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Review

Cellular landscaping of cisplatin resistance in cervical cancer

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ABSTRACT

Cervical cancer (CC) caused by human papillomavirus (HPV) is one of the largest causes of malignancies in women worldwide. Cisplatin is one of the widely used drugs for the treatment of CC is rendered ineffective owing to drug resistance. This review highlights the cause of resistance and the mechanism of cisplatin resistance cells in CC to develop therapeutic ventures and strategies that could be utilized to overcome the aforementioned issue. These strategies would include the application of nanocarries, miRNA, CRIPSR/Cas system, and chemotherapeutics in synergy with cisplatin to not only overcome the issues of drug resistance but also enhance its anti-cancer efficiency. Moreover, we have also discussed the signaling network of cisplatin resistance cells in CC that would provide insights to develop therapeutic target sites and inhibitors. Furthermore, we have discussed the role of CC metabolism on cisplatin resistance cells and the physical and biological factors affecting the tumor microenvironments.

1. Introduction

Cervical cancer (CC) being the fourth most frequently diagnosed cancer in women, shows a survival probability of 10%–20% per year in patients with advanced stages and poor prognosis [1,2]. The constitutive expression of viral oncogenes accompanied by prolonged human papillomavirus (HPV) infection causing CC in females, specifically with higher mortality rate and drug resistance, is the fourth-largest cause of cancer death in women as per 2020 reports of GLOBOCON [2]. The risk factors that might cause or worsen the occurrence of CC are polymorphic genes, intercourse with many different partners, lamin A/C deficit, and smoking. The significance of this virus is underscored by its capacity to cause 5% of all human malignancies through HPV encoded oncoproteins (E5, E6, and E7) as key players in viral pathogenesis [3,4]. Despite being the canonical therapy, chemotherapy is deemed ineffective owing to the developing drug resistance [5].

The platinum-based chemotherapeutic small-molecule, cisplatin-based drugs (Fig. 1) was characterized as an antibacterial agent before being recognized as an anti-cancer drug to treat advanced or recurrent CC [6]. Despite its widespread use in cancer chemotherapy since its approval in 1978, cisplatin is linked to extreme complications concerning doses as well as tumor resistance [7,8]. Multiple interconnected

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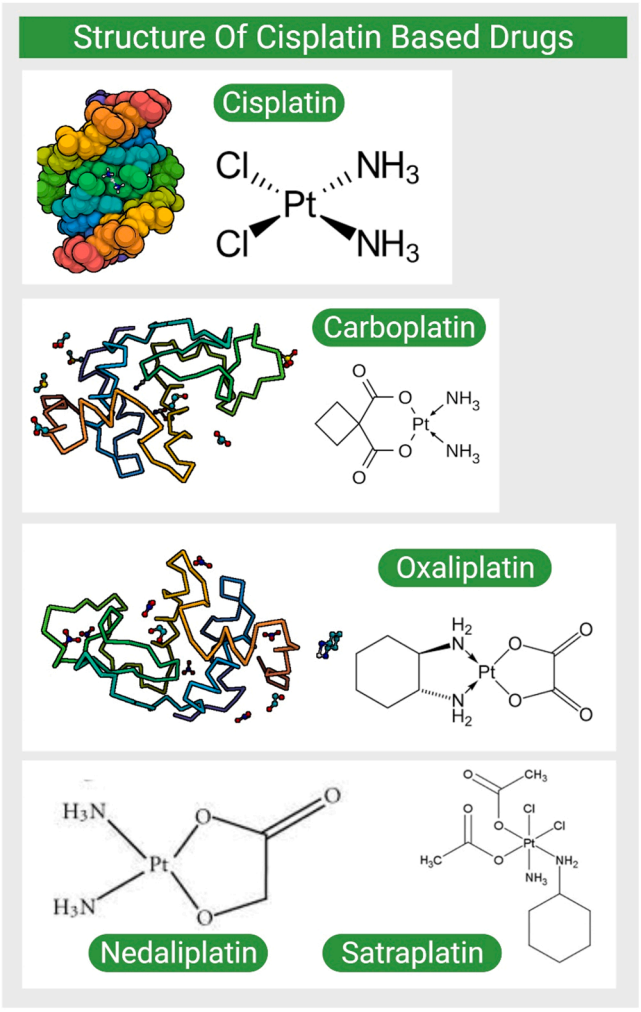

Fig. 1. Structure of cisplatin-based drugs used for the treatment of CC.

signaling pathways are implicated in the molecular mechanism underlying the anti-cancer impact of cisplatin [9]. Chemotherapy inhibits malignant cells by specifically targeting and damaging their DNA to inhibit the development and proliferation of cancer cells [10]. Considering the breakthroughs in chemotherapy, resistance to the anti-cancer drugs became a major challenge for cancer treatment due to genetic and epigenetic alterations, increased drug efflux, and decreased drug accumulation [11]. The MAPK pathway, which includes ERK, JNK, and p38 kinase, is essential for tumor cell survival, proliferation, and migration [12–14]. Targeting these signaling pathways is debatable because cisplatin-induced apoptosis is either promoted or prevented due to the hindrance to this pathway. Cisplatin along with other agents having the potential to initiate the action of cisplatin against tumor cells while having less toxic effects are administered [15–18].

In this review, we have discussed the recent developments of the mechanisms, causes, and signaling of cisplatin resistance (CPR) in CC and suggested approaches to overcome CPR in CC. These novel strategies would include the application of cisplatin in synergy with CRISPR/Cas, miRNA, phototherapy, radiotherapy, nanocarriers, and chemotherapeutics. Moreover, we have elucidated the factor affecting tumor microenvironment (TME) with cisplatin resistance cells (CRC) in CC and the role of CC metabolism with CRC contributing towards pathogenesis. This review will pave a road for not only the clinical studies to develop immunotherapies based on the combinatorial approach but also provide critical insights into the development of inhibitor and drug targets based on the understanding of the metabolism and mechanism of CRC in CC.

2. Causes of CRC

The platinum-containing drugs such as cisplatin, carboplatin, and oxaliplatin are critical in treating different types of cancers [19–24]. Studies have revealed numerous causes inducing intrinsic or acquired resistance to cancer cells against cisplatin. The molecular and cellular changes caused by epigenetics reduce platinum accumulation by either compromised influx or active efflux, minimize toxicity by glutathione (GSH) conjugates, metallothioneins, and antioxidants, changes methylation in DNA, upregulate repair of damaged DNA by mismatch repair (MMR) and nucleotide excision repair (NER), and alter membrane protein trafficking for defective cytoskeleton organization and distribution, overexpress chaperones, miRNA, transcription factors, and small GTPases as probable causes of CPR in cancer cells as illustrated in Fig. 2 [19–24].

