



Molecular Pathways and Epigenetic Factors Regulating Chemoresistance in Cancer

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Abstract

Chemoresistance in cancer therapeutics is an emerging problem and led to relapse and poor prognosis. Development, progression, and metastasis of tumor is regulated by signaling pathways including PI3K, Akt, mTOR, NF- κ B, ERK, MAPK, MEK, JAK/STAT, mTOR, HER-2, and EGFR signaling pathways. However, aberrant expression of these pathways as well as of epigenetic regulation including methylation, acetylation, microRNAs, and lncRNAs imparts chemo resistance in cancer. Chemoresistance in cancer is also mediated by change in drug transporters, change in pH, drug influx, drug efflux, EMT, and thick stroma. Other factors including angiogenesis, inflammation, apoptosis, autophagy, and change in energy metabolism also play a role in chemoresistance. Thus, an in-depth understanding of the involvement of these factors in chemoresistance and targeting them to overcome resistance and sensitizing tumor cells to chemotherapy is warranted. Targeting these factors has been discussed in the literature with promising results and given the importance of targeting these pathways; we have discussed the role of various signaling pathways and epigenetic factors in imparting chemoresistance.

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Introduction

The multifaceted problem of drug resistance in cancer therapy is ascribed by tumor burden, growth kinetics, tumor heterogeneity, tumor microenvironment, the immune system, and undruggable cancer drivers [1]. Drug resistance can also be due to drug inactivation, drug efflux, alteration in target molecules, the epithelial-mesenchymal transition, DNA damage repair, cell death inhibition, metabolic changes, DNA mutations, genetic

and epigenetic modification, and presence of non-coding RNAs [2-4]. Alteration in membrane transport, altered autophagy and micropinocytosis, altered target enzymes, altered drug-metabolizing enzyme expression leading to increased drug degradation, drug inactivation, altered subcellular redistribution, and drug-drug interaction is an additional cause for the development of drug resistance in cancer [3-5] (Figure 1).



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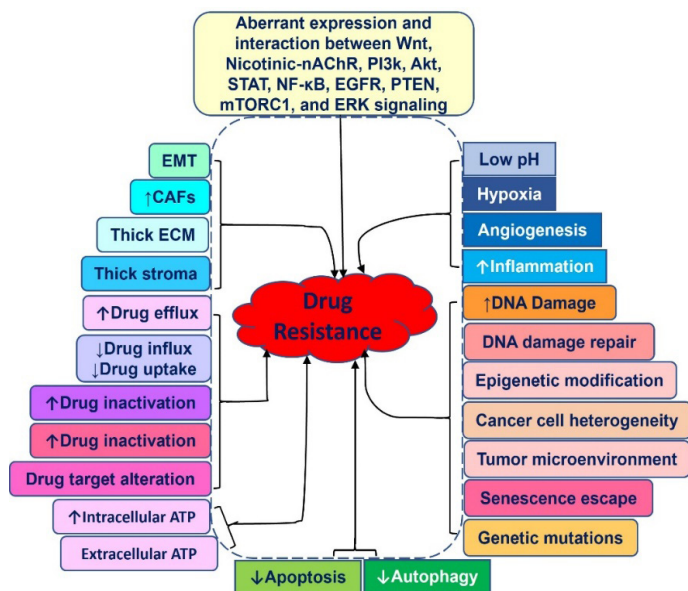


Figure 1: Biological, molecular, and epigenetic factors imparting chemoresistance in cancer.

AChR-Acetylcholine receptor, PI3k-Phosphoinositide 3 kinase, Akt-Protein kinase B, STAT-signal transducer, and activator of transcription, NF-κB- nuclear factor kappa-light-chain-enhancer of activated B cells, EGFR- epidermal growth factor receptor, PTEN-Phosphatase and tensin homolog, mTORC-mammalian target of rapamycin complex, ERK-Extracellular signal-regulated kinase.

Drug resistance may be intrinsic (de novo) or extrinsic (acquired). Intrinsic resistance is characterized by the nonresponsive tumor to the chemotherapeutic agent and extrinsic resistance is characterized by nonresponsive tumor after initial therapeutic response [6]. Drug resistance continues to be a limiting factor for cure in cancer patients and is one of the factors causing treatment failure. Poly chemotherapy and combination chemotherapy combined with surgery and radiotherapy were proven beneficial, but the success plateaued due to drug resistance. Higher doses of chemotherapy, shorter intervals, and different dose intensity and intervals combined with growth factors were proven beneficial [1]. However, drug resistance remains a major challenge in cancer therapeutics. The four aspects including earlier detection of tumors allowing intervention in cancer therapeutics, the addition of novel drugs and better pharmacological principles, using the high-throughput screen to detect cancer cell dependencies, strictly monitoring drug therapy and its response, and integrating clinic-genomic data using bioinformatics have been suggested as a solution of drug resistance in cancer therapeutics [1,3]. Additionally, not all cancers are resistant to cancer, early detection of cancer resistant to chemotherapeutic agents is a must. Combination chemotherapy with minimally overlapping toxicities allowing the use of maximal dosages with shorter cycle intervals aids in bone marrow recovery, however, the development of drug resistance in cancer continues to be a persistent problem in local and disseminated cancer treatment [1,3]. The presence of thick stroma with poor angiogenesis makes drug delivery difficult. Metabolic reprogramming promoting tumor growth and metastasis may also contribute to therapeutic insufficiency and drug resistance. The resistance to recent drug treatment (gemcitabine) involving alteration in the expression of metabolic enzymes (glucose metabolism, lipid metabolism, amino-acid, and nucleotide metabolism) has been discussed [5]. Similarly, the involvement of molecular pathways (NADPH oxidase/ROS/NF-κB/STAT3 pathway, C-X-C motif chemokine receptor 4 (CXCR4), hedge-

