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REVIEW

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Molecular and cellular paradigms of multidrug resistance in cancer

Foram U. Vaidya[1] | Abu Sufiyan Chhipa[1] | Vinita Mishra[1] | Vishal Kumar Gupta[2] | Shiv Govind Rawat[2] | Ajay Kumar[2] | Chandramani Pathak[1]

[1]Cell Biology Laboratory, School of Biological Sciences & Biotechnology, Indian Institute of Advanced Research, Gandhinagar, India

[2]Department of Zoology, Banaras Hindu University, Varanasi, India

Correspondence
Chandramani Pathak, Cell Biology Laboratory, School of Biological Sciences & Biotechnology, Indian Institute of Advanced Research, Koba Institutional Area, Gandhinagar-382426, Gujarat, India.
Email: cmpathak@iiar.res.in, pathakcm@gmail.com

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Abstract

Background: The acquisition of resistance to chemotherapy is a major hurdle in the successful application of cancer therapy. Several anticancer approaches, including chemotherapies, radiotherapy, surgery and targeted therapies are being employed for the treatment of cancer. However, cancer cells reprogram themselves in multiple ways to evade the effect of these therapies, and over a period of time, the drug becomes inactive due to the development of multi-drug resistance (MDR). MDR is a complex phenomenon where malignant cells become insensitive to anticancer drugs and attain the ability to survive even after several exposures of anticancer drugs. In this review, we have discussed the molecular and cellular paradigms of multidrug resistance in cancer.

Recent Findings: An Extensive research in cancer biology revealed that drug resistance in cancer is the result of perpetuated intracellular and extracellular mechanisms such as drug efflux, drug inactivation, drug target alteration, oncogenic mutations, altered DNA damage repair mechanism, inhibition of programmed cell death signaling, metabolic reprogramming, epithelial mesenchymal transition (EMT), inherent cell heterogeneity, epigenetic changes, redox imbalance, or any combination of these mechanisms. An inevitable cross-link between inflammation and drug resistance has been discussed. This review provided insight molecular mechanism to understand the vulnerabilities of cancer cells to develop drug resistance.

Conclusion: MDR is an outcome of interplays between multiple intricate pathways responsible for the inactivation of drug and development of resistance. MDR is a major obstacle in regimens of successful application of anti-cancer therapy. An improved understanding of the molecular mechanism of multi drug resistance and cellular reprogramming can provide a promising opportunity to combat drug resistance in cancer and intensify anti-cancer therapy for the upcoming future.

KEYWORDS

Multi drug resistance and cancer, Tumor microenvironment, Cellular reprogramming, Cancer metabolism, Programmed cell death, Inflammation

1 | INTRODUCTION

Cancer is the second leading cause of death and it is a socio-economic problem worldwide.[1] In the current scenario, incidences and mortality rates of cancer are increasing gradually. The advancements in cancer therapies, including chemotherapy, surgery, radiation therapy, precise anticancer therapy, immunotherapy, and targeted therapy are still challenging and not satisfactory. In clinical practices, chemotherapy and surgery are most often therapy offered against cancer, but cancer cells become chemo resistant over a short span of treatment with anticancer drugs. The acquisition of resistance to chemotherapy is a major obstacle in successful application of anti-cancer therapy. It is well accepted that chemotherapy has adverse side effects such as systemic toxicities, immune surveillance and drug resistance. The majority of chemotherapeutic drugs approved by the FDA having lower molecular weight and require a higher concentration for their pharmacological actions. Many anti-cancer drugs act indiscriminately adjacent to cancerous and healthy cells.[2-4] Many types of cancers show susceptibility toward chemotherapy at initial stage, but after some time start developing resistance because of multiple intrinsic and extrinsic factors such as cellular reprogramming, oncogenic stimulation, drug efflux due to over expression of multi-drug resistance (MDR) genes and metabolic changes that promote drug inactivation and inhibition, altered DNA damage repair mechanism, evasion of programmed cell death, epithelial mesenchymal transition (EMT), inherent cell heterogeneity, epigenetic changes, metabolic reprogramming or any combination of these mechanisms. [5] The immune surveillance also may impair due to the unpredictable cell death escape strategies acquired by cancer cells.[6] Moreover, the link between cancer and oxidative stress has been extensively studied, which denotes the significant involvement of ROS in the progression of cancer. [7] In addition, the imbalance in redox homeostasis is also behaving as a critical factor in the development of drug resistance in cancer. The oxidative stress plays crucial role in cell survival and therefore, it may confers drug resistance in cancer. [8]

Resistance could be restricted to the drug which was used to treat the patient (single-agent resistance) or execute simultaneous failure against structurally and functionally different anti-cancer drugs (Multi drug resistance, MDR).[9] Resistance against multiple drugs during cancer therapy has been a “clinician's nightmare,” owing to its capacity to subvert the desired drug response in cancer patients. Therefore, a regimen of cancer therapy is particularly challenged to deal with drug resistance. In this review, we have attempted to shed light on various mechanisms of drug resistance, those were adopted by cancer cells to ensure for their survival.

2 | TYPES OF DRUG RESISTANCE

The drug resistance can be categorized as intrinsic or acquired resistance. Intrinsic resistance is the innate resistance, which exists prior to the treatment of chemotherapeutic drug.[10] Intrinsic resistance may be acquired by different mechanisms including (a) inherent genetic mutations in the tumor cells, (b) development of resistant population such as cancer stem cells in heterogeneous tumors, and (c) commencement of intrinsic pathways that are responsible for the detoxification under normal physiological conditions. On the other hand, acquired resistance can develop after receving anti-cancer therapy.

Acquired resistance can be an outcome of various cellular and molecular responses including: (a) activation of second proto-oncogene after treatment; Cancer cells can acquire resistance against targeted drugs by the generation of new mutation or alteration in the expression; (b) alterations in drug targets; (c) Drug metabolisms in the tumor; (d) efflux of drugs by transmembrane transporters (ATP binding cassettes, ABCs transporters); (e) Epigenomic alteration due to acetylation, methylation and altered level of microRNAs which creates changes in the downstream or upstream receptors; (f) changes in the tumor microenvironment (TME) after treatment.[10] All these mechanisms of drug resistance can act independently or in combination to favor multidrug resistance in cancer.

Here, we have briefly described the cellular and molecular events, which are majorly involved in the development of drug resistance in cancer (Figure 1).

3 | MECHANISMS OF DRUG RESISTANCE

3.1 | Drug efflux by the ATP binding cassette (ABC) transporter family

A major factor that governs drug resistance in cancer is the overexpression of ABC transporter proteins that efflux many structurally and functionally distinct substrates via cell membrane by utilizing ATP hydrolysis.[11] These drug efflux transporters decrease the intracellular drug concentration and impede the drug response, which limits successful application of chemotherapy.[12] The current literature revealed that there are 48 ABC transporters have been identified in humans.[13] Many of them are involved in normal tissue protection and mainly expressed in the kidney, pancreas, liver, gastrointestinal (GI) tract, and the endothelium vessels of the testes and brain.[14] 13 different types of ABC transporters have been identified those are directly or indirectly involved in multiple drug resistance in cancer. In the recent past, major transporters such as ABCB1 (Permeability glycoprotein /MDR1), ABCC1 (multidrug resistance associated protein-1, MRP1) and ABCG2 (breast cancer resistance protein (BCRP) are extensively studied for exploring the mechanism of MDR.[15] Physiologically, ABCs transporters have function to remove the xenobiotics and toxic endogenous substances from the cells and organs to maintain their interstitium homeostasis. Cancer cells employ these membrane bound transporters system to acquire drug resistance.[16] The basic domain structures of ABCB1, ABCC1 and ABCG 2 are shown in Figure 2. Sequences and their domain information were retrieved from Uniprot Database[17] and domains were created with Illustrator of Biological Sequences (IBS).[18]

The mechanisms of these ABC transporters are significantly governed by ATP. Drug resistant cancer cells are known to maintain

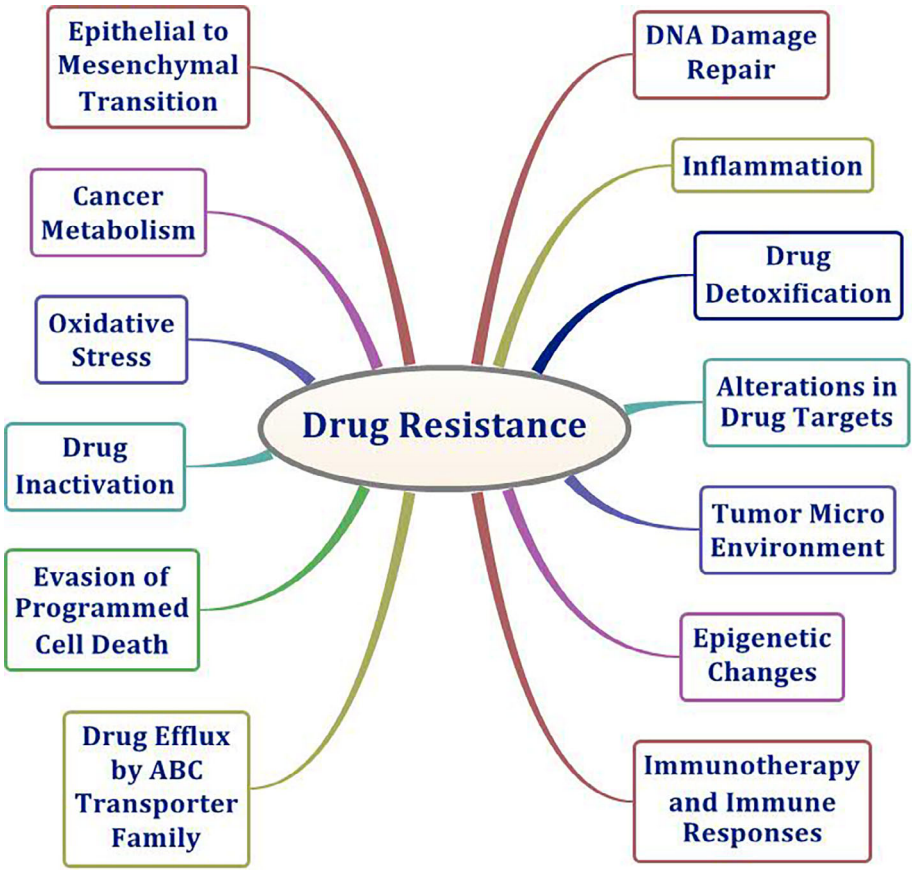

FIGURE 1 Cellular and molecular events involved in the development of drug resistance in cancer

