The mechanisms and challenges of cancer chemotherapy resistance: A current overview

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ABSTRACT

Chemotherapy remains one of the principal modes of treatment for cancer patients. Despite advances in anticancer agents for multiple cancers, development of resistance to classical chemotherapeutic drugs and targeted drugs continues to be a major challenge. Drug resistance which can be either intrinsic or acquired, leads to treatment failure and tumor progression. Drug resistance occurs because of mechanisms that are associated with individual cancer cells or through mechanisms that relate to the microenvironment within tumors. Multiple molecular determinants of intrinsic and acquired resistance including genetic, epigenetic factors, as well as other factors which act at the genomic or cellular level have been identified. This review provides a conspectus on some of the recent discoveries on mechanisms of anticancer drug resistance and the possible ways to revert resistance and thereby improve cancer therapy.

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INTRODUCTION

Cancer continues to be a serious threat to human life and health and also a leading cause of death in humans. Worldwide, 14.1 million new cases and 8.2 million cancer related deaths had been reported. The number of new cases has been estimated to reach 23.6 million by 2030 (**Stewart & Wild, 2019**). For the management of cancer patients, surgery, radiotherapy, cytotoxic chemotherapy, immunotherapy and targeted therapy are commonly employed. Chemotherapy is the first line treatment for hematological malignancies such as leukemia, lymphoma, multiple myeloma, and also for small cell lung cancer. As an auxiliary treatment, chemotherapy is used for other solid tumors to eradicate post-surgical residual nodules to prevent relapse or as pre-local tumor before surgery or radiotherapy. Additionally, in patients who cannot undergo radical surgery, chemotherapy is used as palliative care also (**Holohan et al. 2013**). Despite the development of many classical and newer anticancer chemotherapeutic drugs and targeted drugs, and remarkable success achieved, resistance of malignant cells to anticancer therapies still continues to be a major obstacle in successful treatment of cancer patients.

Anticancer drug resistance involves decrease in the efficacy and potency of a drug to produce therapeutic merits which render the malignant cells, the ability to survive and grow despite anticancer therapy. In the case of malignancies treated with chemotherapeutic drugs, resistance results in lack of response to drug-induced tumor growth inhibition. This often leads to treatment failure. Some cancer patients can become resistant to one specific drug but remain sensitive to other drugs (one drug resistance) whereas some other cancer patients can become resistant to one drug as well as other unrelated drugs (multiple drug resistance). Posing as a major obstacle to successful treatment, anticancer chemotherapy resistance has been reported to account for more than 90 % deaths of cancer patients (**Li et al. 2008; Longley& Johnston, 2005**).

Chemotherapy resistance can develop as a result of a multitude of reasons and is a complex phenomenon. Principal mechanisms of drug resistance include altered target enzyme (e.g. mutated lopoisomerase II), decreased drug activation, increased drug degradation due to altered expression of drug metabolizing enzymes, altered membrane transport involving the P-glycoprotein product of the multidrug resistance (MDR) gene, as well as other associated proteins, drug inactivation due to conjugation with increased glutathione, subcellular redistribution of drug interaction, enhanced DNA repair and failure to apoptose as a result of mutated cell cycle proteins such as P53 etc. (**Luqmani 2005**). In addition to these, few other *in vivo* mechanisms involving epigenetics, microRNAs, cancer stem cells, cell signaling, exosomes, tumor heterogeneity, tumor microenvironment, endoplasmic reticulum etc. have also been implicated as to play critical roles in cancer chemotherapy resistance. These mechanisms fall into several distinct categories and often occur together, which makes attempts to combat them complicated. This review outlines the current knowledge based on new discoveries in chemotherapy resistance mechanisms and possible strategies to improve efficacy for fighting drug resistance in cancer.

Intrinsic and acquired resistance

Based on the time of onset, two types of drug resistance are identified: intrinsic and acquired. Intrinsic resistance is the innate resistance that exists in a subpopulation of heterogeneous cancer cells, before the patient is administered with drugs. This usually leads to reduced efficacy of the exposed

