drugs used for the treatment of patients, reduces doses of anticancer drugs, thus the inefficient benefit [132]. The multifactorial nature of MDR is another obstacle, causing inefficient therapy of patients. However, not only ABC transporter but also different other transporters could be responsible for removal of an anticancer drug [133]. Several properties of membrane such as the fluidity and lipid density are also interested in MDR.

However, MDR could be prevented by targeting both pH changes and transporters.

Some challenges yet to resolved related ocancer therapy

Not only anticancer drug resistance, but also inevitable recurrences, cancer progression and metastasis are also still-remained challenging to be solved [134]. The combine efficacy, safety of the healthy cells, convenience and narrow therapeutic index of some drugs are also some potential challenges in the development of anticancer drugs [135]. Doubtless, an inherited/acquired drug resistance is one of the major challenges of the chemotherapy [136]. A complete molecular mechanisms underlying combination or multi-drug treatment is often unclear [137]. Incomplete elucidation of anticancer drug resistance is another important problem [138]. The side effects, toxicity, lack of selectivity and rapid resistance rate of most of the chemotherapeutic agents limiting their use in anticancer treatments [139]. Correction of the host factors, mainly the pathophysiology and related other factors are a great challenge in cancer therapy.

CONCLUSION

Undoubtedly, cancer remains one of the main sources of research in the world. Along with some effective treatments, a number of ways have been identified to cause resistance in cancer, stimulating scientists to search more effective, safer as well as compatible treatment strategies in this fearful disease. Existing problems must be solved before getting others. From this viewpoint, existing challenges are the crucial facts in an effective cancer treatment.

Conflicts of interest

None declared.

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