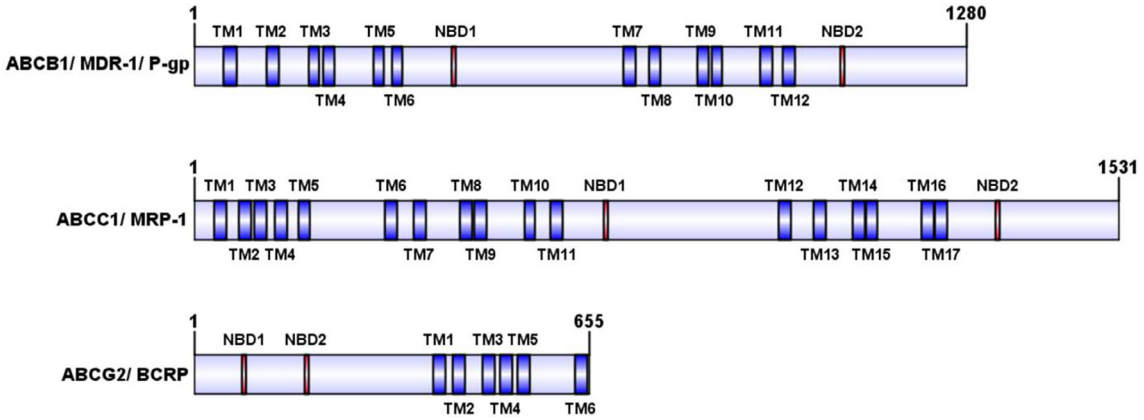

FIGURE 2 Domain structural organization of ABCB1, ABCC1, and ABCG2. Sequences and their domain information were retrieved from Uniprot Database and domains were created with Illustrator of Biological Sequences (IBS). TM, Transmembrane region; NBD, Nucleotide Binding Domain

comparatively higher ATP levels than their parental cancer cells.[19] Depletion of ATP inside the cancer cells significantly sensitizes them to chemotherapy. Conversely, higher intracellular concentrations of ATP transform the sensitive cells to drug resistant.[20] Moreover, the extracellular ATP also enhances the expression of ABC transporters, causing an increased rate of drug efflux.[21] The concentration of extracellular ATP promotes TME.[5] This increased ATP in the extracellular space of the cancer cells get internalized through a process termed as "macropinocytosis." As a result, the remarkable increase in intracellular ATP concentration causes resistance against multiple chemotherapeutic drugs.[22] The major transporters involved in the efflux of the chemotherapeutic drugs are outlined below:

3.1.1 | Permeability glycoprotein (P-gp)/MDR-1

P-glycoprotein is a conserved, high molecular weight plasma membrane glycoprotein and first discovered human ABC transporter

(encoded by the ABCB1 [adenosine Triphosphate binding cassette, subfamily B, member 1] gene). The ABCB1 gene is located on chromosome 7 in humans, which comprises 1280 amino acids and consisting molecular weight of ~ 170 kDa.[23] It has a transmembrane domain (TMD) and nucleotide-binding domain (NBD). P-gp holds two homologous halves each with 6 membrane-spanning helices, and nucleotide binding domain which is present in the cytosol. The protein comprises of a large flexible drug binding cavity embedded within the membrane-bound domain. This pocket contains several sub-sites where the drug can bind through different sets of interactions. Binding of ATP at the NBDs, and subsequent ATP hydrolysis leads to conformational changes in TMDs, results in switching the conformation of transporter from inward to outward of the cells for unidirectional transport.[24] The substrates of P-gp are usually lipid-soluble protein, which interacts with the membrane protein before either being pumped out into the extracellular aqueous phase or moved to the extracellular membrane leaflet. The basal expression of P-gp has been found in several normal tissues, such as liver, intestine, kidney, testes, placenta, and blood brain barrier to provide protection against xenobiotics and toxic substances.[25] The P-gp transporters are the most commonly summoned transporter proteins and they play a critical role in the development of drug resistance in cancer cells. Several biochemical changes are associated with multidrug resistant cancer cells, where overexpression of P-gp is the most common phenomenon in many types of cancers. P-gp holds the central position in multidrug resistant cells by diminishing the intracellular accumulation of chemotherapeutic agents.[26,27] The P-gp plays a vital role in the intestinal transport and efflux, which alters the bioavailability and pharmaceutical effects of orally administered pharmaceutical drugs. In recent past compiling evidence revealed that overexpression of P-gp is associated with the development of MDR phenomenon in cancer.[26] P-gp displays broad substrate specificity; therefore, P-gp overexpressed cells execute cross resistance against multiple cytotoxic drugs, and help to develop multidrug resistance (MDR) in cancer cells. Initially, it was believed that efflux pumps are responsible for inhibiting the intake of conventional genotoxic anticancer drugs such as vinblastine, paclitaxel, and doxorubicin, but, burgeoning reports on P-gp revealed its influence on around 300 compounds including the newly added "kinase inhibitors" in the list. [28] The P-gp expression is one of the primary defensive mechanisms adopted by the cancer cells upon exposure to a cytotoxic agent. Moreover, the frequent confrontations of cancer cells with chemotherapeutic agents subsequently induce the expression of P-gp to efflux and deplete the intracellular drug concentrations.[26] Besides this, the altered cellular signaling of cancer tends to fabricate a favorable environment for P-gp expression. Tumor hypoxia, Warburg effect and acidosis in TME collectively impose a remarkable advantage to upregulate P-gp expression in cancer cells for subverting the drug action.[28] Further, oncogenic stimulation, epigenetic alterations and aberrant cell death signaling simultaneously activate the expression of different genes, which promotes cancer cells to acquire drug resistance. A previous report also suggests that MDR cells hold P-gp expression in the nuclear and mitochondrial membrane to efflux of anticancer drugs from nuclei and mitochondria to the cytosol for accelerating multidrug resistance in cancer.[29]

3.1.2 | Multidrug resistance protein (MRPs/ABCC1)

Multidrug resistance protein (MRPs/ABCC1) comprises of three hydrophobic TMD containing 17 membrane spanning helices, two NBD and an extra N-terminal domain having molecular weight ~190 kDa.[30] Similar to P-gp, MRP1 also belongs to the family of ABC transporters comprising 13 members. MRP member proteins 1-9 were primarily found to be expressed in the tumor cells and associated with drug resistance against anticancer therapy.[31] MRP contains three TMD and two NBD. The expression of MDR associated protein 1 (MRP1/ABCC1) has been found in non-P-gp MDR cells.[32] The MRP1 has a similar function as P-gp to pump out toxic substances in an ATP-dependent manner.[33] The prime location of MRP is the proximal tubules and majorly involved in the excretory function of the kidney. MRP1 expresses constitutively in the testes, kidneys, placenta, and pharmacological barriers. However, a considerably higher expression of MRP1 was noticed in a number of tumors including lung, pancreatic, prostate, brain, and breast cancer.[16] MRP1 significantly contributes to the efflux of the number of anticancer agents, including anthracyclines, vinca alkaloids, methotrexate, camptothecins, and epipodophyllotoxins as well as organic anion substrates including compounds which are conjugated with glucuronide, sulfate and glutathione. Apart from these, the expression of MRP1 is also favored under hypoxic conditions. A positive relation between the HIF-1α and MRP1 expression was observed in colon cancer cells.[34] However, the expression of MRP1 in cancer cells is more likely the result of induction of MDR by multiple factors that are peculiar to cancer cells.

3.1.3 | Breast cancer resistance protein (BCRP/ABCG2)

BCRP/ABCG2 is another transporter protein that acquires the function to extrude the toxic substances in the extracellular spaces under normal physiological conditions. It has one TMD and one NBD consisting molecular weight of ~72 kDa. This protein is normally expressed in stem cells and in the apical membranes of the epithelium, which has involvement in the process of drug disposition.[35] It also expressed in liver, placenta, prostate, kidney, luminal surface of the endothelial cells of human brain microvessel, breast and adrenal gland. ABCG2 is also known as mitoxantrone resistance protein (MXR), which is responsible for efflux of the mitoxantrone in carcinoma cells.[36] In addition to P-gp, the upregulated expression of BCRP is yet another mechanism has been employed by the cancer cells to prevent themselves from the actions of cytotoxic drugs. [35,37] BCRP induces the drug resistance against a wide range of anticancer drugs, including the conventionally employed genotoxic agents and novel tyrosine kinase inhibitors. BCRP is a major drug efflux transporter associated with breast cancer but several growing

bodies of evidences suggest that it was also found in other cancers such as leukemia and lung cancer. [38,39] It can also be considered as a marker of CSCs in some cancers. ABCG2 can efficiently transport a number of chemotherapeutic drugs such as epipodophyllotoxin, mitoxantrone, camptothecins, bisantrene, anthracyclines, and flavopiridol as well as Tyrosine kinase inhibitor including gefitinib and imatinib.[40,41] Collectively, these drug efflux transporters have significant role in the development of multiple drug resistance in cancer. We have analyzed the interaction of ABCB1, ABCC1 and ABCG2 with the genes that are also involved in cancer pathology. STRING database [42] was used to identify interacting partners of proteins of interest. These interacting partner proteins were searched in Comparative Toxicogenomics Database (CTD)[43] by their gene name to confirm their involvement in cancer pathology and all of these were found to be involved in cancer pathology (details are not included in this review and can be found in CTD by gene name). Network view and molecular action view (inhibition or activation of interacting partners by the protein of interest) were shown in Figure 3.