hog pathways, PI3K/Akt, EGFR, HER2, PTEN, IGF1R, ERK1/2), cancer stem cells, cancer-associated fibroblasts, and tumor-associated macrophages heterogeneity and targeting them to alleviate drug resistance including MEK inhibition, attenuating MUC1, and targeting autophagy have been discussed [5,7-9]. The mechanisms of cancer therapy and drug resistance in cancer have been reviewed extensively [1-3,5,7-9] but there is a paucity of literature comprehensively describing and focusing on the crucial role of molecular pathways including Wnt signaling, tyrosine kinase, MEK kinase, PI3K, PTEN, Akt, JAK1/2, GSK-3β, EGFR, mTORC, NF-κB signaling, and Hippo pathway ending cancer resistance. An in-depth understanding of the molecular mechanism imparting drug resistance (intrinsic or acquired) is important to design novel therapeutics by modulating these pathways. Here we have focused the discussion on various molecular pathways imparting drug resistance in various types of cancers.

Wingless-related integration site (Wnt) signaling

Wnt (Wingless-related integration site)/β-catenin signaling regulates embryonic development, tissue morphogenesis, cell migration and proliferation, cell polarization, cell regeneration, and adult tissue homeostasis. Tightly regulated and fine-tuned normal expression of Wnt signaling regulates cellular homeostasis, however, aberrant expression of Wnt signaling due to genetic alterations involves in cancer development, cancer progression, the proliferation of cancer stem cells, and drug resistance [10-13]. Dysregulated Wnt signaling imparts drug resistance in cancer therapy through stemness, increased DNA damage repair, immune evasion promotion, and enabling transcriptional plasticity [4,10,11]. The aberrant expression of Wnt genes and Wnt/β-catenin signaling including *Int-1* (mammary cancer), APC (colorectal cancer), β-catenin, APC, and *AXIN1* (Liver cancer), APC, *AXIN1*, *CTNNB1*, *RNF43*, *ZNRF3*, *RSPO2*, and *RSPO3* in the stomach, large intestine, liver, pancreas, colon cancer, ovary, cervical, endometrium, kidney, adrenal gland, biliary tract, pituitary, lung, oral, head and neck, leukemia, melanoma, and soft tissue cancers have been reviewed in the literature [11-16]. Similarly, the role of DNA methylation in manipulating Wnt signaling causing colorectal, breast, gastric, and ovarian cancers have been discussed [11,17,18]. The role of Wnt signaling mediating stemness via CD34⁺ cancer cell in cutaneous cancer [19], *RSPO2* in pancreatic cancer [20], microRNA-146a in colorectal cancer [21], *lncTCF7* in liver cancer [22], miR-142 in breast cancer [23], and miR-582-3p in non-small cell lung cancer [24] has been documented [17]. Wnt signaling plays a crucial role in the maintenance and renewal of the leucocytes as well as in promoting immune tolerance and cancer cell stemness [12]. Tumor microenvironment mediates cancer metastasis via Epithelial-Mesenchymal Transition (EMT) involving TGF-β, NF-κB, Notch, Wnt, and receptor tyrosine kinase [25] and TME activates Wnt signaling thereby promoting EMT and drug resistance in cancer [4,10,26]. The role of Wnt signaling in imparting cancer drug resistance has been discussed in detail by Xu et al. [18]. Increased tumor heterogeneity, increased drug efflux, and endocrine therapy resistance due to activated Wnt signaling mediate drug resistance in breast cancer. Another strategy of inducing cancer drug resistance is increased expression of v-ATPase (vacuolar H⁺-ATPase; an electrogenic H⁺ transporter) which activates Wnt signaling [27,28]. Further, inhibition of EMT, self-renewal activity of cancer stem cells, and reversal of drug resistance in breast cancer stem cells with the combination of Docetaxel (DTX) and Sulforaphane (SFN) and Pyrvinium Pamoate (PP) suggest the role of activated Wnt signaling in cancer resistance [13,29]. In-

creased expression of Wnt transcription factor TCF7L2 associates with resistance to 5-FU in colorectal cancer [30]. Further sensitization of cancer cells (in-vitro studies as discussed in [4]) to anticancer drugs on silencing or attenuating Wnt/ β -catenin and improved chemosensitivity with Wnt inhibitors [31,32] support the notion of Wnt signaling in cancer drug resistance. Activated Wnt signaling mediating resistance to the PARP inhibitor Olaparib by increased DNA damage repair in ovarian cancer [33,34], activated noncanonical Wnt signaling due to ectopic WNT5A and WNT7B expression mediating resistance to androgen receptor inhibitor by increased tumor cell proliferation in prostate cancer [35], Wnt signaling pathway activation in Sox2-expressing cells conferring resistance to tamoxifen by increased tumor cell proliferation in breast cancer [36], and activated Wnt signaling mediated resistance to PI3K/AKT/mTOR inhibitors in colorectal cancer via resistance to FOXO3a-mediated apoptosis [37,38] are other examples of Wnt-mediated chemoresistance. Activated Wnt signaling is also associated with tumor relapse due to increased tumor cell differentiation in basal cell carcinoma because LGR5+ cells in basal cell carcinoma escape from Hedgehog signaling inhibitor vismodegib due to aberrant Wnt activation [39,40]. In hepatocellular carcinoma, activated Wnt signaling imparts resistance to IFN- α and 5-fluorouracil and cause increased tumor cell proliferation [41]. Further, the association of various miRNAs including miR-224, miR-506, miR-552, miR-522, and miR-372/373 regulating Wnt signaling and cancer resistance has been discussed [4]. Due to the involvement of Wnt signaling in the pathogenesis of drug resistance in cancer therapy, Wnt is an emerging target for drug development. Inhibitors of the Wnt signaling and their effects in cancer along with the mechanism of action, various approaches to target and inhibit Wnt/ β -catenin downstream signaling, and phases of development of various upstream and downstream inhibitors have been reviewed [11,17].