The major alterations in gene expression levels in CPR cells lead to cell survival, reduced apoptosis, enhanced DNA damage repair, cell cycle, overexpression of chaperones, transporters, transcription factors, membrane trafficking proteins, oncogenes, small GTPases, GSH and related enzymes, cytoskeletal and mitochondrial proteins [19–24,27], resulting in lower accumulation of cisplatin and thereby reducing in platinum-DNA adduct levels; changing the phenotype of CPR cells. The expression of MRP1 and MRP2, and aquaporins AQP2 and AQP9 [28,29] are downregulated with folate-binding protein (FBP) and MRP1 [28,30] for mislocalized CPR causing reduced expression of CTR1 in CC cells. A membrane protein TMEM205 is highly expressed in CPR cells [31] and

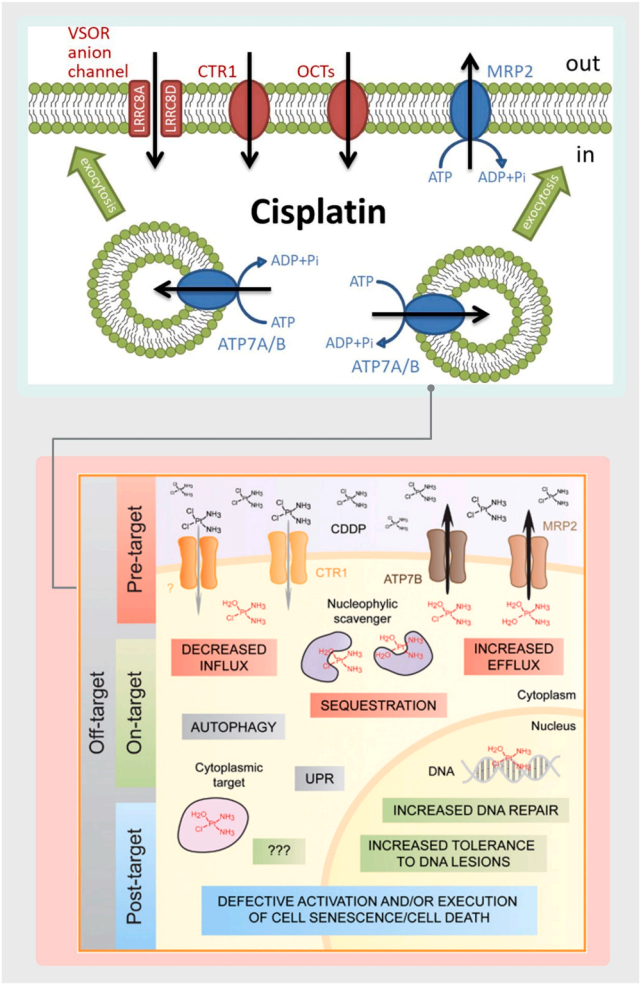

Fig. 2. Schematic representation of the causes of CRC.
Reproduced and adapted from references [25,26].

plays a major role as a biomarker in chemotherapy. The expression of glucose transporter, Glut1 is reduced and thereby influencing low glucose uptake by the cells for induction of Stir1 in CPR cells [22]. Protein homeostasis is maintained by a stress-induced molecular chaperone, heat shock protein 60 (HSP60) to protect CPR CC cells against oxidant-induced DNA damage and apoptosis. The lowered expression of small GTPases Rab5, Rac1, and RhoA, and the ribosomal protein L36 in CRC cells enhance CPR in CC [20,27]. Enhanced chromatin condensation due to overexpression of Piwi12 leads to CPR in CC cells. The promoter hypermethylation and consequent gene silencing owing to epigenetic changes play a distinct role in inducing MDR phenotypes in cells [32]. Histone modification plays a distinguished role in maintaining chromatin dynamics. The over expression of the transcription factor, p300/CBP-associated factor (PCAF), and Dishevelled protein (Dvl2) of Wnt signaling is associated in CRC cells in CC [33]. PDK1, which promotes EMT in cardiac development, is highly manifested in human CC line KB-CP-r [34].

3. Mechanism of cisplatin resistance in CC

Cisplatin is the conventional chemotherapy against CC and it is generally known as CDDP (Cis-Dichloro-Diamine-Platinum) [35]. Metastatic or recurrent CC is sensitive towards the Cisplatin and Paclitaxel conjugation in therapy and patients show an overall median survival of 12.87 months and 29.1%−67% of cases showed an overall positive response to the combined therapy [36,37]. Cisplatin is also administered in combination with other chemotherapeutic agents and immunotherapy [38]. Nevertheless, inherent or acquired resistance to cisplatin adversely affects its anticancer efficacy in cancer cells. The CPR in CC cells is mainly due to the alterations in molecular mechanisms and TME. The molecular mechanisms causing CPR are complex and herein we have highlighted all the feasible molecular mechanisms of CPR in CC as illustrated in Fig. 3.

3.1. Reduced intracellular accumulation of cisplatin

3.1.1. Reduced uptake

CC cells uptake reduced the amount of Cisplatin by 50% and 77% in CPR (HeLa-CPR) [39] and A431 (A431/Pt) cells [40]. The quantity of cisplatin-DNA adducts in HeLa-CPR is twice or thrice less than in parent cells [41]. Upon brief cisplatin, exposure DNA binding platinum and inter-strand cross-link frequency are all downregulated in CPR CC cells [42]. Cisplatin is transported across the cell membrane via passive diffusion via cisplatin lipophilicity [26,43] and its diffusion rate. Trans-membrane protein CTR1 (copper transporter 1) which maintains copper homeostasis is downregulated in CPR cell lines [44]. The co-expression of upregulated DNA–cisplatin dimer is associated with CTR1 in a murine model for controlling cisplatin absorption *in vivo*. Cisplatin DNA dimers were found to be corelated with the expression of CTR1 mRNA in the various organism, suggesting that CTR1 regulates cisplatin uptake in cells [45]. The parental cell A431 and its cisplatin-resistant cell line, A431/Pt shows over expression of CTR1 but on the contrary, over expression of CTR1 is ineffective towards cisplatin assimilation and susceptibility in the cell [40,45]. Thus, the involvement of CTR1 in cisplatin transport across the membrane may differ in different CC cells.