3.2 | Drug inactivation and reduced cellular uptake

Systemic distribution and absorption of the drug directs the cellular function and response in the body. Drugs once entered into the body, undergo biochemical transformation by a variety of drug metabolism enzymes. Many anticancer agents require metabolic activation to execute their mode of action. However, the alteration or mutation in metabolic enzymes leads to drug inactivation. The enzymes, including cytochrome P450 (CYP) system, glutathione-S-transferase (GST) superfamily, and uridine diphospho-glucuronosyltransferase (UGT) superfamily have been found in association with drug activation and inactivation in cancer cells.[44] Cytochrome P450s (CYP) is the member of a superfamily of heme proteins, and it has a significant role in endobiotic biosynthesis, xenobiotic biotransformation, and catabolism of bile acid, fatty acid, human steroid hormones and lipid-soluble vitamins. There are almost 57 human microsomal CYPs out of which 15 seemed to be involved in drug metabolism. Alteration in CYP may change the metabolic capabilities of these proteins, such as the

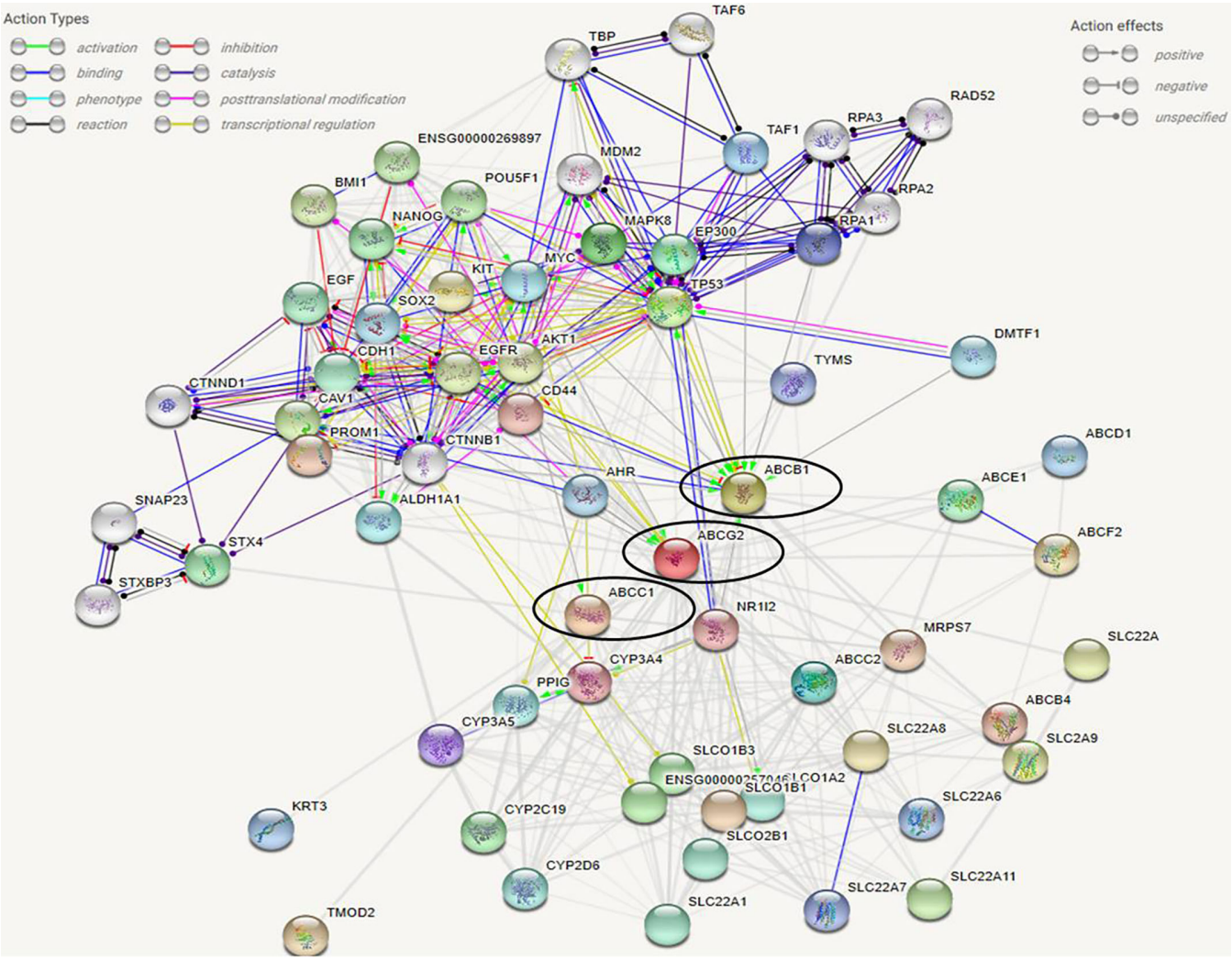

FIGURE 3 Interaction of ABCB1, ABCC1 and ABCG2 with the genes that are involved in cancer pathology. Interaction map was created with STRING database. The network and Molecular action view of protein-protein interactions (by their gene name) were created by STRING version 11.0 with high confidence (0.700) and custom value for numbers of interactions were set to 50. Modes of action are shown in different colors

breakdown of the drug, and a significant increase in its secretion. As an outcome, the intratumoral concentration of drug will decline in patients, and drug becomes inactive. For instance, as Tamoxifen is a chemotherapeutic agent, which has been widely used for the treatment and prevention of breast cancer, but due to mutation or alteration in CYP2D6 gene, the efficacy of drug drastically decreases and drug becomes ineffective in the long term.[45] Moreover, a reduction in cellular drug uptake is also associated with another possible mechanism to develop drug resistance in cancer cells. Generally, cellular uptake of the drug executed via endocytosis or receptor mediated endocytosis, where the defective process may cause drug resistance.[10] Altered expression of Caveolin -1 (CAV1) is associated with the grade of cancer progression and invasion. It plays a key role in modulating the interaction between tumor and host by promoting metastasis, tumor growth, drug resistance for cell survival.[46]

Further, the therapeutic efficacy of anticancer agents can be restricted by activation of detoxification systems that act as a guard against environmental toxins. In cancer cells, impaired detoxification system renders the ineffective drug response and promotes resistance. The exclusion of drugs by Glutathione S-transferase is one of the major causative factors to create drug resistance in cancer.[47] Glutathione S-transferase plays a vital role in multiple cellular processes, including cell proliferation, differentiation and apoptosis. An upregulation in GSH level contributes to drug resistance by multiple ways. A previous study suggests that it can bind or react with drugs, interact with ROS, prevents DNA/protein damage or involve in DNA repair mechanism and create resistance against cisplatin,[48] 5-fluorouracil[49] and doxorubicin.[50] During the treatment of the drug, an upregulated level of GST can modify the balance of kinases and favors the tumor growth. In brief, the binding sites for the transcriptional regulators, including AP-1, AP-2, NF-kB, and Nrf-2 are present on the promoter regions encoding γGCL and GST. Upon exposure of oxidative stimuli, Nrf-2 dissociates from its negative regulator Keap1 and translocates to the nucleus. After translocation, it heterodimerizes with Maf proteins and binds with antioxidant responsive element (ARE) sequences.[51] This binding triggers the cytoprotective adaptive response by upregulating detoxification and cytoprotective genes such as GSH-*S*-reductase (GSR), GCLM, GCLC, GST, ferritin, MRP, heme oxygenase-1 (HO-1) and phase-I drug oxidation enzyme NAD(P)H:quinone oxidoreductase 1 (NQO1), which creates favorable TME.[52] The mutation in Nrf-2 and keap1 in various human cancers promotes the constitutive expression of cytoprotective (prosurvival) genes due to continuous activation of Nrf-2 and contributes to drug resistance in cancer.[53] UGT is the superfamily of enzymes that catalyze glucuronidation and regulates the formation of inactive hydrophilic glucuronides along with substrates including steroids, xenobiotic, bile acids, cytotoxics, and xenobiotics. The *UGT1* and *UGT2* genes code multiple functional UGTs in humans and facilitates first line metabolic defense against pathogenic substrates in multiple tissues including breast, skin, gut, placenta and prostate gland. However, in the cancerous state the *UGT1A1* transcription and microsomal activity were found downregulated. DNA methylation negatively regulates the expression of *UGT1A1* that facilitates the functional activity of irinotecan, which is a topoisomerase I inhibitor.[44] Nevertheless, the expression of *UGT1A1* gets increased due to epigenetic changes, which deactivates the drug and enables the resistance against irinotecan as well as other drugs. Collectively, the mechanism of drug inactivation which develops the resistance in cancer cells needs further investigations.