PI3K, Akt, mTOR, and NF- κ B signaling

Non-Small Cell Lung Cancer (NSCLC) is the most predominant constituting 80-85 % of all lung cancers. Multidrug resistance in NSCLC is facilitated by the tumor microenvironment with abundant Cancer-Associated Fibroblasts (CAF). CAF secretes cytokines like IGF2, VEGF α , EGF in an unregulated manner. Among these IGF2 secretion is very significant. IGF2 binds to the membrane receptor IGF-1R in NSCLC cells to activate IGF2/IGF-1R paracrine pathway. Also, CAF and/or IGF2 induce high expression of Sox2 transcriptional factor in NSCLC cells which activates the AKT signaling pathway [42,43]. AKT, a classic downstream molecule of this pathway is activated by phosphorylation and it facilitates the nuclear translocation of transcription factor Sox2. In the nucleus, Sox2 binds to the promoter region of the ABCB1 (ATPase binding cassette transporter) gene encoding P-gp. Thus P-gp expression is upregulated which leads to activation of IGF2/AKT/Sox2/ABCB1 signaling pathway and drug resistance of NSCLC cells by decreasing drug retention and increasing the drug efflux [42]. Activated PI3K/Akt signaling increasing Bcl-2 family proteins and X-linked apoptosis proteins (XIAP) expression and decreasing Bax expression associates with drug resistance [44-46].

Increased expression of nuclear β -catenin associated with resistance to PI3K and AKT inhibitors and this notion is supported by the fact that treatment with Wnt/tankyrase inhibitor attenuates nuclear β -catenin expression and promotes apoptosis in colorectal cancer cell resistant to PI3K inhibitor or AKT inhibitors [37]. Upregulation of PI3K/Akt via activation of epidermal

growth factor receptor and epidermal growth factor confers drug resistance in pancreatic cancer [47]. Activated Akt signaling associated with higher expression of PROM2 confers resistance to gemcitabine in pancreatic cancer [48]. Crosstalk between Akt signaling and scaffolding protein immune philin FKBP51 regulating PHLPP-AKT interaction involves chemoresistance in pancreatic cancer [49]. Further, increased activity of the SRPX2-PI3K/AKT/mTOR axis imparts chemoresistance in pancreatic cancer [50]. Wang et al. [51] reported chemoresistance by activated Akt/CREB/BCL-2/BAX signaling pathway modulating BAX/BCL-2 function and COL11A1 modulating apoptotic inhibition in pancreatic cancer. The interaction of activated Wnt signaling with PI3K/AKT/GSK-3 β cascade in glioblastoma imparts chemoresistance to temozolomide [52]. Activated PI3K/Akt signaling pathway via phosphorylation mediated by overexpressed tripartite motif-containing 31 (TRIM31) imparts chemoresistance in glioblastoma [53]. Similarly, an interaction between Wnt- β -catenin and PI3K-Akt signaling in leukemia stem cells [14] and interaction between Wnt/ β -catenin and Akt/mTOR pathways in hepatocellular carcinoma [15] promote resistance to therapy. Elevated expression of Akt signaling conferring chemoresistance to 5-Fluorouracil using human colon cancer cells (SNU-C5/5-FU cells) has been reported [54]. Further, crosstalk between miR-567 and PIK3AP1 activated AKT phosphorylation imparts chemoresistance in gastric cancer [55]. Cancer drug resistance in breast cancer cell line MCF-7 due to aberrant expression of GSK-3 β mediated by PI3K/PTEN/Akt/GSK-3 β pathway has been documented [56]. The authors reported that MCF-7 cells expressing Kinase Dead (KD) form of GSK-3 β were resistant to doxorubicin and tamoxifen. The crosstalk between EGFR/PI3K/PTEN/Akt/mTORC1 pathways and cancer drug resistance in breast cancer has been reviewed by Davis et al. [57]. The role of T798M mutation in HER2 imparting resistance to lapatinib, mis-splicing in HER-2 imparting resistance to Herceptin, L755S mutation in HER-2 imparting resistance to lapatinib, role of EGFR3, Ras activation imparting resistance to Akt inhibitors, activation of the PI3K/PTEN/Akt/mTORC1 pathway, mutations at PIK3CA and PTEN conferring resistance to Herceptin, the role of GSK-3 β pathway, and the role of IL-6 in imparting chemoresistance in breast cancer has been summarized. Unrestrained proliferation and genetic instability in cancer cells due to activation of PI3K/Akt/mTOR pathway and incomplete mTOR inhibition by the mTOR inhibitor (rapalogs) also results in acquired drug resistance [58,59]. Further, activation of PI3K/AKT/mTOR regulating micro-RNA expression and GSK-3 β phosphorylation with activated PI3K/AKT also contributes to chemoresistance [46]. Aurora-A-mediated activation of AKT/mTOR signaling with phosphorylation of AKT/4E-BP1 induces chemoresistance in endometrial cancer [60]. Involvement of activated PI3K/Akt/mTOR signaling In Association With Expression Of Epithelial-Mesenchymal Transition (EMT) And Cancer stem cell (CSC) marker in imparting chemoresistance in ovarian cancer and alleviation of chemoresistance in epithelial ovarian cancer by inhibiting PI3K/Akt/mTOR signaling support the role of activated PI3K/Akt/mTOR signaling in inducing chemoresistance [61].