3.1.2. Enhanced efflux

The cisplatin export is mediated by ATP-binding cassette (ABC) transporters including MRP1, MRP2, MRP3, and MRP5 [46,47]. MRP1

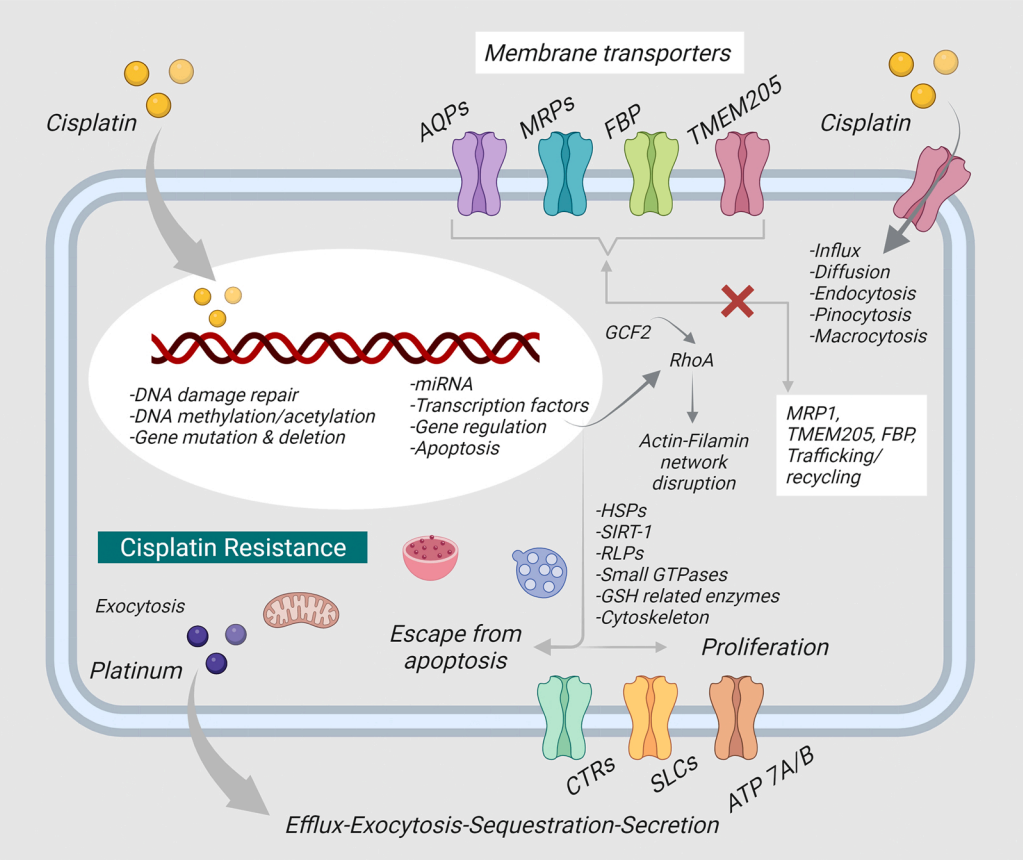

Fig. 3. Schematic representation of the mechanism of cisplatin resistance in CC.

overexpression has been linked to CPR in CC cells [48] but MRP2 expression is considerably less in CPR CC cells exhibiting elevated levels in cisplatin-sensitive cells depicting an inverse role. P-glycoprotein is an ABC transporter (P-gp, ABCB1), up-regulated in CPR CC cell line [48], influences cisplatin efflux, and when HeLa cell line [49] is introduced to cisplatin, higher expression of P-gp limits apoptosis. P-gp action was minimized in cisplatin-resistant HeLa cells indicating P-gp is a non-significant promoter of cisplatin resistance in the HeLa cell line [50]. As compared to parental cells, genes such as CTR1, MRP-2, GSR, GSS, GPX, MGST1, ATP7A, and ATP7B, are copper-transporting ATPases involved in cisplatin efflux [40,44] and are upregulated 1.4- and 2.5-fold in SiHaCIS-R cells [51]. Nucleolin (NCL) is a nucleoplasmic multifunctional protein that induces cisplatin resistance in CC via the YB1-MDR1 pathway [52]. Overexpression of NCL in CRC HeLa cells was linked to enhanced expression of MDR1 (Multidrug Resistant Protein 1) leading to more efflux of cisplatin. NCL overexpression also induces increased expression of the YB1 (Y-Box Protein 1) transcription factor [52]. The organic cation transporter 3 (OCT3), is a cisplatin transporter that transports both intrinsic and extrinsic organic cations. The overexpression of OCT3 upregulates cisplatin aggregation and toxicity in cells whereas OCT3 suppression by siRNA or pharmacological inhibitors promotes cisplatin tolerance in CC cells [53]. The OCT3 expression in CPR CC cells is much lower than in the parental cell lines. A member of the mammalian 4-tetratransmembrane spanning protein superfamily is Lysosome-associated protein transmembrane 4B-35 (LAPTM4B-35) which is significantly upregulated in CC cells and associated with poor prospects [54]. The activation of PI3K/AKT signaling by the interaction of LAPTM4B-35 with P-gp decreases apoptosis and produces MDR in CC cells by booming efflux of drugs [55].

3.1.3. Inactivation of thiol-containing protein

DNA damage caused by DNA-Cisplatin dimer results in cytotoxicity and thereby triggers DNA damage-induced apoptosis cascade [47]. When cisplatin binds to nucleophilic substances in cytoplasm such as glutathione (GSH), metallothioneins (MTs), methionine, and thiol-containing proteins, it causes oxidative stress and decreases the availability of reactive cisplatin [47]. The enhanced expression of enzymes promotes synthesis and conjugation of GSH, a tripeptide (Glu--Cys-Gly) consisting of thiols, such as GSH-S-transferase (GST), gamma-glutamyl transferase, and gamma-glutamyl cysteine synthase and aid in the development of CPR. GSH binds to cisplatin thus hindering the attachment to DNA targets, quenching pro-apoptotic ROS generated by cisplatin, and decreasing cell susceptibility to cell death signals [47]. GSH associated with CPR in CC cell lines [56–58] induces gene up-regulation of *GSTP1*, *GSTA4*, and *GSTK1* [59]. The involvement of metallothionein in cisplatin-resistant squamous CC cells of humans exposed a strong connection between MT expression and CPR [57]. Chao et al. [60] exhibited that neither intracellular GSH levels nor GST activity was increased in CPR HeLa cells whereas the GSH level in the CPR remained unchanged in CC [48]. Thus, there is a scope of study on the responsibility of GSH and its metabolic activity in CPR in CC. MTs are thiol-containing proteins with a low molecular weight that regulate the metal balance and elimination and may bind to cisplatin, resulting in the CPR phenotype [61].