Further, a remarkable influence of penetrability and tissue diffusion of drugs to the tumor site on drug resistance is also evident from several reports. For a drug to be effective, it is imperative for it to reach the target site at a lethal concentration.[54] Cancer cells and TME adopt multiple approaches to restrict the intracellular accumulation of the drug. It has been observed that cancer stem cells survive preferably in low oxygen tension to create a perfusion barrier against the movement of the drug inside cells. Moreover, the overwhelming clonal expansion of cancer tissue limits the presence of adequate vasculature around the newly developed tumor regions. This further limits the availability of the administered drug to the tumor site. Furthermore, the physical barrier to the drug penetration developed due to the presence of extracellular matrix (ECM), also remarkably restricts the movement of drug to the target sites.[55]

3.3 | Genomic instability and drug resistance

3.3.1 | Alteration of drug targets and mutations

Genomic instability has a crucial role in the initiation and progression of cancer. It can arise by different mechanisms such as a mutation in the DNA, chromosomal abnormalities, telomere damage, and DNA repair mechanism, which fosters tumor growth.[56] Recent report highlighted that chromosomal instability underlies neoplastic cell transformation and tumor heterogeneity along with acquired drug resistance, which is tightly associated with drug responses and survival of cancer patients.[57] Genomic instability has been commonly observed in solid tumors and hematological malignancies, where alternation may occur from single nucleotide to chromosomal level.[58] Genomic instability of cancer cells can cause mutations or aberrant expression of drug targets such as genes or proteins, which may be the major causative factors for drug resistance. Alteration in the cellular targets of anti-cancer agents reduces their therapeutic potential and promotes drug resistance. A compiling report suggests that due to alteration in the estrogen receptor of tumor cells, patients developed resistance against tamoxifen (anti-estrogen) mediated endocrine therapy in breast cancer.[59] Cancer cells develop the mutations in a variety of genes that may significantly restrict the efficacy of chemotherapeutic drugs. The clinical study suggests that approximately 20-30% of patients of chronic myelogenous leukemia developed resistance and experience relapse due to the generation of the point mutation in isoleucine (T315I) of the fusion tyrosine kinase protein after the treatment of tyrosine kinase inhibitor (TKI), imatinib.[60] Further, mutations in tumor suppressor gene p53 result in impaired functions and aberrant pro-apoptotic balance, which further encourage the circumstance of drug resistance.[61,62] Report suggests that mutation in p53, induce resistance to cisplatin in non-small cell

lung cancer (NSCLC) cells by up-regulating the expression of Nrf-2, which may be incremental in developing MDR.[63] Furthermore, the nuclear stabilization of mutant p53 upon drug treatment also resulted in the development of resistance against gemcitabine in cancer.[64]

3.3.2 | DNA damage repair

DNA damaging drug have been used for the treatment of cancer for the induction of cell death or mitotic catastrophe.[65] However, the repair in the DNA damage also leads to the development of drug resistance as these drugs exert their effect by DNA damage. There are multiple DNA Damage Response (DDR) pathways including Nucleotide excision repair (NER), Base-excision repair (BER), non-homologous end joining (NHEJ), mismatch repair (MMR), Fanconi anemia (FA) pathway, translesion synthesis (TLS) and homologous recombination (HR) which are involved in the repair of single strand breaks (SSB), DNA lesions and double strand breaks (DSB). The deregulated expressions of these pathways in cancer cells increase the ability of cells for DNA damage repair and evasion of apoptosis. [66] The chemotherapeutic agents such as 5-fluorouracil (5-FU) and cisplatin induce DNA damage in cancer cells. However, due to the upregulation of the genes associated with the mechanism of DNA repair, the efficacy of anti-cancer agents gets reduced and cancer cells eventually develop the drug resistant phenomenon.[67] A previous report suggests that loss of p53 and DNA mismatch repair leads to cisplatin induced drug resistance in cancer.[68] Clinical set of data revealed that human colorectal cells which were resistant to 5-FU, showed upregulated expression of genes responsible for DNA repairs such as RAD23B, FANCG and FEN1. The altered DNA damage repair mechanisms significantly reduced the cell cycle arrest and skip the programmed cell death which leads to the development of drug resistance in cancer.[69]

3.3.3 | Epigenetic changes and drug resistance

Epigenetics play a pivotal role in the determination of cell fate and pathological provenience. It has seemed that the non-genetic heterogeneity leads to the formation of tumor-initiating cells and/or drug-resistance. Epigenetic changes lead to the impaired gene expression, which persists for multiple cell divisions that eventually develop non-genetic heterogeneity and drug non-responsiveness.[70] The epigenetic alterations influence gene transcription by manipulating chromatin packaging and subsequently regulate the accessibility of DNA to sequence-specific transcription factors. DNA methylation, chromatin remodeling, histone modification, and alterations in non-coding RNA are associated with epigenetic alteration which is also driving force for the development of chemoresistance in cancer.[71] The molecular mechanisms revealed that aberrant methylation of CpG islands present at or near to the promoter region of the genes leads to the inactivation of gene during tumor development.[72] DNA methylation is linked with the binding of methyl-binding domain (MBD) proteins followed by the recruitment of histone methyltransferases and histone deacetylases (HDACs) with subsequent events of histone modification, chromatin condensation and finally transcriptional inactivation of the associated genes.[73] The frequency of these kinds of epi-mutations is significantly higher as compared to genetic mutations. It was reported that during metastasis ~61 infrequent mutations were observed, out of which 15 were reported as driver genes and remaining were mutated passenger genes.[74] As a result, these mutations tend to exhibit a greater impact on the selection of subpopulations, which are associated with tumor progression and development of resistance against chemotherapeutic agents. The growing body of evidence suggests that acquisition of MDR phenomenon in many tumor cells is associated with the demethylation of the MDR1 promoter. Therefore, methylation at this promoter, decreases drug accumulation, controls MDR1 transcription, and increases the drug resistance in cancer cells. Epigenetic alterations also favor the DNA damage repair in cancer cells and develop acquired resistance against methylating chemotherapeutic agent by reactivating the DNA repair enzyme MGMT that promotes the survival of tumor cells.[75] Several reports suggested that methylation and epigenetic silencing in proapoptotic genes, including APAF1 and hMLH1 as well as in tumor suppressor genes such BRCA1 and E-cadherin, results in development of resistance in cancer cells.[73,76] Moreover, the current compiling report also suggested the prominent role of exosomes in epigenetic alterations. [77] Recent report advocates that exosomes are also involved in the progression of the tumor, cell proliferation, and metastasis. Extracellular vesicles directly or indirectly can transfer the proteins and nucleic acids to the recipient cells, which can modulate histone modification, DNA methylation, and RNA post-transcriptional regulation.[78] Exosomes are largely secreted by fibroblasts and immunocytes in the TME and transferre different cargos and microRNAs (miRNAs). The mechanisms of drug resistance, including drug efflux, alterations in drug metabolism, mutation of drug target, DNA damage repair, altered metabolism, cancer stem cells, and epigenetic changes are also regulated by exosomal miRNAs.[79] Thus, exosomal miRNA also play a vital role in the development of drug resistance.

3.4 | Evasion of programmed cell death and drug resistance

Cancer cells ensure their overwhelming proliferative potential by evading the programmed cell death. Dysregulation of apoptosis is a characteristic feature and one of the hallmarks of cancer.[80] In the recent past, several reports advocate that inhibition of apoptosis and altered gene expression, mutation of apoptotic and anti-apoptotic genes may contribute to drug resistance. Overexpression of several anti-apoptotic genes and proteins such as Bcl-2 family, decoy receptors (such as TRAIL-R3/DcR1 and TRAIL-R4/DcR2), cFLIP and inhibitor of apoptotic proteins (IAPs) have been found to be associated

with resistance against chemotherapy. [81,82] Compelling evidence revealed that upregulation of BCL2, BCL-XL, and MCL-1, is associated with chemotherapy induced drug resistance in cancer.[83] Moreover, overexpression of death receptor such as TRAIL-R1, TRAIL-R2, and FAS has been found to associate with chemotherapy resistance.[84,85] The programmed cell death mechanism is intricately regulated by complex signaling mechanism. The cell death or survival signaling stimulated by intracellular or extracellular stimuli, targets various transcription factors such as NF-kB, HIF-1, c-MYC, AP-1 and STAT-3 to mediate cellular response and fate of cells.[86] Chemotherapeutic drugs may induce cell death by distinct mechanisms including apoptosis, autophagy, and necroptosis. Apoptosis suppresses the inflammation but usually evaded by the immune cells, whereas necrotic cell death may cause inflammation and activate survival signaling by nuclear translocation of NF-kB and secretion of pro-inflammatory cytokines. This process promotes the TME and cell survival mechanisms. An activation of NF-κB in response to drug exposure is also an approach adopted by sensitive cells to subvert the drug action. Activation and subsequent translocation of NF-κB to nucleus activates the transcription factors, which are also responsible for the induction of chemoresistance in cancer cells. The molecular mechanisms of cell signaling are intricate to the drug response. Chemotherapeutic drugs instigate cell death through cytotoxic response by up-regulating reactive oxygen species (ROS), changes in the mitochondrial membrane permeability, DNA damage, activation of tumor suppressor genes, and proteins as well as alteration of immune cells.[86] Cancer cells acquired several molecular changes for their survival. For instance, mutations in p53 gene alter the anticancer response of a chemotherapeutic agent that relies on the p53 mediated apoptosis in cancer cells.[87] Survivin is an anti-apoptotic protein, which expresses in higher level in resistant cancer cells, apparently due to the down regulation of tumor suppressor genes. The overexpressed survivin in cancer cells promote evasion of cell death and favor anti-cancer drug resistance. [88] In addition, cancer cells develop resistance against cisplatin due to DNA repair mechanism as the mode of action of cisplatin, relies on the DNA damage. Wip1, a protein that negatively regulates the ATM pathway of DNA damage was found in the resistant cells. Following this, the knockdown of Wip1 in oral squamous carcinoma cells (SCC) sensitized the cisplatin resistant cells.[89] The expression of P-gp also interferes with the apoptotic signaling in cancer cells, thus providing "two-way" protection to cancer cells from cell death. There is an inverse relationship between the expression patterns of P-gp and TNF related apoptosis inducing ligand (TRAIL). It has been reported that P-gp expression in cancer cells limits the action of TRAIL and therefore inhibits the apoptosis in transformed cells.[90]