The activated PI3K/AKT pathway stimulates its downstream molecular protein nuclear factor-kappa beta (NF- κ B), a transcription factor, plays an important role in the inflammatory response, development, growth, progression, and metastasis of various tumor and metabolic reprogramming [5,46,62]. However, activated NF- κ B signaling has been associated with cancer drug resistance [63]. Various mechanisms involving growth factor-mediated NF- κ B activation via PI3K/AKT pathway, apop-

totic MAPK and c-jun N-terminal kinase activation, EGFR phosphorylation via PI3K/AKT/NF- κ B pathway, PI3K/AKT dependent mTORC1 activation, AKT mediated NF- κ B activation, EGFR mutation mediated NF- κ B activation, KRAS mediated NF- κ B activation, and other mechanisms have been associated with resistance to DNA damaging agents [63]. Further, the role of NF- κ B in drug resistance in colon cancer via regulation of *mdr1* gene expression has been reported [64]. NF- κ B mediated drug resistance via *mdr1* regulation in liver cancer was reported based on increased NF- κ B and MDR1 expression in drug-resistant HepG2/ADM cells [65]. An association of activated PI3K/AKT/NF- κ B with the acceleration of cell cycle processes and increased P-gp expression imparts chemoresistance [46]. Increased expression of PI3K, Akt, and NF- κ B inducing the expression of ABC transporters P-gp, MRP1, and BCRP associates with drug resistance in cancer therapeutics, and the mechanisms of inducing chemoresistance has also been summarized [46].

Mitogen-activated protein kinase kinase (MEK) and Extracellular Signal-regulated Kinase (ERK) pathway

Activation of MEK and ERK due to Ras dimerization in the presence of active Ras under non-saturating B-RAF inhibitors conditions results in the limited therapeutic effect of first-generation B-RAF inhibitors (acquired drug resistance). The current focus is to generate inhibitors targeting both monomeric and dimeric Raf equally [66] in melanoma. Further, ERK mutation and amplification of ERK2 confer therapeutic resistance to ERK inhibitors [67]. However, combinational therapy of ERK with MEK inhibitors has been suggested for better results in patients with RAF/MEK inhibitors. Signaling network adaptation with ERK activation, reactivation of ERK signaling, activation of alternative pathways promoting cancer cell proliferation and survival, BRAF/CRAF amplification, genetic amplification, and mutations, and enhanced RAF protein dimerization are possible mechanisms for cancer drug resistance to RAF inhibitors [68,69]. Cancer drug resistance to ERK inhibitors is also mediated by the JNK pathway. Crosstalk between JNK and activated mTORC1 promoting tumor cell survival supports the role of JNK in inducing resistance to BRAF and MEK inhibitors in melanoma [70]. Further, Neuropilin-1 (NRP1) increased expression in association with JNK signaling confer adaptive resistance to BRAF inhibitors in melanoma [71]. JNK mediated resistance to chemotherapy is also mediated by increased Bcl2 and BclX phosphorylation and increased pro-survival protein expression [69]. Amplification of MEK1/2 and hyperactive ERK1/2 associated with drug resistance in patients with metastatic castration-resistant prostate cancer who had failed multiple treatments [72]. Mutations in ERK1/2, overexpression of EGFR/ERBB2, and amplification and overexpression of ERK2 have been proposed to confer acquired resistance [67]. Using MEK inhibitors in combination with RAF inhibitors to overcome acquired resistance in various cancers due to KRAS, NRAS, NF1, BRAF^{non-V600}, and BRAF^{V600} mutations suggests the role of overexpressed MEK signaling in ending cancer resistance [73]. The role of RAF-MEK signaling in conferring resistance and targeting alteration in these pathways for therapeutics and overcoming resistance reviewed by Yeager and Corcoran support the role of MEK signaling in cancer drug resistance [74]. This notion is further supported by decreased cell survival with enhanced induction of apoptosis in EGFR-mutant NSCLC cells with the combination of Osimertinib with a MEK or ERK inhibitor [75]. MEK/ERK-mediated drug resistance is also evidenced by resistance to cisplatin in lung cancer due to transcriptional activation of *Gstp1* by MEK/ERK signaling [76]. Targeting MEK/ERK signaling to overcome acquired resistance to

third-Generation EGFR tyrosine kinase inhibitors indicates the role of MEK/ERK in drug resistance [77]. Relapse of metastatic melanoma due to acquired resistance caused by reactivation of MEK/ERK/MYC signaling leading to ABL1/2 drive BRAF and BRAF/MEK inhibitor resistance support the role of MEK/ERK/MYC signaling in drug resistance and targeting Abl1/2-mediated reactivation of MEK/ERK/MYC signaling to attenuate resistance has been proposed as effective therapeutics to prolong survival [78]. The resistance to MEK/ERK inhibitors through SRC activation via mutation in Protein Tyrosine Phosphatase Receptor S (PTPRS) has been reported [79].