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drug and treatment failure. According to Wang *et al* (2019) (**Wang et al. 2019a)** intrinsic resistance has been attributed to: (1) pre-existing genetic mutations that result in decreased responsiveness of cancer cells to both target drugs as well as other anticancer drugs, (2)selection of pre-existing insensitive subpopulation including cancer stem cells (CSCs) from a heterogeneous population of tumor cells during drug treatment, which further leads to relapse in later stages of therapeutic treatment, (3) use of activated intrinsic pathways as defense against the anticancer therapeutic drugs. Intrinsic resistance as a result of emergence of pre-existing resistant CSC subclones in tumors have been reported in multiple cancer types including glioblastoma (**Eramo et al. 2006**), pancreatic cancer (**Hermann et al. 2007)** and leukemia (**Viale et al. 2009**). Intrinsic resistance has also been attributed to a) drug breakdown b) altered expression and/or function of the drug target c) altered drug transport across the cellular membrane or d) reduced interaction efficiency between the drug and its molecular target (**Mansoori et al. 2017; Sherlach & Roepe 2014, Nikolaou et al. 2018**). Acquired resistance on the other hand, involves resistance induced after the drug treatment which will be manifested by gradual reduction of anticancer efficacy of a drug. Tumors that are not initially resistant to a particular drug, develop resistance and often quickly. This happens due to prevailing selection and overgrowth of drug resistant variant subclones in the tumor (**Liu 2009; Allen & Weiss, 2010**). Acquired resistance involves the influence of genetic or environmental factors that facilitate the development of drug-resistant cancer cell clones or induce mutations of enzymes involved in relevant metabolic pathways (**Mansoori et al. 2017; Nikolaou et al. 2018**). Intratumor heterogeneity as a result of genetic instability (in the form of aneuploidy, deletions, point mutations, chromosomal translocations and gene amplification) epigenetic and few other factors play a key role in the development of acquired resistance. In about 50% of cancer patients, drug resistance occur either by intrinsic or extrinsic mechanisms and is responsible for most relapses of cancer. Either it be intrinsic or extrinsic, drug resistance is a reflex of the result of numerous genetic and epigenetic alterations in malignant cells (**Chen et al.2013; Wang et al. 2012a; Wang et al. 2012b**).

Cell signaling and drug resistance

Many signaling pathways exist inside the cell and these have diversified roles. These pathways are an interconnecting webbing network in the modulation of a complex phenomenon through the cellular signaling Network (**Panda & Biswal 2019**). These signaling pathways play a significant role not only in tumor transformation, metastasis, inhibition of apoptosis and cancer stem cell, but also in cancer drug resistance.

Recently, it has been reported that aberrant activation of one or more of these various signaling pathways like EGFR, Ras, PI3K/Akt, Wnt, Notch, TGF-β, Integrin-ECM signaling play critical roles in drug resistance. The EGFR signaling pathway has been reported to play pleiotropic functions in cell growth, differentiation, adhesion, migration by activation of either Ras/Raf/Mek/Erk or P13k/Akt/mTOR pathways (**Nussinov et al. 2014**). Dysregulation of EGFR signaling has been reported to be involved in the development of different cancers as well as resistance to anticancer drugs (**Panda and Biswal 2019**). Aberrant EGFR signaling (due to mutation or amplification) will lead to activation of either Ras/Raf/Mek/Erk or PI3K/Akt/mTOR pathways. Aberrent activation of Ras/Raf/MAPK signaling or PI3K/Akt/mTOR signaling can lead to development of chemoresistance in various cancers (**Liu et al. 2015**). Likewise, dysregulation of Wnt/B-catenin signaling pathway which results in abnormal expression of Wnt/B-catenin is another cause of cancer drug resistance (**Panda and Biswal 2019**). Besides these, Notch signaling and TGF-B signaling also have been suggested to play important roles in drug resistance in various cancers (**Panda and Biswal 2019**).

Epigenetics in chemotherapy resistance

Epigenetic mechanisms play significant role in human diseases, especially in the initiation and development of cancers. Since epigenetic mechanisms are involved in regulating genes and pathways, epigenetic modifications play crucial role in drug resistance also. DNA methylation and histone modification are the two main types of epigenetic changes that are involved in carcinogenesis. DNA methylation involves binding of methyl groups to cytosines at CG-dinucleotides within regions known as CpG islands, primarily found in upstream promoter regions of genes. Histone modifications alter chromatin conformation either by histone acetylation (which opens the chromatin) or by deacetylation (which closes the chromatin). The expressions of several genes throughout the genome are regulated by these mechanisms. Hypermethylation can silence tumor suppressor genes whereas hypomethylation can result in overexpression of oncogenes (**Housman et al. 2014**). DNA methylation and chromatin remodeling contribute greatly to drug tolerance (**Balch & Nephew 2013**). A series of genes that exhibited promoter hypermethylation in the cisplatin resistant ovarian cancer cells compared to their drug sensitive counterparts were identified by **Zeller et al (2012).** As hypermethylation of gene promoters are associated with transcriptional gene silencing, demethylation of several of these genes were shown to lead to gene reactivation and restore chemosensitivity in cancer cells (**Deaton & Bird, 2011**).

Another study (**Bhatla et al. 2012**) demonstrated that inhibition of histone deacetylation and DNA methylation could result in the preferential activation of methylated and repressed genes in relapsed pediatric acute lymphoblastic leukemia and thus restore drug sensitivity. In a recent study, chemoresistance was reversed in heterogeneous multiple myeloma by targeting of DNA methylation transferases effectors of DNA methylation and histone modification (**Issa et al. 2017**). Many epigenetic drugs such as HDAC inhibitors and DNMT inhibitors that can interfere with tumor progression and overcome drug resistance have been developed.