Autophagy is also another way of programmed cell death, which activates under stress condition. Autophagy has been defined as a lysosomal mediated degradation pathway that helps to degrade damaged organelles and cellular components to maintain homoeostasis.[91] At normal physiological condition, autophagy function as tumor suppression, but defective autophagy is associated with cell proliferation in cancer. The insight molecular mechanism of autophagy revealed that cells have an innate capacity to restore their energy balance during nutrients deprivation condition. Indeed, an upregulated autophagic flux can favor cell survival via activation of pro-death signals.[92] Cancer cells also gain energy from the dead cells for their survival. The autophagic cell death during nutrient depreciation or stress condition developed from the cytotoxic drug may contribute to drug resistance during cancer therapy. However, the role of autophagy in cancer therapy is still controversial. Recent report highlighted that autophagy is a frequently confronted phenomenon during chemotherapy and has proven to be protective against the drug treatment in cancer. Autophagy is a widely recognized accomplice that drives a cancer cell toward MDR.[57] Supportively, inhibition of autophagy re-sensitizes the resistant cells against chemotherapeutic agents. The upregulation of autophagy function as a constructive factor for developing drug resistance against chemotherapy, radiation therapy and even targeted therapies. Moreover, autophagy mediated MDR is regulated through a diverse signaling pathways that work in an intervention, context and type of cancer dependent manner.[93] For instance, resistance to doxorubicin, methotrexate and cisplatin in osteosarcoma cells is mediated through the activation of HSP90AA1 gene that regulates the activation of autophagy through PI3K/Akt/mTOR pathway.[94] A multifunctional protein, p62 is also reported to play a critical role in autophagy mediated drug resistance.[95] Similarly, another study revealed that triple resistant HEp-2 cells were found to deplete p62 levels with simultaneous increases in Nrf-2 (an antioxidant protein) and autophagy. Interestingly, cells with reduced p62 accompanied by an increased Nrf-2 and autophagic flux were resistant to oxidative stress induced autophagy.[96] However, one contradictory report is also available which suggests that the overexpression of p62 in human hepatocarcinoma cells (HCC) is positively associated with Sorafenib resistance due to drug and cancer type dependent functions of p62.[97] In addition, IL-6 mediated autophagy is yet another mechanism through which some cancer cells acquire MDR. Transglutaminase (TG2) mediated constitutive activation of NF-kB initiates IL-6 activation and subsequent autophagic response in resistant cells. Existing report advocates that IL-6 mediated autophagy follows a positive loop mechanism for its consistent activation through the release of ATG5, an autophagic protein involved in autophagosome formation.[98] Autophagy also poses a significant impact on the response of cancer cells toward the radiotherapy or ionization therapy. Moreover, resistance to radiation therapy in breast cancer was found to be mediated through autophagy. [99] In another study, resistance to radiation therapy in cancer cells was reported to be mediated through Liver kinase B1 (LKB1), a tumor suppressor protein that activated autophagy via AMP- activated protein kinase (AMPK) with concurrent inhibition of apoptosis in resistant cells.[100] Collectively, inhibition of autophagy with simultaneous activation of apoptosis following the exposure of cancer cells to different interventions can be a lucrative approach to curb the transformation of sensitive cells to resistant phenotype on repeated exposure to chemotherapies.

Necrosis is an accidental cell death. It has been considered as caspase-independent programmed cell death and termed as Necroptosis, which is morphologically analogous to necrosis and mechanically resembles to apoptosis.[101] The key necrotic component HMGB1 is known to be released from necrotic cells and triggers activation of the inflammatory signaling cascade to constitute TME.[102]

High mobility group box 1 (HMGB1) is highly conserved chromatin associated nuclear protein that plays an important role in maintaining homeostasis of the cells. It translocates in between cytoplasm and nucleus and mainly resides in the nucleus to orchestrate the various nuclear events. HMGB1 is a critical regulator of cell death and survival signaling and also known as an alarming molecule, released by stressed cells which are undergoing necrosis and acts as endogenous danger signals to promote and exacerbate the inflammatory response that leads to the progression of cancer.[103] A previous study highlighted that HMGB1 releases after chemotherapy and promotes cell survival and drug resistance in cancer.[104] Mechanistically, necrosis triggers the release of danger-associated molecular pattern molecules (DAMPs) that activate inflammasome components to secret the pro-inflammatory cytokines, that is, IL-1β, IL-18, and TNF-α, which build up inflammatory TME that aid resistance against anti-cancer therapy. Chronic inflammatory responses have long been observed to be associated with various types of cancer and play decisive roles at different stages of cancer development. The release of danger signaling molecule HMGB1 can activate immune cells, including dendritic cells (DCs), via Toll-like receptors (TLRs), RAGE, NF-kB signaling for cell survival.[105] Thus, these reports suggest that defective programmed cell death signaling has a closed link with initiation and progression of cancer to acquire drug resistance.

3.5 | Immunotherapy, Immune responses and drug resistance

Chemotherapy attributes an immunological response. Cell death, survival and drug resistance are intricately associated with immune response, and cell functions. Cancer cells hijack normal function and response of immune cell and direct the signals in their own favor. In recent years, immunotherapy has shown emerging interest and challenges for treating cancer patients. The advancement of cancer immunotherapy has considerably changed the paradigm of cancer therapy. Immunotherapy aims to restore or boost the immune response that is typically subverted by cancer cells through multiple mechanisms. Therefore, immunotherapy is predicated to underly the long-term effects of conventional or targeted therapies. Tumor induces an immunosuppressive response, which counteracts the effective response of immunotherapy. Tumor microenvironment and infiltrating immune cells generate immunosuppressive response, which restrict immunotherapy and anti-tumor immune response. Dendritic cells (DCs) are the most potent Antigen presenting cells (APCs) for initiating immune responses. Tumor-derived pro-inflammatory cytokines and other factors that is, VEGF and CSF1 interfere with DCs maturation and restricting the migration to the tumor-draining lymphoid organs and stimulate the oncogenic immune response to other immune cells for invasion and migration.[106] Thus, the modulation of immunological response favors tumor growth and drug resistance. The commonly employed immunotherapy approaches include the checkpoint inhibitors (anti-CTLA-4, anti-PD-1), monoclonal antibodies, tumor infiltrating lymphocytes and chimeric antigenic receptor (CAR-T) influences immunogenic cell death.[107,108] But, still immunotherapy is also challenging as cancer emerges to develop resistance. Recent report revealed that resistance to immunotherapy also occurs as either primary or acquired resistance similar to the drug resistance mechanisms developed against conventional chemotherapeutic drugs.[109] The resistance to immunotherapy is largely governed by the tumor intrinsic (absence of antigenic proteins or antigen presentation, T-cells instability), and tumor extrinsic factors (presence of inhibitory immune checkpoints or immunosuppressive cells, deficiency of T- cells).[110] Some commonly encountered pathways that prevent the immunotherapy response include the activation of MAPK and Wnt/β-catenin pathways, abrogation/alteration of interferon-gamma (IFN-γ) signaling, reduced T-cell response, and tumor antigen expression.[109]

The activation of MAPK signaling results in the increased expression of VEGF and IL-8, which restricts T cell recruitment and function.[110] Also, the stabilization of β-catenin and subsequent activation of Wnt signaling results in reduced response to checkpoint inhibitors. The increased expression of β-catenin negatively regulates CCL4, a chemokine protein that is known to attract the dendritic cells.[111] Continuous activation to interferon-gamma (IFN-γ) signaling due to consistent tumor specific T-cell activation helps immune response escape mechanism in cancer cells apparently by inhibiting the expression of molecules associated with downstream IFN-γ signaling.[112] Recent clinical investigation showed that resistance to anti-CTLA4 molecule ipilimumab showed considerable mutations in Interferon-gamma (IFN-γ) receptors and interferon regulatory factor 1 (IRF1).[113] Another tumor intrinsic factor known as innate anti PD-1 resistance signature (IPRES), is expressed in various types of cancer, which are irresponsive to anti-PD-1 therapy.[114] In addition to the tumor intrinsic mechanisms, several extratumoral factors such as T_{reg} cells, M2 macrophages, and myeloid derived suppressor cells (MDSCs) act as the extrinsic causes in determining the resistance against the cancer immunotherapy. T_{regs} are inhibitory cells that suppress the action of effector T cells (T_{eff}) either through direct interaction with T_{eff} cells or through the secretion of inhibitory cytokines (IL-8, IL-10, TGF-β). Furthermore, the instances of acquired resistance to cancer immunotherapy are also reported extensively, where patients develop resistance in the later stage of therapy. Several regulating mechanisms are reported that govern the consequence of acquired drug resistance against the immunotherapy in cancer due to an altered response of antigen presenting machinery. For instance, patients responding to tumor infiltrating lymphocytes (TIL), tend to lose their sensitivity to the therapy due to the loss of a component of HLA class 1 molecules known as B2M that is required for the HLA class 1 folding and transport to the cell surface.[111] Undoubtedly, a loss of HLA class function would considerably affect the T-cell recognition process. The underlying molecular mechanisms of intrinsic and acquired resistance to cancer immunotherapy are largely needed to explore in the near future. Further, in-depth knowledge of the molecular mechanism of immunogenic cell death influenced immunotherapy could be beneficial for cancer therapeutics.