Human epidermal growth factor receptor 2 (HER-2) signaling

Targeting HER-2 with anti-HER2 therapies (trastuzumab, lapatinib, neratinib) has led to significant improvement in HER-2 positive breast cancers with better survival. However, reports of relapse and metastatic disease in breast cancer after treatment suggest acquired drug resistance [80]. The acquired resistance against HER-2 inhibitors associates with overexpression of HER2, the complexity of HER2 signaling, mode of therapeutic action of HER2 inhibitors, heterogeneity of tumor, and loss of various proteins in HER-2 positive cancers [81]. Constitutive activation of PI3K/Akt/mTOR and MAPK signaling cascade, loss of function mutation in tumor suppressor gene PTEN, activating mutation in PI3K [82], expression of p95HER2 in HER-2 overexpressing tumor cells [83], activation of Src kinases, upregulation of FGFR-2 and IGF-1, alterations in immune response and cell cycle control mechanisms, presence of cancer stem cells, and hyperactivation of the PI3K have been suggested as the possible mechanisms of acquired cancer drug resistance against HER-2 inhibitors [58,84,85]. Overexpression of HER-2 associated with increased expression and activation of IL1 α , IL6, NF κ B, and STAT3 mediating maintenance of breast cancer stem cells and promote resistance to chemotherapy in breast cancer [86]. Further, crosstalk between upregulated EGFR/ErbB pathway genes and activated compensatory pathways including Notch, Wnt, GPCR, hedgehog, insulin receptor/IGF1R, and TGF- β receptor has been documented as a cause for drug resistance in breast cancer [87]. Kang et al. reported that increased expression of NRF-2 target proteins HO-1 and MRP5 due to co-expression of constitutively active HER2 (HER2CA) and NRF2 imparts drug resistance in MCF7 cells [88]. HER-2 mediated drug resistance to trastuzumab due to overexpressed HER-2 mediated by histone demethylase PHF8 signifies the role of HER2-PHF8-IL6 signaling in inducing resistance in breast cancer [89]. HER-2 overexpression causes increased Her2 nuclear translocation and this induces paclitaxel resistance in MCF-7 breast cancer cells [90]. Targeting HER-2 overexpression with a combination of anti-HER2 agents with programmed cell death-1 ligand or cyclin-dependent kinase 4/6 inhibitors to overcome resistance in HER-2 positive breast cancer suggests the role of overexpressing HER-2 in imparting drug resistance in breast cancer. Further, the therapeutic approach of targeting HER-2 in breast cancer for better prognosis supports the role of HER-2 in chemoresistance [91]. Overcoming drug resistance to HER-2 inhibitors with a recombinant enzymatically inactive mutant of human peptidase D (PEPD^{G278D}) suggests targeting HER-2 and its role in drug resistance [92]. The role of neuromedin U (NmU) in conferring drug resistance in HER-2 positive breast cancer and association of Extracellular Vesicles (EVs) related increased TGF β 1 with chemoresistance in HER-2 positive breast cancer cells support the role of HER-2 in drug resistance [93]. Crosstalk between HER2-HER3 signaling and type-1 transmembrane sorting receptor,

sortilin-related receptor (SorLA; SORL1) attenuating lysosomal degradation imparts resistance in breast cancer [92]. Acquired resistance after initial treatment with HER-2 inhibitors occurs partially due to loss of HER-2 expression on tumor cells and Nami et al. reported that epigenetic downregulation of HER-2 during epithelial-mesenchymal transition leading to ERBB2 gene silencing imparts chemoresistance in breast cancer [94]. Fibroblasts from primary or metastatic tumors activate mTOR signaling and antiapoptotic pathway proteins Bcl-XL and MCL-1 and contribute to HER-2 kinase inhibitor lapatinib resistance in breast cancer [95]. Increased resistance to EGFR antibody inhibitor cetuximab in colorectal cancer was found due to activated ErbB2 signaling [96]. Signaling pathway redundancy due to mutations has emerged as an important mechanism for cancer drug resistance for tyrosine kinase inhibitors (cetuximab, trastuzumab, erlotinib, gefitinib, and lapatinib) in NSCLC [97,98]. Intrinsic and extrinsic resistance to EGFR inhibitors in NSCLC has also been reported due to the amplification of MET receptors activating ERBB3/PI3K/AKT signaling [99]. Cancer drug resistance to EGFR inhibitors involving ErbB2 signaling, HER-2 signaling, EGFR signaling, up-regulated TGF β and IL-6 signaling, IGF1R signaling, activated PI3K signaling, and Src kinase signaling in breast, lung, pancreatic, and colon cancer has been reviewed in the literature [6,100].

Signal transducers and activators of transcription 3 (STAT 3) signaling

Constitutively activated STAT3 associated with tumor cell proliferation, invasion, migration, and angiogenesis regulating tumor growth and metastasis [101]. However, overexpressed and activated STAT3 also imparts resistance to Src family kinase inhibitors (dasatinib) [102]. Overexpressed STAT3 confers resistance to chemotherapy-induced apoptosis in ovarian cancer by nuclear translocation and modulating mitochondrial energy metabolism via phosphorylation at S727 [103]. The association of increased mitochondrial STAT3 compared to nuclear STAT3 has also been associated with chemoresistance in ovarian cancer [104]. Activation of the IL-6/STAT3/OXPHOS axis has also been associated with stromal cell-mediated chemoresistance in acute myeloid leukemia cells and is indicative of the role of mitochondrial STAT3 [105]. Further, increased IL-6 secretion via DNA binding 1 (ID1) induced NF- κ B signaling activates STAT3 through protein phosphorylation at Y705 which further promotes activating transcription factor 6 (ATF6) transcription and confer resistance in ovarian cancer-inducing autophagy [106]. Further, the evidence of decreased expression of anti-apoptotic proteins Bcl-xL and Bcl-2, increased expression of pro-apoptotic protein Bax, and increased release of cytochrome C by silencing STAT3 in combination with cisplatin suggest that STAT3 downregulation promote anti-tumorigenesis factors. The study concluded that STAT3 silencing is associated with reversal of inherent and induced chemoresistance in ovarian cancer [107]. Moreira et al. [108] documented STAT3 as a promising biomarker of chemoresistance in triple negative breast cancer. Activated STAT3 signaling promote chemoresistance in triple negative breast cancer by regulating expression of miR-181a, TNFR1, NF- κ B, Oct-4, c-Myc, ABCC2, P-gp, ABCC6, MRP1, and transcription factors ZEB1, TWIST, SNAIL, NANOG, FOXM1, and SLUG [109]. A cross-talk between CD109-GP130 interaction through STAT3 imparts chemoresistance in glioblastoma stem cells [110]. Additionally, the role of STAT3 in conferring radiotherapy resistance in cancer has been documented [111]. STAT3-mediated MID-2 upregulation imparts chemoresistance in breast cancer through overexpression of a breast cancer-associated anti-apoptotic onco pro-