3.2. Increased repair of damaged DNA

CC cells with inherited CPR are more capable of repairing cisplatin-induced DNA lesions or tolerating a greater number of undamaged DNA lesions than their parental cisplatin-sensitive cells [26]. CPR cells exhibit a greater number of repair-linked DNA strand breaks as well as increased activity of DNA excision repair [39,41]. DNA repair pathways such as MMR and NER are the most common pathways that determine and overhaul cisplatin-induced DNA lesions. The DNA–cisplatin adducts are majorly repaired by the highly conserved NER pathway [35]. Excision repair cross-complementation group 1 (ERCC1) is one among more than 20 proteins involved in NER. ERCC1, which is overexpressed in CPR CC cells HCA-1R, is a ss-DNA endonuclease that interacts with ERCC4 to cleave DNA on the 5′ side of DNA–cisplatin adducts [47]. Lower expression of ERCC1 is associated with sensitivity toward cisplatin-based chemotherapy leading to the survival of patients [62,63]. The mismatches that occur during DNA replication but escape proofreading, are corrected by DNA MMR [63]. MMR deficiency might result in tolerance to DNA damage and resistance to CDDP. MutS homolog 2 (MSH2) protein, being one of the MMR proteins are found to promote the development of CPR in CC cells [64]. Expression of MSH2 protein was downregulated in CPR A431 cells than in parental cells [42]. While PMS2 (post-meiotic segregation) overexpression in HeLa cells greatly increases the activity of caspase-3 and cisplatin-promoted apoptosis, it is a key component of the MMR that is downregulated in CC. [65]. Furthermore, REV3L a catalytic component of DNA polymerase plays an important role in avoiding DNA damage during trans-lession synthesis. REV3L provided CRC in CC cells by modulating apoptosis and production of anti-apoptotic proteins (B-cell lymphoma 2 (Bcl-2), myeloid cell leukemia sequence 1 (Mcl-1), Bcl-xL, and pro-apoptotic Bcl-2-associated x protein (Bax) [66].

3.3. Apoptotic pathway inactivation

The extrinsic death receptor pathway or the intrinsic mitochondrial pathway of apoptosis is triggered by cisplatin. Caspases play significant roles in apoptosis when activated by pro-apoptotic proteins and the action of caspase-3, 8, and 9 is reduced in CRC [67]. Caspase-3 activation is reduced in MDR cells than that of drug-sensitive parental cells upon CPR in CC [68]. Studies showed that caspase-3 and caspase-8 remain downregulated when MALAT1 is overexpressed in CC promoting CPR and cell proliferation [69]. When exposed to cisplatin, anti-apoptotic proteins are overexpressed in CPR CC cells leading to programmed cell death [70]. In comparison to the parental cell line, Bcl-2 was found to increase significantly in CRC HeLa cells [71]. A higher level of Bcl-xL and Bag-1 has been expressed in MDR endo-cervical HEN-16–2/cisplatin cells compared to that of their drug-sensitive parent cell [68]. Bag-1 is overexpressed in C33A cells, causing hindrance to cisplatin-induced apoptosis [70]. Furthermore, HeLa cells are protected against cisplatin-promoted apoptosis by regulating Raf/Ras signaling and production of Mcl-1 and heat shock proteins (HSPs) due to overexpression of Bag-1 L [48]. CPR growth is aided by the inhibition of pro-apoptotic effector proteins as well as the overexpression of anti-apoptotic proteins [67].

Wang et al. exhibited that lncRNA, MALAT1 promotes cisplatin resistance in CC via PIK3/AKT pathway [69]. MALAT1 upregulated anti-apoptotic proteins such as Bcl-2 and Bcl-xL and down-regulated apoptotic genes such as Caspases 3 and 8 to inhibit apoptosis in cisplatin-treated CC cells [72,73]. An apoptotic promoter and target gene of miR-181a, PRKCD was negatively regulated by miR-181a and its overexpression in CC inhibited therapeutic response to cisplatin [74]. Wang et al. showed the upregulation of stanniocalcin 2 (STC2) in CC altered the MAPK signaling pathway and promoted cell proliferation and CRC [75]. It was found that the apoptosis was inhibited by the overexpression of DEC1 (Differentiated embryonic chondrocyte gene in cisplatin-treated HeLa cells), which promotes anti-apoptosis via stem cell biomarkers, SOX2, and cMyc in CC [76]. The probable curative prospects of Cisplatin and NF-κB suppressors in the treatment of CC are well studied. The suppression of NF-κB made SiHa cells more susceptible to cisplatin-promoted apoptosis, demonstrating that the combination of these therapies causes tumor regression [77].

3.4. Activation of epithelial-mesenchymal transition (EMT)

The EMT is instigated in CC cells through activation of the TGF-β pathway by administering a minimum cisplatin concentration (1 μM) as therapy. TWIST1 is a transcription factor playing a key role in EMT by

downregulating MDR1/P-gp expression, reducing cell growth, inhibiting rhodamine 123 efflux, and sensitizing cells to cisplatin in HeLa cells [78]. High CPR in CC cells causes up-regulation of SNAIL1 and E-cadherin but low CPR cells did not, suggesting that SNAIL1 and E-cadherin overexpression occur at a later stage of CPR formation, facilitating cell survival under high-dose cisplatin [78]. Sema4C, the target of many miRNAs such as miR-31–3p, is over-expressed in CRC with CC and induces EMT [79]. The high level of expression of the protein, iASPP, is translated from gene PPP1R13L gene and linked to human tumors [80]. It inhibits the function of p53 via miR-20a-FBXL5/BTG3 signaling and attenuates cisplatin-induced apoptosis, promoting EMT [81].