4 | CELLULAR REPROGRAMMING AND DRUG RESISTANCE

4.1 | Cancer stem cells, Epithelial to mesenchymal transition and drug resistance

In multicellular organisms, stem cells play a fundamental role in the maintenance of tissue homeostasis, and, therefore, potentiate to develop daughter cells with the self-renewal capacity.[115] Cancer stem cells (CSCs) are the key drivers for the progression of tumor and the development of drug resistance.[116] CSCs tend to display the potential for self-renewal, differentiation with tumorigenicity, which are the key factors for the chemotherapeutic failure that eventually leads to tumor reoccurrence and metastasis. Cancer stem cells are also known as tumor initiating cells (TCIs), which reside in the specific microenvironment termed as "niche" which is filled with mesenchymal, endothelial, and immune cells. These are the neighboring cells of the CSCs and endorse the signaling pathways which are essential for the maintenance and survival of CSCs. These surrounding molecules are major causative factors for the development of endogenous drug resistance in CSCs.[117] Indeed, a recent report suggests the presence of a few subpopulation of quiescent, highly tumorigenic and pluripotent cancer stem cells (CSCs) along with population of stem cells. The "cancer stem cell theory" advocates that the sensitivity of chemotherapy relies upon several intrinsic and extrinsic resistance properties of CSCs malignant progenitors, which promote drug relapse.[36] An alteration in the Wnt/β-catenin, Notch and Hedgehog, are the characteristics feature of cancer stem cells. A previous report advocated that the upregulation of Wnt/β-catenin signaling results in the dedifferentiation of tumor cells and also generates fundic gland polyps in gastric epithelial cells.[118] Moreover, Wnt/β-catenin also promotes the expression of stemness markers (ALDH and CD44) and drug resistant marker (ABCC4 and ABCG2). Collectively, these will result in the development of cisplatin induced resistance in head and neck squamous cell carcinoma.[119] Further, upregulation of the Hedgehog pathway favors the self-renewal tendency of CSCs by regulating the expression of multiple genes such as SOX2, BMI1 and OCT4 in glioma, lung squamous cell carcinoma, breast cancer and colon cancer.[120-122] An alteration in Notch signaling pathways also regulate the expression of TWIST and SLUG in oral squamous cell carcinoma and trigger the self-renewal tendency in breast CSCs.[123] Dysregulation of these signaling pathways of stem cells promotes EMT (Epithelial to mesenchymal transition) in cancer cells. Interestingly, cancer cells attain CSCs phenotype by EMT, where epithelial cells lose their polarity, change the morphology, become elongated and inhibit the cadherin, which ultimately results in the upregulation of N-cadherin and downregulation of E-cadherin.[124] EMT has an essential role in the developmental process of the neural tube and mesoderm formation as well as in the process of wound healing which favors the tumor growth and reoccurrence.[125] EMT regulates several transcriptional factors which are also common in CSCs such as SLUG, SNAIL, TWIST, ZEB1/2, HIFs, Notch, Wnt/β-catenin, Hedgehog, Wnt/β-catenin and signaling pathway of TGF- β. A previous report suggests that, NFκB/Twist signal axis induces EMT and increases mesenchymal properties of cancer cells upon stimulation of TNF α.[126] These cells will acquire the ability of mammosphere formation and increases the subpopulation of $CD44^{high}/CD24^{low}$, which is widely known as CSCs.[127] Moreover, in the case of prostate cancer, it was observed that the cells with EMT phenotype also upregulated the expression of prostate CSC markers such as NANOG, LIN28B, SOX2, NOTCH1, and OCT4.[128] Apart from these signaling pathways, telomerase reactivation also contributes to favor self-renewal capacity of tumor cells to promote CSCs. In normal physiology, telomere shorting leads to chromosomal instability and fusion collectively known as DNA damage response (DDR), which ultimately results in cellular senescence. In the case of cancer, instead of shortening, an expansion in the terminal repeats at the 3' end of telomerase by an alternative lengthening of the telomeres (ALT) pathway, extend the long term self-renewal capacity of CSCs.[129] In many drug resistant tumors, an activated telomerase were found which made tumors more difficult to treat and invasive.[130] CSCs population found to overexpress $CD133^{+}$ which develops resistance towards chemotherapy and radiation in number of cancers including colon cancer, glioblastoma and non-small cell lung cancer.[131] Moreover, CSCs tend to skip cell senescence and apoptosis that eventually lead to the development of resistance against multiple drugs, specifically docetaxel, cisplatin, cetuximab, and paclitaxel.

Moreover, mesenchymal stromal cells are also one of the major factors responsible for chemotherapeutic drug resistance in the number of cancers. MSCs are elongated spindle shaped adherent cells, which can be isolated from various types of tissue origins such as adipose and bone marrow. MSCs are multipotent, which differentiate into various types of cells. Cell expressing CD105+, CD73+, CD90+, and negative to CD45−, CD34− CD14−, CD19−, CD3−, HLA DR− are considered as MSCs. Accumulating evidence suggests that MSCs are able to stimulate tumor growth and promote chemoresistance through direct interactions with tumor cells.[132] Moreover, MSCs can release various factors including cytokines, growth factors, exosomes, and fatty acids which promote metastasis and drug resistance in cancer.[133] It has been noticed that IL-6 and IL-8 secreted by MSCs, protect cancer cells against platinum-based chemotherapeutics.[134] Additionally, it was found that MSCs secret polyunsaturated fatty acids (PUFAs) such as 12-oxo-5,8,10-heptadecatrienoic acid (KHT) and hexadeca-4,7,10,13-tetraenoic acid (16:4(n-3)) in response to platinum-based chemotherapy that may be responsible for drug resistance to platinum-based therapies in colon cancer, lung cancer, and breast cancer.[135] Similarly, MSCs secreted CXCL1 and IL-8 induce the doxorubicin resistance in triple negative breast cancer (TNBC) through the up-regulation of ABCG2 which also known as breast cancer resistance protein (BCRP).[136,137] Moreover, NO produced by TA-MSCs, and elevated release of IL-1beta by the tumor cells shown to reduce the sensitivity of etoposide in pancreatic tumor cells.[138] Therefore, it could be considered that EMT, CSCs and MSCs may contribute in the development of multi drug resistance in cancer cells.

4.2 | Cancer associated fibroblasts (CAF) and drug resistance

Cancer-associated fibroblasts (CAFs) are a critical component of the TME. It has diverse functions including tissue remolding, matrix deposition, interactions with immune cells and intensive cross-talk with cancer cells.[139] CAFs tend to show phenotypic and functional heterogeneity, based on their source and the type of stimulation. Apart from playing crucial roles in the tumor development, CAFs are also responsible for the development of MDR during anti-cancer therapy.[140] Upon receiving the stimulation from tissue derived factors such as fibroblast growth factors monocyte chemotactic protein 1 (MCP1), platelet-derived growth factor (PDGF), tissue inhibitor of metalloproteinase 1 (TIMP-1) and tumor transforming growth factor β (TGF-β), normal fibroblasts transform into cancer associated fibroblasts (CAFs) and exert their role in pathological consequences. The involvement of CAF in drug resistant is emerging evidence where it was noticed that the inhibition of CAF reversed the drug resistance and improved the therapeutic efficacy. Recent report suggested that the administration of 5-FU (as a metronomic agent) in combination with taxol attenuated the tumor growth by overcoming drug resistance through the downregulation of P-gp and simultaneous targeting of CAF.[141] Moreover, an emerging report suggests that upon the treatment of conditioned medium filled with breast cancer associated fibroblast, the human triple negative breast cancer cells (MDA-MB-231) attain the resistance against doxorubicin due to the release of HMGB1 that led to sustained autophagy in treated cells.[142] Taken together, the wide range of approaches governed by different CAFs to cause drug resistance in cancer cells (along with the transporter proteins) require further attention to overcome the chemo resistance.

4.3 | Tumor microenvironment (TME) and drug resistance

The interaction between the drug resistant cells and TME remarkably modulates the efficacy of efflux pumps and other ECM components.[143] The acidic pH of TME considerably depletes the uptake of drug that is weakly acidic through "ion trapping," a phenomenon that is generally observed in case of therapeutic agents carrying large permeability differences between their ionized and unionized form. Concurrently, a low acidic pH of the TME also promotes the efflux of drugs through P-gp. A long term exposure to acidic pH also promotes the expression of proteins responsible for resistance, such as heat shock protein 27 (HSP27).[144] In addition, the different components of ECM in TME are also known to generate chemoresistance. For example, Type I collagen (a ECM constituent) is implicated in the development of chemoresistance to oxaliplatin. Moreover, the stiffening of tumor stroma is an important contributor to epithelial to mesenchymal transition (EMT) and resistance to paclitaxel. Further, the stromal cells encourage drug resistance in the surrounding cells through a process of cell-cell interaction termed as "trogocytosis" by utilizing the integrin receptors present on cancer cells and their binding with the ligands generated by the stromal cells. Ultimately, the receptor- ligand interaction activates the intracellular pathways including mTOR, NF-κB, AKT, and STAT3 signaling to sustain the mechanisms of drug resistance.[144,145] Recent report advocate that matrix cells in the TME exchange the communication network with cancer cells through exosomes, which play critical roles in evasion and metastasis.[146] Exosomes are tiny bilayered molecules secreted by both cancer cells and several stromal cells in the TME which participate in endocrine, paracrine, and autocrine signaling. Exosomes potentiate to convey the resistant trait to recipient cells.[147] A study suggests that exosomes mediated transfer of various non-coding RNAs (ncRNAs), including long non coding RNAs (lncRNAs) and microRNAs (miRNAs) is a possible mechanism for procuring drug resistance in cancer cells by inducing genetic and epigenetic mutations. A previous report revealed that drug-sensitive cells produce less extracellular microvesicles such as exosomes and microvesicles compared to drug-resistant cancer cells and exosomal proteins can be used as a biomarker in cancer diagnostics.[148] It has been found that exosomal transfer of lncRNA-ROR and urothelial carcinoma-associated 1 (UCA1) induce chemoresistance in Hepatocellular carcinoma and ER-positive MCF-7 cells respectively.[149,150] It was reported that exosomes secreted by HER2-overexpressing tumor cell lines SKBR3 and BT474 can express full-length human epidermal growth factor 2 molecules (EGF-2) and manifest MDR effect by hampering the activity of Trastuzumab in breast cancer.[151] In addition, circulating exosome-associated miRNAs were found to be responsible for bortezomib resistance in multiple myeloma.[152] Moreover, tumor associated mesenchymal stromal cells (TA-MSCs) derived exosomes also promote drug resistance.[153] These available reports strongly suggest that exosomes secreted from tumor stromal cells, confer drug resistance against anti-cancer therapy.