tein MORC4 [112]. Further, chemoresistance in hepatocellular carcinoma mediated by STAT3 activation by phosphorylation at Ser727 site via MAPK/ERK1/2 pathway has been reported [113]. Activated JAK/STAT3 signaling plays a crucial role in epithelial-mesenchymal transition and the generation of cancer stem cells and endues chemoresistance in Cancer [114].

Nicotinic acetylcholine receptors (nAChR)

Nicotine activates nicotinic acetylcholine receptors (nAChRs) and regulates cell proliferation, cell survival, apoptosis inhibition, and resistance to chemotherapy [115]. Nicotine, a primary component in cigarettes, and its metabolites contribute to lung cancer risk, cancer survival, and progression. Nicotine can induce chemoresistance in Non-Small Cell Lung Cancer (NSCLC) via induction of nicotinic acetylcholine receptors (nAChRs) which are membrane ligand-gated ion channels on cancer cells. Nicotine/nAChR coupling regulates signaling pathways downstream of nAChRs like JAK, PI3K/AKT, RAS, RAF, Mcl-1, caspase-3/caspase-9, apoptotic and anti-apoptotic protein expression, and MAPK signaling cascade via activation of the transcription factors STAT, NF- κ B, Jun/Fos, and E2F and mediates chemoresistance by inhibiting chemotherapy-induced apoptosis. Crosstalk between α 1nAChR and EGFR/AKT/ ERK signaling pathways promotes cancer drug resistance [115,116]. Sirtuins are the members of the family NAD⁺ dependent deacetylases, which are involved in the oxidative stress response by limiting the ROS. SIRT1 is over-expressed in the brain metastatic tissues of patients with NSCLC [117], human prostate cancer cells, and ovarian cancer. It promotes cancer cell survival, acquisition of aggressiveness, and drug resistance by inactivating cell death pathways [118]. α 5nAChR/AKT signaling and several mitochondria proteins including Bcl-2, Bax, survivin, and caspase 3 [119], α 7nAChR and NAD⁺/SIRT1 pathway [120], and nAChR signaling crosstalk with SIRT1/ 3/5-7 can promote chemotherapeutic drug resistance. Activation of these signaling pathways triggers several mechanisms like overexpression of sirtuin proteins, multisite phosphorylation of BAD, and blockade of BAX translocation, which promote drug resistance and tumor progression [121]. Besides the above-mentioned signaling pathways nicotine and its metabolites, induced chemoresistance can be partly attributed to the phosphoinositide 3-kinase (PI3K)/AKT, nuclear factor- κ B (NF- κ B), and mitochondrial signaling pathways [122-124]. α 7-Nicotine acetylcholine receptor plays a role in nicotine-induced resistance against cisplatin in oral cancer [125].

Hippo pathway

The hippo signaling pathway regulates cellular proliferation, survival, differentiation, apoptosis, stem cell self-renewal, cellular fate determination, organ size, and tissue homeostasis. Hippo signaling consists of mammalian Ste20-like serine/threonine kinase (Mst)1/2 kinases and SAV1 complex phosphorylating and activating LATS1/2 kinase which in turn phosphorylate and inhibit Yes-Associated Protein 1 (YAP) and TAZ. However, aberrant expression of the Hippo pathway has been associated with hyperproliferation, cellular invasion, metastasis, and cancer drug resistance. Increased YAP and TAZ expression involving Cyclin-Dependent Kinase 1 (CDK1) and decreased LATS1/2 expression promote Taxol resistance [126]. Zeng and Dong have summarized the Hippo components including YAP, TAZ, MST1, LATS1/2, RASSF1A, hEx, MYPT1, RASSF6, Ajuba, and Merlin imparting resistance to anti-cancer drug including paclitaxel, cisplatin, doxorubicin, 5-Fluorouracil, gemcitabine, EGFR inhibitor, anti-EGFR antibody, HER2 inhibitors, CDK4/6 inhibitor, and RAF and MEK inhibitors [127]. The molecular mechanism

involving MST1/2, SAV1, LATS1/2, MOB1, YAP, and TAZ kinases and interactive activation of MST1/2-SAV1, LATS1/2-MOB1, YAP, TAZ, RASSF1A, RASSF6, KIBRA, hEx, and Merlin in imparting resistance in various cancers have been summarized in the literature [127,128]. Increased therapeutic resistance and poor prognosis in thoracic, gastric, genitourinary, gynecological, skin, bone, and brain cancers have been associated with increased expression of YAP/TAZ and TEAD proteins in the nucleus [129]. YAP pathway plays an important role in conferring resistance to crizotinib in ROS1-positive lung cancer by regulating transcription of Epithelial-To-Mesenchymal Transition (EMT) proteins including ZEB1, SNAIL, SLUG, and VIMENTIN [130]. The role of the Hippo pathway (YAP) in imparting chemoresistance in various cancers involving KRAS signaling, MAPK/ERK signaling, miR-874-3p, circRNAs, and TEAD1 has been summarized elsewhere [131]. Cyclin-Dependent Kinase 5 (CDK5) activated Hippo pathway (TAZ) upregulation confer resistance to radiation therapy in lung cancer [132]. Overexpressed YAP-mediated activated AKT signaling and enhanced EMT, miRNA181c suppressing MST1, LATS2, MOB1, and SAV1 and activating YAP and TAZ, and miR-455-3p regulating MST1, LATS2, MOB1, SAV1, phosphor (p) YAP, and pTAZ expression confer resistance in pancreatic cancer [133,134]. Crosstalk between CD133 regulating YAP1 expression associates with radiation resistance in small-cell lung cancer [135]. The hippo pathway also regulates resistance to BET protein inhibitors in non-small cell lung cancer [136].