Demethylation of DNA at the promoter region of an oncogene has been found to upregulate the expression of the gene and thus induce drug resistance (**Wang et al. 2019b**). In a resistant hepatocellular carcinoma (HCC) cell line, **Ohata et al (2017)** demonstrated that a G- actin monomer binding protein thymosin βU (TβU) was enticed through demethylation and histone H3 active modification of the promoter region. This HCC cell line acquired stem cell like capacity due to over expression of TβU which further induced resistance to VEGFR inhibitor sorafenib in vivo (**Ohata et al. 2017**).

In addition to these epigenetic modifications, noncoding RNAs including microRNAs (miRNAs) and long noncoding RNA (lncRNAs) have also been reported (**Chen et al. 2017; Malek et al. 2014**) to play critical role in anticancer drug resistance.

MicroRNAs in chemoresistance

MicroRNAs (miRNAs) constitute a class of small endogenous non-protein-coding RNA molecules approximately 18 – 24 nucleotides in length. miRNAs bind to the untranslated region (3'-UTR) of target messenger RNA (mRNA) and regulate gene expression in the post-transcriptional level by sequence specific targeting of mRNAs, causing mRNA degradation or inhibiting translation (translational repression) of the targeted mRNAS. Through post- transcriptional gene regulation, miRNAs contribute to cellular processes such as development, cell differentiation, cell signaling, regulation of cell cycle, and several metabolic pathways as well as pathological and physiological processes such as disease development, immune response, drug response and carcinogenesis (**Kloosterman & Plasterk 2006; Tutar 2012).** Furthermore, through complex and interactive transcription factor

miRNA regulatory networks, miRNAs regulate a variety of biological processes including cell cycle progression, DNA damage responses and apoptosis, autophagy, epithelial to mesenchymal transition (EMT), cell motility and stemness (**Markopoulos et al. 2017**).

Besides that, further accumulated evidence suggested that impairment of candidate miRNAs could affect the sensitivity of cancer cells to drugs and could lead to acquisition of resistance by cancer cells to conventional chemotherapy and also to novel biological agents. As miRNAs regulate most protein coding genes including genes involved in generation of cancer drug resistance, aberrantly expressed miRNAs play key role in resistance to chemotherapy. Recent studies suggest that chemotherapy response of a patient is accompanied by changes in the expression of specific miRNA. According to **Manossori et al. (2017)** some miRNAs could increase the efficacy of tumors to chemotherapeutic drug whereas some other miRNAs could avoid cancer drug resistance.

In MCF-7 breast cancer cell line, miR-21 was shown to promote doxorubicin /adriamycin (DOX) resistance by downregulating PTEN (**Wang et al. 2011**) whereas in another breast cancer cell line MDA-MB-453, miR-21 conferred trastuzumab resistance via PTEN silencing (**Gong et al. 2011).** On the contrary, miR-137 was found to reduce the resistance of MCF-7 cells to DOX (**Zhu et al. 2013**). Furthermore, miR-149 (**He et al. 2014b**), miR-195 (**Yang et al. 2013**), miR-452 (**Hu et al. 2014**), miR-489 (**Wu et al. 2014**), miR-181a (**Zhu et al. 2013**), miR-320a (**He et al. 2014a**) were found to be inducers of resistance to DOX in breast cancer cells. miR-155 by directly targeting FOX03a and decreasing its expression, was reported to induce resistance to a variety of chemotherapy drugs including DOX, etoposide (VP-16) and PTX (**Kong et al. 2010).** In MCF-7 breast cancer cells, miR-210 overexpression was shown to result in tamoxifen resistance and cell proliferation whereas, miR-17/20 increased tamoxifen sensitivity and reduced DOX resistance (**Egeland et al. 2015**). Upregulation of miR-218 was reported to sensitize MCF-7cells to cisplatin whereas miR-27b which was epigenetically downregulated in tamoxifen resistant breast cancer cells, was found to regulate tamoxifen sensitivity (**Egeland et al. 2015**). Many other miRNAs associated with drug resistance in breast cancer have been identified. microRNAs play a major role in modulating resistance in lung cancer. For lung cancer, CDDP is a first line chemotherapy drug. miRNAs such as miR-let-7c, miR-31, miR-138, miR-182, miR-205, miR-224, miR-106a, miR-15b, miR-27a, miR-513-a-3p, miR-34a, miR- 92b etc were documented to regulate CDDP tolerance of non-small cell lung cancer (NSCLC) by targeting different genes (**Si et al. 2019**). In NSCLC, overexpression of miRNA-134, miRNA-487b, and miRNA-655 were found to promote TGF-β induced EMT and drug resistance to gefitinib (**Kitamura et al. 2014**). MicroRNAs 200, 34a, 21, 221/222, 30b/c, 103, 203, 200b, 20b, 193a-3p and let –7c etc which act as either oncomiRs or tumor suppressors, were also reported to be chemotherapy resistance inducers in lung cancer (**Magee et al. 2015**).