4.4 | Oxidative stress and drug resistance

Oxidative stress is the result of an imbalance between the generation of free oxygen radicals and their elimination through the antioxidant defense system. It is generally produced by disruption of the respiratory chain and aberrant mitochondrial function leading to the generation of ROS.[154] ROS provoke DNA mutation, genome instability, and cell proliferation, which required initially for tumor development and progression.[155] However, excess ROS also induce apoptosis and ceases the tumor progression.[156] Therefore, ROS play a dual role in the development and treatment of cancer through regulating several transcription factors such as NF-κB, AP-1, p53, HIF-1α, PPAR-γ, Wnt/β-catenin, & Nrf2 and enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase, catalase, and nonenzymatic antioxidants including glutathione (GSH), vitamins C and D. Further, several reports suggest that anticancer drugs such as cisplatin, doxorubicin, vincristine and vinblastine exert their anticancer efficacy through the generation of ROS.[156-158] However, prolonged use of these drugs also promotes resistance through the reduction in ROS production.[159] Generally, ROS trigger mitochondrial dysfunction

and apoptosis, but tumor cells have several survival mechanisms acquired by genetic alterations that promote tumor survival. Further, ROS also lead to mutagenesis through promoting instability of genetic material and continuous mutations, which results in tumor heterogeneity.[160] Next, chronic hypoxia is an indispensable need of a cancer cell. The perpetuated hypoxic conditions in transformed cells encourage the expression of different oncogenes to ensure cancer proliferation. Hypoxic conditions favor chemoresistance in different types of cancer.[161] Anticancer drugs that rely on excessive ROS production to cause DNA damage and subsequent cell death depends upon the presence of oxygen inside the cells to generate sufficient ROS. The limited supply of oxygen, therefore, enables the cancer cells to escape from death by maintaining the ROS concentration below the lethal threshold. [161] Under such conditions, the failure of anticancer drugs that exert their anticancer effect through free radical generation is undoubtedly perceivable. Cells employ several other alternative pathways to restrict their undesired proliferation. Cell senescence is a stable form of cell cycle arrest that is activated under stressful conditions in a cellular environment.[162] The induction of senescence is a mechanism employed by various anticancer agents to halt the cancer progression.[161] Importantly, the prevalence of hypoxia in cancer cells substantially limits the drug induced senescence in cancer cells, thus, apparently developing resistance against such interventions.[163] The transcription of multidrug resistance genes in response to hypoxia is a widely acknowledged phenomenon that occurs in cancer cells. The hypoxia mediated activation of HIF1α subunit of HIF acts as a transcription factor that initiates the expression of drug resistance genes including, MDR-1 and BCRP.[161] Cancer cells also manage to evade drug action by sustaining autophagy. Autophagy induction in cancer cells has been observed as a mechanism of resistance against multiple anticancer drugs.[57] Importantly, the HIF1 axis considerably regulates the autophagy mediated drug resistance.[161] Moreover, the paradoxical role of anti-oxidant defense system in the perpetuation of MDR gene (P-gp) expression was also inferable from the study, where the selective upregulation of P-gp expression in HEP-G2 cells upon treatment with anti-oxidant enzyme catalase was regulated through the JNK signaling pathway. A possible mechanism has been proposed in such a case, where activation of JNK signaling was suggested as a result of reduced intracellular ROS concentration.[164] However, JNK dependent activation of P-gp is also advocated to be independent of ROS levels. Specifically, the hypoxia mediated activation of JNK is observed to be independent of concurrently increased ROS levels in cancer cells.[165] In addition, upregulated expression of P-gp was found in colorectal cancer cells and suggested that COX-2 mediated activation of P-gp expression was associated with JNK dependent pathway.[166] Moreover, a previous report advocate that activation of MDR gene (P-gp) is associated with other kinases including the cAMP dependent protein kinase, Protein kinase C and P13K.[26] Therefore, impertinent of ROS and redox signaling in context to multidrug resistance in cancer is remain elusive and needed further investigations to explore the mechanism of drug resistance in cancer.

4.5 | Cancer metabolism and drug resistance

Metabolic reprogramming is one of the key features and hallmarks of cancer cells. Cancer cells adapted TME through chronically elevated oxidative stress and metabolic reprogramming to ascertain its energy demands. Almost a century ago, Otto Warburg made a revolutionary remark on cancer and explained reprogrammed metabolism in cancer. The bizarre behavior of cancer cells allows them to shift toward the less energy efficient aerobic glycolytic pathway and sidelining an energy efficient oxidative phosphorylation pathway for its energy production. The phenomenon is popularly known as the "Warburg effect," which still remains a large enigma in cancer biology. However, today, this reprogrammed metabolism is not only constrained to glucose metabolism but also extended to lipid and glutamine metabolism. A recent understanding of cancer cell metabolism has brought the knowledge in the way that cancer cells generate oxidative stress and TME to ensure continuous synthesis of amino acids and proteins even in the presence of a chronically low level of ATP inside the cells.[167] Compiling reports suggested the prominent roles of lactate, produced as a result of aerobic glycolysis, in cancer progression. In line with these findings, it can be inferred that lactate is a deliberately produced product of cancer cells and is one of the reasons behind the shifting of cell metabolism toward the glycolytic pathway.[168,169] Pyruvate kinase isoform 2 (PKM2) is a glycolytic enzyme, that is commonly upregulated in many human cancers. PKM2 functions to regulate the glycolytic flux and hinders oxidative phosphorylation in cancer cells. PKM2 has been found to play a critical role in gene transcription and cell cycle progression along with metabolism reprogramming. The number of non-metabolic roles of PKM2 has been reported including the regulation of programmed cell death and drug resistance in cancer cells.[170] Further, 2-Deoxyglucose (2-DG) is a glycolytic inhibitor that regulates various signaling pathways. Normal cells and tissues during radio- and chemo-sensitization of the tumor were found to be protected by 2-deoxy-D-glucose.[171] It was well evident that many oncogenes, tumor suppressor genes and proteins influence signal transduction pathways and metabolism, that is, HIF1, MYC, p53, and Bcl2 family proteins. The interplay between drug resistant genes such as MDR1 (P-gp), MRP1 & BCRP and tumor metabolism genes such as HIF1-α, LDHA, HK II, and c-Myc has been shown in the tumor progression.[172] A Study by Wartenberg et al, has shown that P-gp expression was downregulated with the inhibition of glycolysis. Inhibition of glycolysis also reduces the production of ATP, which is required for the P-gp-ATPase activity. The possible underlying mechanisms include decreased expression of HIF1-α regulated glycolytic enzymes such as LDHA, PDHA1, and HK1.[173] Altered tumor metabolism and upregulated expression of P- gp have revealed many secrets of drug metabolism and chemoresistance. Moreover, the development of hypoxia in cancer cells plays a critical role in altered tumor metabolism and acidic microenvironment, which has been attributed to the induction of P-gp expression.[174] Reprogramming of cancer cell metabolism promotes drug resistance that attributes major obstacles in cancer therapy.[175] Therefore, additional studies are required

to investigate the cross-talk between cancer metabolism and chemo resistant to overcome the drug resistance in cancer.

4.5.1 | Reverse pH gradient

Tumor acidosis has been recently recognized as one of the emerging hallmarks of cancer. [176] It is the outcome of an accumulation of metabolic acids due to the high rate of metabolic demands by cancer cells. Lactic acid and carbonic acid have been noticed as one of the major driving forces for the creation of acidic TME.[177,178] Cancer cells extrude these harmful metabolic acids to the extracellular environment in order to protect themselves from intracellular acidification-induced apoptosis and thus causes reverse pH gradient, that is, lower pH (pHe 5.6 - 6.8) of the extracellular region and higher pH (pHi 7.2-7.5) of the intracellular region.[177,179] Reverse pH gradient provides several benefits to the cancer cells and helps in exaggerating proliferation, inhibition of apoptosis, and invasion and metastasis.[178,180] Further, reverse pH gradient has also been reported in providing the chemoresistance property to the cancerous cells by elevating the expression of multidrug resistance proteins, affecting distribution and uptake of chemotherapeutic drugs.[180] Previous reports demonstrated the crucial role of reverse pH gradient in the uptake of weakly acidic or weakly basic chemotherapeutic drugs by the tumor cells due to their protonated or unprotonated forms.[181,182] Indeed lower extracellular pH influences reduced cytotoxic response of many anti-cancer drugs like paclitaxel, mitoxantrone, and topotecan against murine mammary carcinoma cells and human bladder carcinoma cells.[183] Further, in support, it has been reported that an increased therapeutic efficacy of a weak basic chemotherapeutic drug doxorubicin against MCF-7 xenografts in vivo was the influence of elevating the extracellular pH maintained through sodium bicarbonate-supplemented water orally.[182] Later on the implication of acidosis in the promotion of chemoresistance has been shown due to increased p-glycoprotein (P-gp) activity. Authors have demonstrated that in vitro and in vivo extracellular acidification (pH 6.6) caused daunorubicin resistance in rat prostate cancer via increasing the P-gp activity through activation of p38.[184] In addition, recent report has shown that several anticancer drugs such as doxorubicin, vincristine, and vinblastine have lower efficacy in the acidic extracellular environment due to protonation as these drugs are mildly basic in nature.[144] It has been assumed that the acidic environment promotes the expression of P-gp and efflux of drugs. A previous report revealed that expression of P gp increased linearly with a decrease in pH of TME through activation of p38/MAPK pathway.[185] Interestingly, current study suggests that alkaline intracellular pH of tumor cells not only inhibits the accumulation of chemotherapeutic drugs (such as weakly basic chemotherapeutic drugs) but also interferes in the binding of their targets such as tubulin and DNA.[186] However, these effects were reversed upon acidic shifts.[186] Moreover, alkaline pHi-mediated chemoresistance also depends on the elevated expression of ABCB1 or P-gp, which enhances the rate of efflux depending upon the protonation of drug.[187] These proteins effectively transport the neutral or positively charged drugs from the intracellular environment to extracellular milleu through binding to the transporter site of the membrane. Further, the expression of lactate dehydrogenase A (LDH-A), an enzyme that catalyzes pyruvate to lactate and supports the acidification of TME, has been reported in the development of chemoresistance in several cancers including breast cancer, and colon cancer.[188,189] It has been shown that inhibition of LDHA by siRNA and its inhibitor, oxamate, promoted the sensitivity of taxol against the taxol resistant breast cancer cells[189]. Tumor acidosis is the result of the orchestrated expression of several pH regulators such as NHE1, CAIX, CAXII and V-ATPase. A previous report revealed that expression of NHE1 has been found to be increased in several cancers such as breast, colon, glioma, and leukemia and imparts tumor acidosis. The over expression of NHE1 is associated with inhibition of apoptosis and promoting resistance to cytarabine in acute myeloid leukemia.[190] There are ample reports suggesting the implication of reverse pH gradient in the promotion of chemoresistance in cancer treatment. However, the role of pH regulators and sensors in the chemoresistance has not been explored much. Therefore, further studies are needed to decipher the cross-talk between reverse pH gradient, pH regulators such as NHE1, CAIX, CAXII, and V-ATPase and chemoresistant genes such as MDR1, MRP1, and BCRP in drug resistance.