Epigenetic factors

Methylation, demethylation, and acetylation

Chemoresistance may also be due to a change in gene expression without changing the genotype-the epigenetic modification: an inheritable change in the gene without a change in DNA sequence [137,138]. Epigenetic modification might be due to DNA methylation, histone methylation (downregulating the gene expression), and acetylation (increasing the gene expression). EZH2 is the functional enzyme regulating embryonic development and differentiation epigenetically, however, its overexpression is associated with chemoresistance. EZH2-mediated methylation (H3K27me3) involving lncRNA HOTAIR in the death receptor 5 (DR5) gene promoter results in resistance to TRAIL-induced apoptosis [139]. Methylation of H3K27 by overexpression of EZH2 leading to attenuation of pro-apoptosis and upregulation of anti-apoptotic pathways in ovarian cancer, attenuated expression of GREB1, the Estrogen Receptor alpha (ER α) cofactor by EZH2 in breast cancer, crosstalk between EZH2 and histone lysine methyltransferases G9a conferring resistance to cisplatin in head and neck squamous cell carcinoma, and G9a mediated miR-145-5p inhibition and activation of PI3K / AKT signaling pathway causing gefitinib resistance in lung cancer has been discussed [138]. G9a also mediate EGFR-tyrosine kinase inhibitor resistance in NSCLC via activated AKT signaling mediated by increased methylation (H3K9me2) and attenuated acetylation (H3K9ac) [140]. Increased expression of H3K9me3 inhibiting Fas expression in colon cancer associates with resistance to Fas-mediated apoptosis and 5-fluorouracil chemoresistance [141]. Since increased EZH2-mediated methylation has been associated with chemoresistance in various cancers, targeting histone methylation has emerged as an attractive target to overcome therapeutic resistance and make tumor cells more sensitive to chemotherapy [142]. Along with increased methylation and attenuated acetylation, epigenetic reprogramming of tumor cells during chemotherapy can also confer drug resistance via the formation of drug-tolerant cells

called “drug-tolerant persisted” [143]. These cells may survive multiple treatment cycles and can ensue relapse and permanent resistance. Additionally, resistance-conferring mutations can also confer chemoresistance. Similarly, crosstalk between cancer cell stemless and epigenetic regulation has also been discussed as a mechanism for chemoresistance [144]. Further, aberrant promoter methylation (hypo-/hyper-methylation) of various genes involving DNMTs and histone modification involving acetylation, methylation, phosphorylation, ubiquitylation, GlcNAcylation, citrullination, crotonylation, isomerization, and lactylation may contribute to chemoresistance in various cancers as summarized in [143]. Histone demethylases (KDMs) including KDM1A, KDM5A, KDM5B, KDM5C, and KDM6A also impart resistance against tyrosine kinase inhibitors (Gefitinib, Sorafenib, Erlotinib, Sunitinib, and Imatinib) in NSCLC, hepatocellular carcinoma, breast, renal cell carcinoma, lung, and lymphoblastic leukemia [145].

Long noncoding circular RNAs (LncRNAs)

Long-noncoding RNA (lncRNA) plays a crucial role in epigenetic regulation of gene expression, DNA methylation, and histone modification. The role of various lncRNA including MRUL, MALATI, LINC01118, LUCAT1, KCNQ10T1, LINC00460, ANRIL, BLACAT1, UCA1, FOXC2-AS1, NEAT1, and H19 regulating the expression of various transporters and affecting the drug transport has been summarized [146]. Increased expression of lncRNA HCC associates with long non-coding RNA (HANR) in promoting tumorigenesis and chemoresistance to doxorubicin in hepatocellular carcinoma by regulating phosphorylation of GSK3 β [147]. The role of lncRNA including HOX Transcript Antisense Intergenic RNA (HOTAIR) and lncRNA Homo sapiens glutathione S-transferase mu 3, transcript variant 2, and non-coding RNA (GSTM3TV2) in imparting gemcitabine resistance by regulating the expression of metabolizing enzymes in pancreatic cancer and lncRNA H19 imparting resistance in colorectal cancer has been documented [148]. The role of lncRNA H19, lncRNA Very-Low-Density Lipoprotein Receptor (VLDLR)1, lncRNA PVT1, lncRNA MDR-Related And Upregulated lncrna (MRUL), lncRNA AK022798, lncRNA Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1), lncRNA ANRIL, lncRNA KCNQ10T1, lncRNA X-Inactive Specific Transcript (XIST), lncRNA linc00518, lncRNA Bladder Cancer-Associated Transcript-1 (BLACAT1), lncRNA E2F1-regulated inhibitor of cell death (ERIC), lncRNA Prostate Cancer Gene Expression Marker 1 (PCGEM1), lncRNA Cancer Upregulated Drug-Resistant Gene (CUDR), lncRNA DNA Damage-Sensitive RNA1 (DDSR1), lncRNA p21 associated ncRNA DNA Damage Activated (PANDA), lncRNAs including ERIC, PDAM, PCGEM1, CUDR, DDSR1, SCAL1, and HOTAIR in imparting chemoresistance in various cancers via inhibition of apoptosis, DNA damage repair, and oxidative stress-mediated cytotoxicity have been summarized [148]. The same article has also summarized the role of various lncRNAs in association with chemoresistance via alteration in drug targets, involvement in Epithelial-Mesenchymal Transition (EMT), exosomal lncRNAs, and lncRNAs with an epigenetic function in cancer and chemoresistance. IFN induced expression of cytoplasmic long noncoding RNA IFN-Responsive Nuclear Factor- κ B Activator (IRENA) in macrophages plays a crucial role in imparting chemoresistance in breast cancer [149]. The probable role of lncRNA nuclear paraspeckle assembly transcript 1 (NEAT1) in imparting resistance in triple-negative breast cancer was reported by Shin et al. [150]. Similarly, the role of lncRNA AX747207 in conferring chemoresistance in breast cancer by targeting RUNX3 has been documented [151]. The role of various lncRNAs in conferring