The miRNA-21 which is upregulated in various cancers, also has been documented to play a crucial role in promoting drug resistance of cancer cells. Overexpression of miRNA-21, as a result of amplification of the chromosomal region 17q23-25 was reported result in low expression of PTEN (the target gene of miRNA-21) in ovarian cancer (**Hirata et al. 2014). Raghavan et al. (2014)** demonstrated that overexpression of miRNA-569 was due to 3q26.2 amplification and thereby established a relationship between miRNA, gene amplification and chemotherapy resistance in a subset of ovarian and breast cancers. The expression levels of miRNA-219-2 and miRNA-199b were reported to be associated with the prognosis and treatment effect of imatinib in chronic myeloid leukemia (CML) patients. Researchers observed that decreased expression of miRNA-199b and miRNA-219-2 rendered resistance to the tyrosine kinase inhibitor drug imatinib mesylate in CML patients (**Joshi et al. 2014; Albano et al. 2009).**

In colorectal cancer, the miRNAs 9, 578, 200c, 451, 302a, 125a/b, and 147, were reported to be involved in chemotherapy resistance, either in upregulated and/or down-regulated state. Furthermore, miR-587 caused 5-FU resistance in colorectal cancer. microRNAS including miR-375, 21, 222, 221, 205, 200b, 466, 24, 200b, 30, 3622b, 138 573, 34a etc were reported to be involved in chemotherapy resistance in prostate cancer (**Goto et al. 2015, Ippolito et al. 2016**).

There are other mechanisms also by which miRNAS regulate drug resistance. These include regulation of apoptosis and autophagy, control of anti-cancer drug metabolism, modulation of drug targets and DNA repair, and regulation of GSH biosynthesis (**An et al. 2017**). All these reports clearly indicate the important role of miRNAs in the development of chemotherapy resistance in a variety of malignancies.

Cancer Stem Cells and Resistance

Cancer stem cells (CSCs) are a rare subpopulation of cancer cells that have the driving forces of carcinogenesis by which they self-renew, differentiate into defined progenies and initiate and sustain tumor growth *in vivo*. Localized in a specific microenvironment called niche, CSCs retain the capacity for self-renewal and differentiate into heterogeneous tumor lineage. CSC niche is composed of a variety of cells including fibroblasts, and endothelial, mesenchymal and immune cells that promote CSC survival and enhance their characteristics (**Prieto-Vila et al. 2017**). CSCs are identified from the expression of tumor –type dependent cell surface markers. Signals from CSCs and CSC niche control the transition between CSCs with cancer cells and other non-CSCs. In order to protect from the devastating effects of chemotherapeutic drugs, CSCs appear to manifest several responses such as epithelial-mesenchymal transition (EMT), induction of signaling pathway that regulate self-renewal or influence tumor microenvironments, expression of drug transporters or detoxification proteins etc (**Phi et al. 2018**). Cancer cells acquire a CSC phenotype by the activation of stem-related signaling pathway such as Notch, Hedgebug and Wnt that promote EMT (**Thiery & Sleeman 2006; Yang et al. 2004**).

The tumor microenvironment not only supplies growth-promoting signals that induce the generation and maintenance of CSCs, but also plays active role in therapeutic resistance. CSCs have been reported to harbour a much higher rate of endogenous resistance mechanisms against chemotherapy than non-CSC (**Bao et al. 2006**). Due to their ability to induce cell cycle arrest, CSCs attain quiescent state which supports their ability to become resistant to chemotherapy (**Fang and Kitamura 2018; Singh and Settleman 2010; Cojoc et al. 2015**). The CSC niche secret multiple factors that promote CSC survival plasticity and drug resistance. On the other hand, CSCs also promote the recruitment of niche components and contribute directly to the microenvironment through differentiation (**Eun et al. 2017**). Thus, there appears to be a bidirectional crosstalk between CSCs and their niche.

CSCs contribute to chemoresistance through several mechanisms including epithelial- mesenchymal transition (EMT), multidrug resistance (MDR), dormancy, tumor microenvironment, and so forth. Although EMT activates SC signaling pathways, the molecular mechanisms responsible for EMT and the resulting resistance remain unclear. **Polyak & Weinberg (2009)** reported that EMT induces cancer cells to exhibit stem cell-like characteristics and this promote cells to invade surrounding tissues and display chemotherapy resistance. According to **Shibue et al. (2017)** CSCs rely on the EMT program as a critical regulator in mediating drug resistance. In this regard, the role of few EMT inducing transcriptional factors (EMT-TFs) are important. For examples, EMT-TFs like Twist, Snail, Slug ZEB and FOXC2 were reported to induce drug resistance (**Deng et al. 2016; Lazarova & Bordonaro 2017; Zhou et al. 2015).** Epigenetic mechanisms such as histone modifications, DNA methylation, histone acetylation have also

been reported to be involved in the regulation of CSC mediated drug resistance.