3.5. *miRNA and molecular chaperons*

The changes in expression of genes for drug response, affecting cancer cell susceptibility to CRC are due to DNA methylation [78]. Shen et al. found that the folate binding (FBP) gene, which was hypermethylated in CPR cells, could be demethylated by DNA demethylation agent 2-deoxy-5-aza-cytidine (DAC) [78]. Various studies revealed that epigenetic mechanisms in cancer dysregulated different miRNAs [82,83]. Satyamoorthy et al. performed microarray data analysis wherein miR-200b and miR-34c promoters were hypomethylated while, miR-424 was identified as hypermethylated [84]. The hypermethylated promoter such as SOCS and ZNF582 exhibited resistance to chemotherapeutic radiation towards CC cells [79,85].

miRNAs regulate numerous pathways associated with cisplatin cellular response [86]. In comparison to the parental KB-3–1 cell line, miR-181 family members were found to be more abundant in KB-CP5 and KB-CP20 CPR cells, and proteins such as DICER and TRBP2 that are essential for microRNA synthesis are silenced leading to a reversal in CPR [87]. The elevated levels of MDR1/P-gp and mitoxantrone resistance protein (MXR)/breast cancer resistance protein-1 (BCRP-1) make the CSC (cancer stem cells) tolerant to chemotherapeutic agents [88]. ALDH was identified as a biomarker for Cervical CSCs (cancer stem cells) and elevated ALDH action was related to greater resistance to CDDP in cervical cancer cells [89]. MiR-20a mediates iASPP-induced EMT and cisplatin resistance whereas miR-31–3p was downregulated significantly in CC than in the surrounding non-tumor cells [79,90]. When Sema4C is directly targeted by miRNAs including miR-125b, miR-25–3p, miR-205, miR-138, and miR-31, is associated with the EMT-mediated CPR in different malignant tumors [91]. The cisplatin resistance of CC cells has been promoted by miR-181a by targeting PRKCD [74].

Molecular chaperones involved in stress responses, like autophagy and HSPs, enhances CPR through a variety of indirect pathways [26,47]. Cisplatin promotes autophagy in HeLa cells, and suppression of it produces ER stress, increasing cisplatin cytotoxicity [92]. The overexpression of HSP 60 in CPR cells in CC and the overexpression of heat shock cognate protein 71 (HSC71) and HSP 60 in CPR cells, A431/Pt cells as compared to parental A431 cells [93,94]. HSP 70 is also highly expressed in CDDP resistant CC cells and HSP 70 knockdown is a suggested strategy to enhance the cisplatin-induced apoptosis in CC [95].

4. Factors affecting TME in CC with CRC

TME plays an essential role in the advancement of tolerance to cisplatin, lowering its therapeutic efficiency in cancer cells as illustrated in Fig. 4 [39,96]. There are two groups of TME factors, physical and biological components, which affect the drug resistance in CC, and herein we have elucidated both of those aforementioned factors.

4.1. *Physical factor*

The physical components like high cell density, fluidic shear stress, and extracellular matrix (ECM) impedes cisplatin distribution and effectiveness in cancer cells. The non-cancerous cells such as stromal cells, tumor-associated fibroblasts, and immune cells and the biochemical implications of cancer progression likely, hypoxic and acidic environments are the constituents of the biological component of TME [97,98]. The diffusion capacity of various chemotherapy drugs, including cisplatin, is limited by the densely packed tumor cells, which are the initial hindrance of TME and reduces cytotoxicity in tumor cells [97,98]. In tumorigenesis, the interaction between the surrounding ECM and disordered adjacent arteries for increased interstitial fluid pressure is known as fluidic shear stress, which is the second physical component of TME that contributes to CPR [99].

The most significant non-cellular component of the TME is the ECM comprising of collagen, laminin, and fibronectin for scaffolding of tissue dynamics [100]. Changes in the flexibility of the ECM provide a physical barrier inhibiting chemotherapeutics from reaching cancer cells. Furthermore, interactions between the ECM and surrounding cells increase chemotherapeutic drug resistance by activating survival proteins [39,40,101]. Recent studies found that hyaluronic acid (HA), a major component of ECM, played a major role in proliferation, migration,

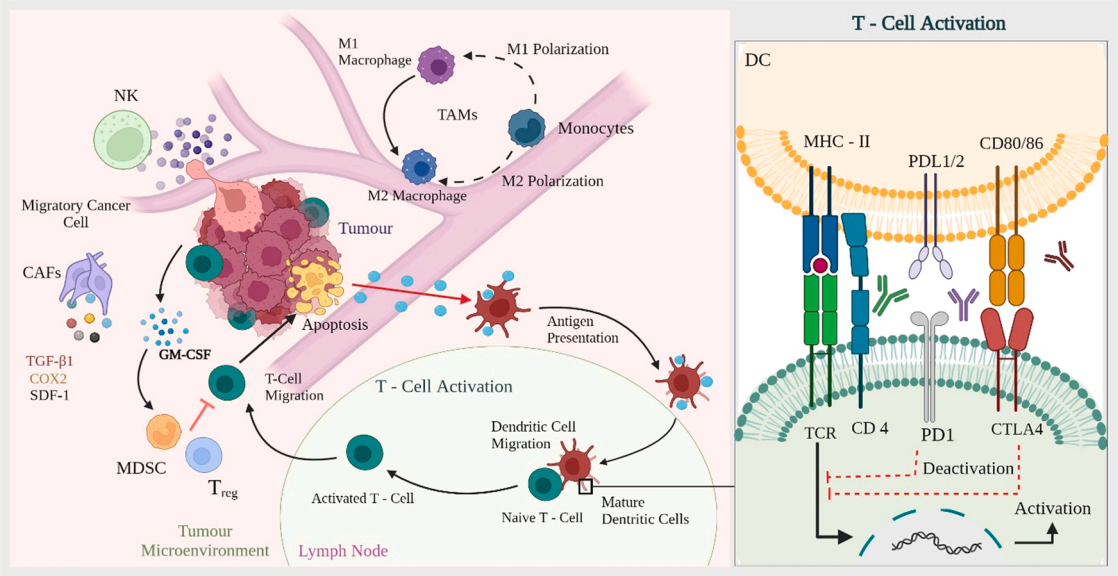

Fig. 4. Graphical model depicting the role of tumor microenvironment in CC.