chemoresistance in ovarian cancer [152], lncRNAs in imparting chemoresistance by modulating autophagy in various cancers [153], lncRNAs regulating autophagy in colorectal cancer [154] have been reviewed.

MicroRNAs (miR)

Post-transcriptional gene expression is regulated by short non-coding RNAs termed microRNAs (miR). miR binds to 3'-UTR and suppresses the gene expression and downregulation of miR enhances gene expression. Along with playing a role in gene expression, miRNAs also play important role in therapeutic resistance. An attenuated expression of miR-181c in MCF-7 breast cancer cell line resistant to doxorubicin via osteopontin regulation suggest the role of miRs in chemoresistance [155]. miR-222 regulates miR222/bim pathway expression and promotes drug resistance to doxorubicin in breast cancer [156]. miR-499a by targeting SOX6 expression imparts chemoresistance in cervical cancer [157]. Wang et al. using bioinformatics analysis reported 10 upregulated miRNAs (e.g., miR-196a-5p, miR-4286, miR-200b-3p, etc.) and 12 downregulated miRNAs (e.g., miR-4472, miR-4467, miR-572, etc.) associated with chemoresistance in breast cancer. The authors also reported that NOTCH1, JUN, NRAS, MAPK1, BCL2, MAPK3, NFKB1, ITGA2, CDK6, and IGF1R were the hub genes for upregulated and MAPK14, PRKCA, SMARCA5, UBE2I, DVL3, WNT7B, CREB5, SLC9A1, FZD3, and NFKB1 were hub genes for downregulated miRNAs [158]. MiRNA let-7g has been reported as a biomarker for chemoresistance in human epithelial ovarian cancer [159]. Similarly, LINC01234/MicroRNA-31-5p/MAGEA3 axis plays a crucial role in conferring chemoresistance in hepatocellular carcinoma by regulating MRP2, MRP3, MDR-1, and ALB expression [160]. Chemoresistance to vincristine in retinoblastoma by increased HIF1 α expression is imparted by downregulation of Von Hippel-Lindau (VHL) tumor suppressor gene mediated by microRNA-222 [161]. Chemoresistance in colorectal cancer is regulated by c-Myc/miR-27b-3p/ATG10 regulatory axis [162]. Downregulated miR-708 expression in pancreatic cancer is associated with poor prognosis and chemoresistance while overexpression of miR-708 inhibits proliferation, invasion, and chemosensitize pancreatic cancer cells [163]. The role of various cellular and exosome microRNAs in imparting chemoresistance in breast, ovarian, lung, colorectal, gastrointestinal, pancreatic, hematological, bladder, and gynecological cancers, esophageal adenocarcinoma (hsa-let-7f-5p, hsa-miRNA-221-3p, hsa-miRNA-31-5p, and hsa-miRNA-191-5p), and glioblastoma via regulation of drug-resistance-related genes, cell survival, cell proliferation, cell cycle, apoptosis, autophagy, drug influx, drug efflux, and transport channels [164-169]. MIRs play crucial role not only imparting chemoresistance but also sensitize the tumor to chemotherapy. The role of miRNA-338-3p in sensitizing colorectal, prostate, ovarian, gastric, bladder, thyroid, liver, renal, breast, lung, and cervical cancer, melanoma, and multiple myeloma to chemotherapy by modulating MACC1, CDK4, Rab23, SphK2, Wnt2B, PTP1B, SOX4, ADAM17, ETS1, Akt3, IRS2, EGFR, and MAPK expression has been reviewed [170]. A cross-talk between miR-7 and tumor proteins YY1 and KLF-4 in inhibition of chemoresistance in Non-Hodgkin's lymphoma suggest the role of miRs in chemoresistance and sensitization [171].

Conclusion

Drug resistance is a continuing problem causing treatment failure in cancer patients and causes relapse. Thus, investigating novel therapeutics targeting factors ending drug resistance is warranted. Identification of novel moieties and targeting them

with improved drug delivery systems to enhance drug specificity and drug efficacy, drug sensitivity, increased drug concentration in cancer cells, and autophagy might be useful in minimizing drug resistance. Increasing cancer cell specificity, using growth factors, small molecules, nanotechnology, and bioinformatics analysis of sequencing data involving personalized medicine seems promising. As discussed above, chemoresistance is regulated by overexpression of multiple signaling pathways and epigenetically via microRNAs, lncRNAs, and post-transcriptional gene expression via methylation and acetylation. Thus, targeting these factors to overcome chemoresistance might overcome the issue of chemoresistance.

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