Having similar characteristics such as self-renewal and differentiation, both normal stem cells and CSCs share numbers of key signaling pathways such as Notch signaling, activation of Hedgehog (Hh) signaling to maintain their existence. In order to regulate their self-renewal and differentiation, other signaling pathways including WNT, TGFβ, P1BK/Akt, EGFR, and JAK/STAT and transcriptional relators such as OCTH, Nanog, YAP/TAZ and MyC have also been found to be activated in various CSCs (**Pattabiraman & Weinberg 2014; Tam et al. 2013**). Thus, activation of developmental signaling pathways especially Wnt, Hh and Notch has been implicated to play an important role in the expansion of CSCs and resistance to chemotherapy (**Kurth et al. 2014; Phi et al. 2018**).

There are several examples where activation of signaling pathways such as Wnt /Catenin, Hh, and Notch-1 have been correlated with chemoresistance (**Phi et al. 2018**). Hence, targeting CSCs to combat chemotherapy resistance could be an ultimate goal to overcome the resistance and poor prognosis of cancer patients which could lead to better patient survival. Several studies targeting essential CSC pathways such as Notch, Wnt, Hh are being developed to block the self-renewal of CSCs (**Pattabiraman &Weinberg 2014**).

Increased activation of drug – efflux pumps, enhanced capacity of DNA damage repair, dysregulation of growth and developmental signaling pathways, alterations of cellular metabolism, environmental niche and impaired apoptotic response are the factors attributed to CSCs in cancer chemotherapy resistance. Researches are not only limited to development of inhibitors of CSC pathways and cell surface markers, but also inhibitors related to EMT and CSC microenvironment. Further studies are ongoing to unravel the molecular mechanisms underlying resistance of CSCs and to develop promising strategies to suppress tumor relapse and metastasis.

Tumor heterogeneity

Tumor heterogeneity is considered as another critical reason for treatment failure. In tumors, four levels of heterogeneity are present which are genetic gheterogeneity, cell type geterogeneity (cancer cells, stromal cells, immune cells etc), metabolic heterogeneity in oxygen/nutrient distribution and temporal heterogeneity in dynamic tumor progression (**Chen et al. 2015**). The co-existence of subpopulations of cancer cells with various genetic makeups has been reported in primary tumors like ovarian cancer **(Bashashati et al. 2013**), renal cell carcinoma (**Gerlinger et al. 2012),** breast cancer (**Navin et al. 2010**) and chronic lymphocytic leukemia (**Landau et al. 2013**). These clonal subpopulation with genetic heterogeneity were found to show different sensitivity to chemo or targeted drugs, so that only a portion of tumor could be killed, leaving those less sensitive cancer cells to survive. These surviving resistant clones proliferate and grow resulting in a tumor with different cell composition portions that are insensitive to initial chemotherapy. Studies reporting the loss of drug sensitivity even to targeted drug supports the contribution of tumor heterogeneity to chemoresistance. So, the high specificity, increased efficacy and reduce side effects of targeted drugs are limited when dealing with tumor heterogeneity.

Genetic heterogeneity among patients result in differences in patient's response to the same treatment. Intra-tumor heterogeneity is usually observed at different cancer cells and this could be due to differently factors. Genomic alterations such as mutation deletion, and amplifications of genes, chromosomal rearrangement such as translocation, transposition of genetic elements, epigenetic factors including microRNA alterations etc. generate genomic disability which further results in genetic heterogeneity (**Arora et al. 2013; Kreso et al. 2013; Nathanson et al. 2014; Mansoori et al. 2017).**

Tumor microenvironment and chemotherapy resistance

Tumors do not consists of homogenous cancer cells, but contain various types of cells and extracellular matrix (ECM), all of which together contribute to all aspects of the hall marks of cancer (**Hanahan & Weinberg 2011; Hanahan & Coussens 2012**). Recent research indicates that tumor microenvironment (TME) plays a very important role in anticancer drug resistance. It has also been reported that intratumor extracellular ATP which is a TME molecule, exert profound impact on tumor cells with regard to drug resistance (**Wang et al. 2017; Di Virgilio et al. 2018**). Cancer cells have been documented to have higher ATP levels for survival and drug resistance. The tumor environment is comprised of normal stromal cells (SC), extracellular matrix (ECM) and several soluble factors such as cytokines and growth factors (**Mansoori et al. 2017**). It has been documented that the factors such as tumor-tumor cell communication, tumor-stromal cell communication as well as tumor-ECM interface all play critical role in directing cell interaction mediated by drug resistance **(Li & Dalton, 2006**). Furthermore, cytokines which are growth factors produced in the tumor microenvironment, also provide additional signals for tumor growth and survival (**Mansoori et al. 2017**).