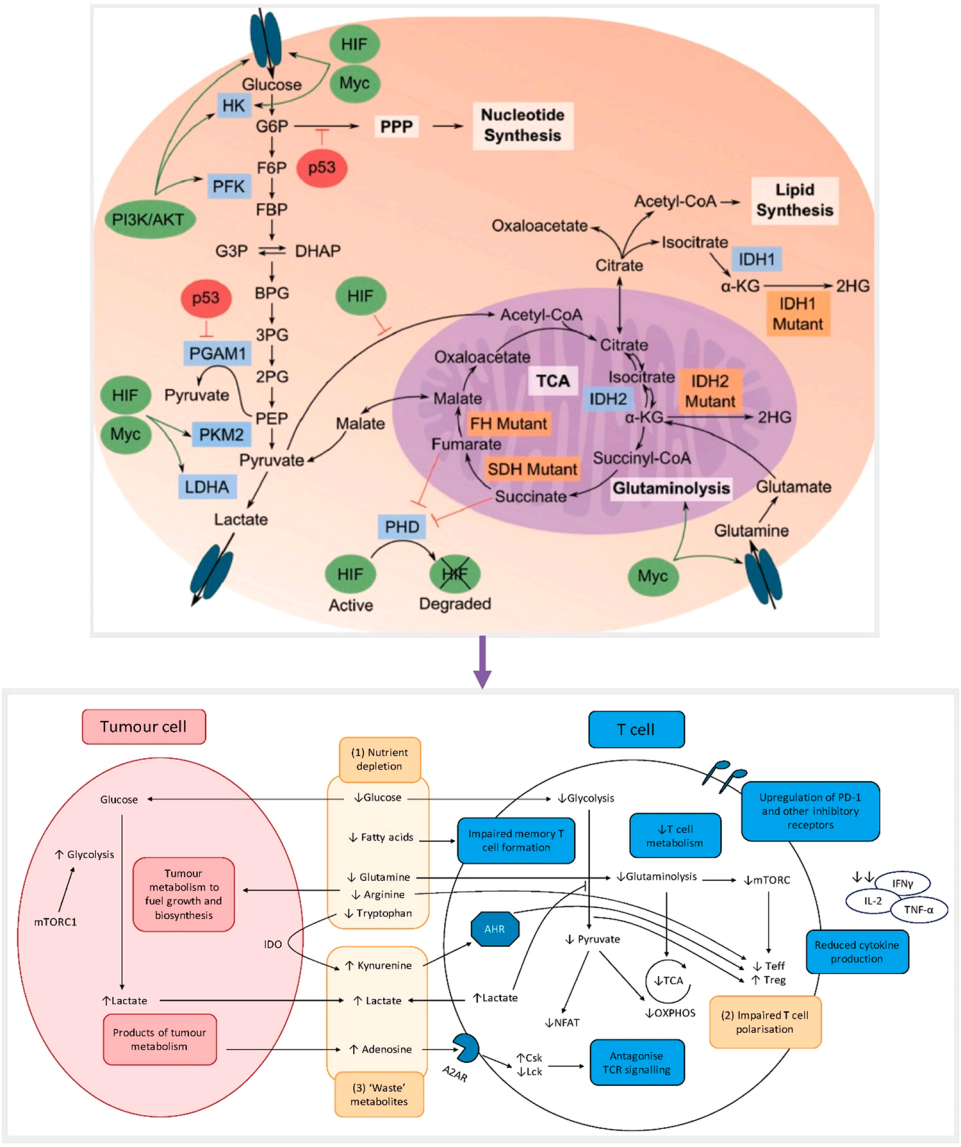

Fig. 5. The signaling cascade of CC metabolism in the TME highlights the relationships between metabolome, proteome, and genome in cancerous cells and metabolic reprogramming of the cancer cell. Reproduced and adapted from ref [142,143]. Glycolysis breaks down glucose into pyruvate, which is then fermented to lactate; pyruvate flux through the tricarboxylic acid (TCA) cycle is down-regulated in cancer cells. Pathways branching off of glycolysis, such as the pentose phosphate pathway (PPP), generate biochemical building blocks to sustain the high proliferative rate of cancer cells. Cancer cells require extensive metabolic reprogramming to fuel anabolic growth via increased nucleotide biosynthesis, protein synthesis, and FA synthesis. There is elevated glycolysis even under aerobic conditions (Warburg effect), which allows for the production of intermediates to be channeled into the PPP for nucleotide biosynthesis. However, a majority of tumors still retain the oxidative capacity to produce ATP via OXPHOS. Glutaminolysis is also upregulated in many tumors for the production of α-KG to fuel the TCA cycle. Increased glutaminolysis also produces glutathione (GSH) to defend against oxidative stress. Central to these metabolic changes is the PI3K/Akt/mTOR pathway. Downstream effectors that are activated by mTORC signaling include the transcription factors HIF-1 and SREBP.

invasion, angiogenesis, and chemo-resistance in Pancreatic ductal adenocarcinoma (PDAC) [101]. Levental et al. showed that overexpression of LOX increases ECM stiffness, leading to focal adhesion assembly and enhanced ERK and PI3K signaling for facilitating oncogenic transformation [102].

Major studies revealed that collagens, which are major components of ECM, are deposited in a high amount during tumorigenesis [103,104]. Various ECM components, such as endostatin, arresten, canstatin, hexastatin, and tumstatin generated from collagen IV and XVIII, have profound stimulatory or inhibitory effects on angiogenesis and interact with pro- or anti-angiogenic factors, such as VEGF to initiate or terminate vascularization [105]. Cell Adhesion Mediated-Drug Resistance (CAM-DR) is a kind of chemo-resistance produced primarily by interactions between tumor cells and ligands in the TME

4.2. Biological factors

Tumor tissue hypoxia occurs as a result of tumor cell aggregation and decreased blood supply. Low oxygen levels at the tumor location promote potency in the cancer cell and expression of multidrug transporter protein, leading to CPR [106–110]. In addition to restricted oxygen delivery, a lack of nutrients from disordered tumor vasculature drives tumor cells towards glycolysis and the formation of more acidic waste [111,112]. This acidic TME can increase the expression of multidrug transporters while decreasing intracellular cisplatin accumulation [113,114].

There are many intercellular interactions in TME that confer CRC in CC cells [111]. Carcinoma-associated fibroblasts (CAFs) are widely studied for their role in providing CPR [112,115–119] through CAF-secreted chemokines or growth factors (IL-6, IL-8, IL-11, IGF-1, and TGF-β). Moreover, TAMs play a critical role in tumor progression and chemotherapy drug resistance [120]. The tumor growth is inhibited by M1-type macrophages by inducing an inflammatory response whereas M2-type macrophages suppress the immune response and help in tumor progression. The promotion of tumor angiogenesis, alteration of ECMs, increasing cancer cell pluripotency, decreasing host immune response, and inducing CPR in tumour cells through TAM-secreted cytokines including IL-6 and type I interferon (IFN) are mediated by TAMs [121,122]. The release of extracellular vehicles (EVs), exosomes and micro-vesicles might be accountable for cell-to-cell interaction in the tumor micro-environment, and they provoked the CPR in tumor cells [123–126].