4.6 | Inflammation and drug resistance

Inflammation is an innate immune response of our body against harmful stimuli such as tissue injury or invading pathogens. It is a multi-step process that initiates upon the activation of immune cells, which subsequently release pro-inflammatory mediators and activates several inflammatory cells to exclude the pathogens or foreign cells. The perpetuation of an inflammatory milieu in TME contributes to progress tumor growth and development. [191] Inflammation plays a significant role in all the major events of tumor development including angiogenesis, evasion from cell death, cancer migration or acquiring resistance against the administered interventions.[192,193] Inflammation has been considered as the seventh hallmark of cancer.[171] Here, with relevance to the present discussion, we will attempt to shed the light on the connection between inflammation and MDR in cancer. Activation of immune cells and immunological response promotes secretion of pro-inflammatory cytokines and inflammatory signaling cascades, which may promote the development of drug resistance. Briefly, at the site of malignant growth, frequent accumulation of inflammatory mediators and inflammatory cells generates the local inflammatory TME which regulates the expression of drug resistant proteins in cancer cells and significantly alters the cellular response of chemotherapeutic agents.[194] Similarly, overexpression of multidrug resistance associated protein 1 (MRP1) was observed in inflamed intestine of patients with ulcerative colitis and Crohn's disease.[195] Moreover, exposure of chemotherapeutic agent to the tumor cells also generates the inflammatory response and promotes metastasis and drug resistance.[196,197] Previous reports demonstrated the close link between Nuclear Factor

(NF)-kappa B (NF-kB) activation, production of cytokines, and drug resistance in cancer.[198,199] The Nuclear Factor (NF)-kappa B is the transcription factor, involved in prosurvival mechanisms by initiating inflammatory pathways. However, NF-kB signaling pathway also gets activated by exposure of multiple chemotherapeutic agents including, paclitaxel, cisplatin, doxorubicin, and docetaxel, which subsequently leads to the development of drug resistance in tumors by growth factor receptor stimulation, PI3K/AKT pathway, MAP kinase/ERK pathway, Janus Kinase/Signal Transducers and Activators of Transcription pathway, DNA repair mechanisms, and deregulating apoptotic mechanisms.[200,201] NF-kB signaling induces drug resistance in cancer cells by multiple mechanisms such as by growth factor receptor stimulation, PI3K/AKT pathway, MAP kinase/ERK pathway, Janus Kinase/Signal Transducers and Activators of Transcription (JAK/STAT) pathway, DNA repair mechanisms and deregulating apoptotic mechanisms. A previous study suggested that upon treatment on A549 cells, cisplatin phosphorylates EGFR and activates PI3K/AKT/NF-κB pathway, which results in the development of cisplatin resistance in NSCLC.[202] In addition, the constitutive activation of NF-kB, up regulate the expression of Snail (transcription factor involved in EMT) in prostate cancer. An elevated level of Snail via NF-kB, inhibits the expression of metastasis suppressor gene Raf kinase inhibitor protein (RKIP), and protects the cancer cells against chemotherapy induced apoptosis.[203] Apart from these, NF-kB can also be activated by Tumor necrosis factor (TNF) receptor signaling in cancer cells, which is associated with chemoresistance. For example, the exogenous addition of TNF-α in breast cancer cells, up regulates the expression of NF-kB which enhances the survival of cancer cells and develops resistance against ionizing radiation.[204]

Moreover, inflammatory cytokines are associated with multiple physiological processes such as cell migration,[205] angiogenesis,[206] apoptosis, [207] and inflammation, which involves tumor development, tumorigenesis and metastasis.[208] Emerging evidences suggest that cancer cells and their stroma secrete the cytokines, which plays a significant role in various drug resistance mechanisms. [209,210] According to the report, prostate cancer cells developed resistance against the enzalutamide, which is an antagonist of androgen, due to IL-6 mediated activation of signal transducer and activator of transcription 3 (STAT3) and its target genes.[211] Further, it was found that IL-6 produced in an autocrine manner, induces the multidrug resistance in breast cancer cells. [212] Moreover, an elevated expression of IL-6 and IL-8 can also induce drug resistance against the inhibitor of Notch signaling axis in the xenograft model.[213] Autocrine motility factor (AMF) is another cytokine secreted from cancer cells involved in drug resistance in fibrosarcoma cells. The secretion of AMF in large amounts resulted in resistance to mitomycine C by degrading Apaf-1 and caspase-9 expression, the key proteins accountable for the execution of intrinsic apoptosis.[214] Several chemokines such as CXCR1/CXCR2, CC chemokine subfamily are associated with drug resistance in cancer. A recent report revealed that CXCR2 and CXCL8 expression level were found higher in dacarbazine induced drug resistant melanoma cells and is suggested marker of drug resistance.[215] Further, CC chemokine subfamily significantly involved in the pro-tumorigenic functions and drug-resistance in cancer cells.[216] Moreover, other inflammatory molecules can also fuel the drug resistance in cancer cells, such as Cyclooxygenase (COX) -1 and COX-2. Cyclooxygenase (COX) isoenzymes function to mediate the synthesis of prostaglandins (PGs) from arachidonic acid. COX-1 and COX-2 are the most extensively studied isoforms of COX.[217] Importantly, an increased expression of COX-2 in tumor cells is also positively associated with the ability of cancer cells to acquire drug efflux mechanisms. The report suggested that the expression of P-gp in the breast tumor is directly related to the expression of COX-2.[218] It was further hypothesized that the manifold increase in COX-2 in breast tumors results in the production of prostaglandins that activates the downstream PKC/c-Jun (JNK) signaling axis to initiate the P-gp expression.[218] In addition, supportive evidence also suggested the remarkable contribution of COX-2 in the activation of P-gp expression via JNK signaling in colorectal cancer cells.[166] Seemingly, the COX-2 facilitated expression of drug efflux proteins is not restricted only to the P-gp transporter. COX-2 also involved in the development of drug resistance by upregulating the expression of MRP and BCRP in cancer cells.[219] Therefore, exploring the molecular mechanism behind inflammation and cancer can be harnessed to overcome MDR in cancer.

5 | CONCLUSION

Cancer cells acquire drug resistance against chemotherapeutic drugs, cause major failure of anti-cancer therapy. The mechanisms of drug resistance including drug efflux, alterations in drug metabolism, drug inactivation and reduced cellular uptake, mutation of drug target, DNA damage repair, genomic instability epigenetic changes, evasion of programmed cell death, and alteration in cellular reprogramming including Epithelial to mesenchymal transition, cancer stem cells, TME, oxidative Stress, altered energy metabolism, compromised immune response contributes to the development of resistance against anti-cancer therapy. Multidrug resistance (MDR) is an outcome of intricate relationship between multiple intricate pathways responsible for the inactivation of drug, cellular reprogramming and genes resposible for development of drug resistance. MDR is a major obstacle in regimens of successful cancer therapy. In the recent past, several attempts have been made to overcome the MDR in cancer but still do not meet with success. An improved understanding of the molecular mechanism of MDR and cellular reprogramming can provide a promising opportunity to combat drug resistance in cancer and intensify cancer therapy for the upcoming future. Subsequently, identification of novel anti-cancer drug candidates and molecular targets can be harnessed to overcome multidrug resistance in cancer.

ETHICAL STATEMENT

Not Applicable.

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CONFLICT OF INTEREST

Authors are not having any conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors had full access to the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Conceptualization*, F.V. and C.P.; *Software*, V.M.; *Validation*, F.V., C.P. and A.K.; *Investigation*, C.P.; *Formal Analysis*, F.V. and C.P.; *Resources*, *Data curation*, F.V., A.S.C., C.P.; *Writing—Original Draft*, F.V., A.S.C., V.K.G., S.G.R., A.K.; *Writing —Review & Editing*, C.P.; *Visualization*, F.V. and C.P.; *Supervision*, C.P.; *Project Administration*, C.P.; *Funding Acquisition*, C.P.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Foram U. Vaidya https://orcid.org/0000-0003-1093-1514
Abu Sufiyan Chhipa https://orcid.org/0000-0003-1208-1162
Chandramani Pathak https://orcid.org/0000-0002-9389-8096

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