On the cell surface, are present, various cell adhesion molecules which mediate cell to cell and cell-ECM interactions. These cell adhesion molecules have been demonstrated to act as a receptor, which ligates with ECM ligands and initiates signal transduction, regulates survival and drug resistance in cancer cells (**Lee & Juliano 2004; Panda and Biswal 2019**). In the microenvironment of the cancer cell, different ECM proteins such as fibronectin, collagen and laminin are present. Earlier, ligation of integrin with ECM has been suggested to initiate antiapoptosis signal transduction in the presence of antineoplastic drug in small cell lung cancers, glioma and multiple myeloma (**Damiano et al. 1999; Panda & Biswal, 2019**). Recently, integrin has also been suggested to mediate drug resistance to anticancer drugs in breast cancer, small cell lung cancers, prostate cancer and hematological malignancies (**Aoudjit and Vuori 2012**).

Extrinsic factors including pH, hypoxia, paracrine signaling interaction with stromal and other tumor cells also are implicated in drug resistance. All these factors about change, either increase or decrease in gene products that are directly involved in generation of drug resistance. pH is one of the important TME factors. Generally, the extracellular pH (7.3 – 7.5) is lightly higher than intracellular pH (6.8 – 7.2) in normal tissues and cells (**Casey et al. 2010**). On the contrary, cancer cells, through the proton pumping of proton transporters and the modulation of pH sensors, develop a so called "reversed pH gradient" which results in increased intracellular pH and decreased extracellular pH (**Swietach et al. 2014; Sharma et al. 2015**). This acidic extracellular environment (pH 6.5 – 7.1) of cancer cell plays an important role in contributing to development of anticancer drug resistance (**Taylor et al. 2015**). Fluctuating hypoxia, which develops because of the variation and dynamic nature of vasculature inside tumors, is another failure of TME that also contributes to drug resistance (**Reynolds et al. 1996**). Oxidative stress produced due to frequent cycles of hypoxia and reoxygenation induce DNA damages in tumor cells, resulting in genetic instability that often leads to accumulation of additional mutations and emergence of genetically divergent clonal subpopulations.

Dynamic changes of TME in the course of treatment also can lead to development of acquired drug resistance. Cross talk exists between tumor cells and their microenvironment during progression of cancer and development of resistance (**Wang et al. 2019b**). Researchers found that exosomes released by cancer and stromal cells are involved in this cross talk. It has been demonstrated that cancer cells and tumor-associated metaphases (TAM) which use these exosomes (released by cancer cells) carry certain miRNAs to communicate with each other

(**Challagundla et al. 2015**). An example has been shown in cisplalin treated neuroblastoma (NBL) tumor. In NBL, **Challagundla et al. (2015**) demonstrated that cancer cells secrete exosomic miRNA-21 to induce TAMs to produce exosomic miR-155 which in turn silence the TERF1 gene in NBL cells. As TERF1 protein is an inhibitor of telomerase, silencing of TERF1 would result in decreased expression of TERF1 which in turn would result in increased telomerase activity and thereby resistance to chemotherapy. This clearly demonstrated that exchange of exosomic miRNAs between tumor cells and stromal cells in TME could promote drug resistance (**Challagundla et al. 2015; Wang et al. 2019b**).

Exosomes in cancer drug resistance

Exosomes are small liquid bilayered nanomolecules secreted by luminal membrane of the extracellular vesicle bodies (EVBs) which carries various biochemical or genetic information (**Yang et al. 2016**). Exosomes have been implicated as major players in increased survival rate of cancerous cells after chemotherapy. They are flattened hemispherical molecules with a density of 1.13-1.21 g/ml and a diameter of 30 – 100 nm. Exosomes transfer mRNAs, miRNAs, DNAs and proteins and mediate cell to cell communication and cause extrinsic therapy resistance. By distributing proteins that increase anti-apoptotic signaling, DNA repair or by delivering ABC transporters, circulating exosomes transfer therapy resistance to drug sensitive cell (**Bebawy et al. 2009**). Furthermore, exosomes also promote environment- mediated therapy resistance by acting as functional mediators of tumor-stroma interaction and also of epithelial to mesenchymal transition (**Yang et al. 2019; Steinbichler et al. 2019**).

Exosomes have been demonstrated to mediate therapy resistance by direct drug export, intracellular reduction of drugs and by the transport of drug efflux pumps (**Steinbichler et al. 2019**). It has been reported that exosomes can support metastasis and drug resistance in leukemia by encompassing many functional factors with an appropriate sorting signals (**Yang et al. 2019**). Tumor derived exosomes (TEX) have the capability to reprogram stromal and immune cells through their miRNA payloads establishing a non-random metastatic niche for cancer in the tumor microenvironment and beyond (**Chen et al. 2019; Xie et al. 2019**). Exosomal long coding RNAs (lncRNAs) play a major role in the transmission of tumor chemoresistance properties and thereby reduce the efficiency of chemotherapeutic drugs (**Zhao et al. 2019**). IncRNAs are a class of > 200 nucleotides (nt) RNA that have no translational function, and are reported to be associated with chromatin remodeling, transcriptional regulation, post – transcriptional modulation (**Esteller, 2011**). According to **Yoon et al. (2016)** IncRNAs function as competing endogenous RNAs (ceRNA) to sponge miRNAs, thus resulting in the mRNA abnormal expression.