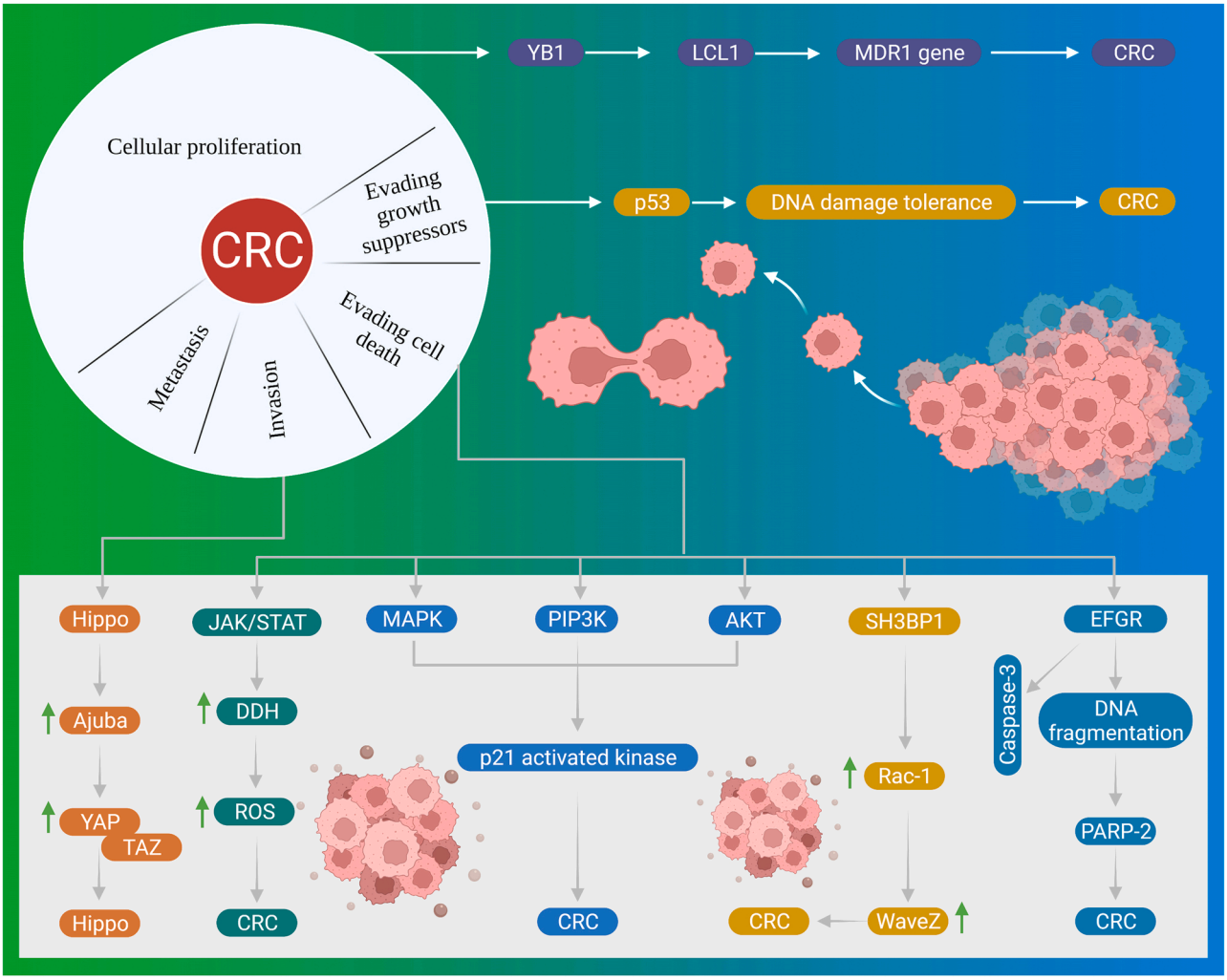

Fig. 6. Schematic model depicting the role of signaling cascade for cisplatin resistance in cervical cancer.

5. Role of CC metabolism in CRC

The interaction between DNA damage repair and metabolism is mediated by alterations in metabolic pathways of glucose, amino acid, and lipid, to influence CPR in CC cells and utilize an altered metabolism to acquire the energy, biosynthesis, and oxidation-reduction reaction causing continuous growth as illustrated in Fig. 5 [127].

Under aerobic circumstances, normal cells undergo the glycolytic–-tricarboxylic acid (TCA) cycle via phosphorylation in tumor cells for glycolysis as the primary mechanism of energy generation because of their higher need for energy. The Warburg effect refers to the remodeling of glucose metabolism in tumor cells involving alterations in the intermediates of metabolism that supply biosynthetic materials for the division and growth of tumor cells [128]. CRP is induced in CC by glucose uptake being upregulated and aerobic glycolysis being enhanced [129]. Glucose transporter 1 (GLUT1) is involved in glucose transport across the membrane to supply energy to cells. Cisplatin reduced glycolysis by reducing the up-regulation of GLUT1, GLUT4, LDHA, and other glycolysis-related proteins in CC cells [130]. The glycolysis level is enhanced for promoting acetate and fatty acid synthesis [131].

Amino acid and its metabolism are critical [132–134] for tumor growth through nutritional stress, oxidative stress, and genotoxicity causing CPR in CC cells. Glutamine enters the mitochondria in the TCA cycle as a respiratory substrate and promotes ATP generation [135], biosynthesis of GSH, production of NADPH and maintains cellular redox homeostasis [136]. ASCT2 (SLC1A5), a glutamine transporter [137] was shown to be overexpressed in A549 wild-type cells and CPR cells but not in normal lung fibroblasts [138]. The antioxidant capacity of CRC cells allows them to endure cytotoxicity enhanced via catabolic breakdown of glutamine through KRAS oncogene. The alteration in lipid metabolism in CC cells is recently identified as the hallmark of cancer indicating abnormal lipid metabolism [139–141], as it not only acts as signaling molecules but also serves as an energy source. Thus, increased lipid absorption, storage, and fat synthesis indicate abnormal tumor development in CC. The lipid metabolism influences cell survival, membrane fluidity, and dynamics, along with chemotherapeutic response through CRC [141].

6. Modulation of CRC in CC through signaling

6.1. p53 pathway

Alterations in the TP53 gene cause functional loss of the tumor suppressor known as p53, which is often seen in cancers as illustrated in Fig. 6. The ability of high-risk HPV to bind with and negate the activity of p53 via viral oncoprotein E6 and is closely connected to CC [144]. E6 interacts with E6-associated protein (E6AP), a 100-kDa cellular protein that serves as a ubiquitin-protein ligase. E6-AP catalysis multi-ubiquitination causes the breakdown of p53 after the dimeric complex attaches to it. E6 through high-risk HPV strains is the only oncoprotein capable of triggering p53 breakdown.