Stromal cell – derived exosomes has been reported to mediate drug resistance in myeloid leukemias and thereby cause treatment failure **(Yang et al. 2019**). CLL plasma – derived exosomes which are enriched with leukemia – associated miRNA signature (including the miR-29 family, miR – 150, miR – 155 and miR – 223) were shown to be associated with drug resistance and poor outcome in CLL patients (**Yeh et al. 2015**). Moreover, Ibrutinib treatment could suppress the exosome level in the plasma of CLL cells. Not only that, by modulating their binding to tumor cells, exosomes could counteract the effect of antibody-based drugs. In myeloid neoplasms also, exosomes have been found to contribute to development of drug resistance (**Jiang et al. 2018**). B – cell Receptor (BCR) was reported to be the key pathway involved in enhanced exosome secretion.

Endoplasmic reticulum and chemoresistance

Endoplasmic reticulum (ER) is an essential site of cellular homeostasis regulation. In maintaining cellular homeostatis, the ER plays significant roles including protein folding protein maturation, and ER quality control (ERQC) (**Yadav et al. 2014**). When normal ERQCM is perturbed, unfolded or misfolded, proteins gets accumulated in the ER lumen and results in a condition called ER stress (ERS) (**Schröder 2008**). The endoplasmic reticulum stress response (ERSR), a pathway which plays a critical in adaptive survival signaling in cancer, has been found to represent an adaptive mechanism that supports survival and chemoresistance in tumor cells. This ERSR is regulated by three ER – resident sensor proteins namely PERK, ATF6 and IRE1a in normal cells (**Dufey et al. 2014**). However, in cancer cells, ERSR is deregulated as a result of activation of oncogenes or depletion of tumor suppressor genes which favors the cancer cells to survive during high protein synthesis and metabolic stress (**Wang & Kaufman, 2014**). It has been reported that ERS – mediated PERK dependent signaling plays a critical role in drug resistance following the initiation of an ERSR (**Bahar et al. 2019**). However, the underlying molecular mechanisms of the relationship between ERSR and anticancer drug resistance still remain unclear.

Cross-resistance

In addition to all the above factors, cross resistance of a particular anticancer drug to another drug having the same target also plays a role in chemoresistance of cancer cells. There are several examples of cross resistance shown by cancer cells. Breast cancer cells showed cross resistance to for chemotherapeutic drugs due to overexpression of antiapoptotic protein BAG3 (**Das et al. 2018**), pancreatic cells that has acquired resistance to gemcitabine showed cross-resistance to 5-fluorouracil (**Yoneyama et al. 2015**), paclitaxel-resistant lung cancer showed cross-resistance to doxorubicin (**Pearce et al. 2018**) colorectal cancer which confers resistance to decitabine, exhibited cross-resistance to gemicitabine (**Hosokawa et al. 2015**), paclitaxel resistant ovarian cancer cell lines showed cross resistance to doxorubicin and vice versa (**Januchowski et al. 2016**), renal cell carcinoma cell showed cross-resistance to other P13K-mTOR inhibitors (**Earwaker et al. 2018**). A recent report (**Lombard et al. 2018**) on advanced prostate cancer showed the existence of both inter and intra-cross-resistance among drugs.

Current Challenges and Future Directions

Identification of drug resistance mechanisms in patients and technical know-how on by passing this resistance still remains a challenge due to high heterogeneity among tumors and high complexity of the resistance mechanisms. Novel targeted drugs such as various tyrosine kinase inhibitors and serine – threonine protein kinase inhibitors originally were developed under the pretext that being molecularly targeted, resistance would not develop. It was presumed that the cancer cells would die rapidly, or cell proliferation would be controlled. Unfortunately, this wishful thinking proved to be incorrect. For example, emergence of resistance to tyrosine kinase inhibitors due to a plethora of mechanisms is commonly observed in patients undergoing treatment with TKIs. A major challenge to the targeted therapy is the recent revelation of (through deep sequencing technologies) high genetic heterogeneity and plasticity of the individual tumors. The widely accepted concept that cancer arises from one single clonogenic cell which accumulates multiple mutations in a stepwise manner, has been shattered as a result of accumulating evidence emerging from a number of whole genome sequencing studies. Due to this genetic heterogeneity, different clones exhibit distinctional mechanisms of resistances. Additionally, fundamental functional and phenotypic differences between cells of the same clone has also been reported (**Cojoc et al. 2015**) which has been explained by the stem cell model of cancer development.

As cancer stem cell niche secretes multiple factors promoting CSC survival, plasticity and drug resistance, targeting these CSC niche

components could be a promising strategy for achieving better treatment outcomes. The challenge remains selective targeting of CSC signaling networks that are essential for self – renewal, proliferation, and differentiation to maintain their stem cell properties. Clinical trials using a combination of conventional treatments which target actively dividing cells, along with adjuvant therapies that specifically target CSCs are being tried. Reducing CSC resistance and sensitizing them to traditional therapies is another strategy being tried. Understanding the mechanisms and oncogenic drivers by which CSCs escape the chemotherapy is yet another challenge. Once these are unraveled, more effective treatments that could improve the clinical outcomes of cancer patients can be developed. Not only targets that inhibit CSCs, pathways and cell surface markers, but also targets that inhibit EMT and CSCs microenvironment also need to be developed. Another point is, there are similarities of some cell surface biomarkers and signaling pathways between CSCs and normal cells. So, development of novel therapeutic agents which target only CSCs is essential to avoid off target effects on non – cancerous cells or normal stem cells. Targeting CSCs with conventional chemotherapeutic drugs is yet another promising strategy for overcoming resistance. Combined therapy which targets both CSCs and most tumor cells could reduce the instrinsic resistance encountered in some cancers.

microRNAs research has opened new avenues in understanding a new molecular mechanism involved in chemotherapy resistance. As microRNAs play very important role in chemotherapy resistance development in a verity of malignancies, modulating microRNAs expression promise to be an ideal strategy to overcome cancer cell resistance. Through miRNA masking and replacement of tumor suppressor miRNA and suppression of oncomiRs, cancerous cells can be regulated, and the target genes involved in drug resistance be suppressed. Targeting miRNAs as therapeutics to guide personalized medicine and use of miRNAs as predictive biomarkers to direct therapies are promising strategies to improve treatment response and outcome. Nevertheless, most of the previous studies on miRNAS have been carried out in *in vitro* cancer cell lines and in animals. So, more attention need to be focused in addressing this issue on non-invasive patient samples such as circulating miRNA in plasma of patients and on *in vivo* and translational studies.

Improved understanding of drug resistance mechanisms is providing more information, especially on the role of various signaling pathways such as EGFR, Ras, P13k/Akt, Wnt, Notch, TGF-B, Integrin – ECM signaling in chemotherapy resistance. Thus, use of a combination of specific signaling pathway inhibitors and a cocktail of chemotherapy drugs might provide a novel strategy to combat the drug resistance and achieve effective treatment, compared to monotherapy.

The acidic tumor microenvironment with low extracellular pH of malignant cells, especially of solid tumors, could be a potential target for cancer therapy. Development of more potential proton pump inhibitors (PPIs) to reduce microenvironment acidity of cancer cells and use them in combination with other anticancers could sensitize cancer cells to chemotherapy drugs, could be a potential approach. For example, Lansoprazole, a PPI when used in combination with paclitaxel has been reported to demonstrate synergistic effects in melanoma cells both *in vitro* and *in vivo* (**Azzarito et al. 2015**). Further understanding of TME and its interaction with tumor cells and targeting/ manipulating TME promises to be a potential approach to enhance chemotherapy response and achieve better clinical outcome. As cancer cells are more rigid in using glucose/energy sources for their survival, blocking the energy supply of tumor cells could be another possible strategy of circumventing resistance.

In the field of exosome mediated drug resistance, isolation of exosome continues to be difficult because of their small nature. There is the need to establish new methods of isolating and identifying exosomes. Furthermore, a nucleic – acid – protein interactome map of exosomes from different cells also need to be established to further our understanding of the role of exosomes in drug resistance. Indepth studies on the role of exosomal IncRNAs in tumor chemoresistance is another potential area of research which might lead to development of biomarkers as novel targets for cancer treatment. In order to improve the effectiveness of conventional chemotherapeutic agents, mimics and for antagonists for each exosomal IncRNA target could be used.

Nano particles, because of their enhanced permeation and retention, neovascular cell targeting and externally triggered drug release properties, have the capability for increased intratumoral accumulation and thus overcome multidrug resistance. Implementation of nanoparticles and utilization of drug – carrying nanoparticles for the delivery of anticancer drugs may greatly increase antitumor effects of cytotoxic agents.

It is quite clear that chemotherapy response and outcome of cancer patients are dependent on multiple redundant and diverse biological processes and molecular mechanisms that modulate the response of cancer cells to anticancer therapeutic drugs. Several factors including genetic and epigenetic events, extracellular signals etc that are involved in activating pathways and which modulate chemotherapy resistance in cancer cells have been identified. Still, more systematic indepth approaches to identifying these mechanisms, synthesis of new drugs and developing strategies to overcome the complex phenomenon of resistance are needed for individualization of treatment and improved response of cancer patients to anticancer therapy.

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