The E6 proteins due to low-risk strains do not possess this ability

although they can bind to p53 [145]. The wild-type p53 gene is found in the majority of CC cells, which is consistent with the E6 function of high-risk HPV strains. However, the protein levels are significantly reduced. The p53 gene is mutated in a small percentage of cervical malignancies in several investigations but appears to be unaffected by the presence or absence of HPV infection and the type of tumor [144]. The stability required for the cisplatin-induced apoptosis is promoted by the p53 pathway. Apoptosis is hampered by p53 depletion, which leads to DNA damage tolerance and increased treatment resistance. Patients with wild-type p53 benefit better from cisplatin-based treatment for CC than those with mutant p53. There are a higher proportion of p53-positive cells in patients who respond well to cisplatin than non-responders [35,146].

6.2. PIP3K/Akt/MAPK pathway

The Phosphatidylinositol 3-kinase (PI3K) and protein kinase B (Akt) pathways are involved in cell growth and programmed cell death via hormones or growth factors that enhance extracellular signaling and are significant in CC development as illustrated in Fig. 6 [147]. Zhang et al. correlated the upregulated PI3K levels in CC tissue than in surrounding normal tissue [148]. PI3K/Akt signaling is implicated in chemo-resistance either directly or indirectly. p21-activated kinases (PAKs), a class of serine/threonine protein kinases, regulate cell cycle progression and hence contribute to cancer progression [149]. The upregulation of PAK4 in CC as compared to pre-tumor tissues reduces the cisplatin treatment rate of response in a PI3K/Akt-dependent manner [150]. MAPK activity in CPR cancer cells is frequently decreased and thus, cisplatin-induced activation of SAPK/JNK is limited in CPR cells [71,151,152]. The inhibiting MEK-ERK with the MEK inhibitor PD98059 promotes CPR in the CC cell line [153].

6.3. EGFR pathway

Epidermal growth factor receptor (EGFR) is an overexpressed oncogene in CC involved in chemo-resistance as illustrated in Fig. 6. EGFR regulates CRC in CC via upregulating tissue factor (TF) and the protease-activated receptors (PAR) 1 and 2 [154]. However, there is a little investigation on the significance of coagulation proteins in the advancement of CC. EGFR, TF, and PAR2 expression levels were higher in the more aggressive cell line CASKI than in C33A. Furthermore, PAR2 transactivated EGFR, which increased the expression of cyclooxygenase-2 (COX2) [154].

The EGFR signaling pathway promotes chemo-resistance in CC through apoptosis characterized by inter-nucleosomal DNA fragmentation in a caspase-3-dependent manner. In a cisplatin dose-dependent manner, PAR2 activation by FVIIa lowers the fraction of cells displaying this apoptotic signal. CASKI cells are protected against cisplatin-induced apoptosis by 25% when treated with FVIIa, a PAR2-AP-induced chemo-resistance. The cisplatin enhanced caspase-3 and PARP cleavage, and reduced cisplatin-induced caspase-3 and PARP cleavage when pre-treatment of CC cells with PAR2-AP [155,156]. The positive feedback loop is indicated by increased production of TF, associated with plasma-derived FVII/FVIIa to form a dimer that cleaves and activates PAR2 on tumor cells. The caspase-3 cleavage induced by cisplatin in CC cells is finally lowered because of the signaling pathways being activated and thus resulting in chemo-resistance and limiting apoptosis. The potential adjuvants to chemotherapeutic agents for CC treatment are non-steroidal anti-inflammatory medications (NSAIDs), EGFR inhibitors, and PAR2 antagonists [155,156].

6.4. JAK-STAT pathway

The Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway is a key regulator of biological activities like cell proliferation, migration, and apoptosis in CC as illustrated in Fig. 6 [157]. In CC cells, STAT3 expression is shown to be much greater. Furthermore, when STAT3 expression levels in patients with no discernible response to chemotherapy were compared to STAT3 expression with cisplatin, higher levels were exhibited [158]. The patients possessing advanced CC locally were responsive to chemo-radiation therapy and possess a greater level of STAT1 than resistant cases, indicating that STAT1 may contribute to enhanced radio-sensitivity [159].

The cisplatin expression is increased in knocked down cells due to phosphorylation of JNK and p38, revealing a relationship between DDH1 overexpression in CPR cells and faulty downstream signaling pathways involved in ROS production and MAP kinase activation [160]. DDH (a cytoplasmic protein) causes CRC in CC which operates in an NADPH-dependent way for being an active carcinogen through ROS amplification [161]. Among the DDH proteins, DDH1 is the most abundant cytoplasmic protein, and DDH3 is the least. DDH3 was reduced in cervical DDH1 knockdowns [161]. Cisplatin treatment of the CC cell line results in ROS production due to alterations in depolarization of the mitochondrial membrane and JNK/p38 phosphorylation [162]. DDH1, a cisplatin-resistant cell line increases mitochondrial membrane depolarization and ROS generation after treating with cisplatin [163,164].

There is a need for clinical studies in CC to determine whether the use of these compounds could improve the survival of the patient, and assess the toxicity of these therapies against chemoresistance induced by STAT3. JAK2, STAT3, and STAT5 suppressors limit cell growth to promote apoptosis and enhance responsiveness to cisplatin in CC [165–167]. The utilization of interfering STAT3 siRNAs which diminish the resilience of CC to CRC is another strategy for inhibiting or reducing STAT3 activity. Furthermore, the administration of certain drugs, such as arctigenin, mahanin, and propofol enhances the induction of cell death by blocking STAT3 [168]. The JAK/STAT pathway is involved in immune activation and regulatory activities, such as tumor cell identification and tumor-driven immune escape [169–172]. The clinically licensed JAK2 inhibitor ruxolitinib works in tandem with cisplatin to induce cell death in HPV+ CC cells. Ruxolitinib and cisplatin alone decrease proliferation and causes apoptosis, indicating that both therapies might synergistically induce apoptosis in HPV+ CC cells [169–172].

6.5. Hippo pathway

The Hippo pathway regulates organ size, tissue homeostasis, regeneration, and signaling dysregulation caused by overexpression of the transcriptional co-activator YAP/TAZ leads to uncontrolled cell growth and malignancy as illustrated in Fig. 6 [173]. The essential components of the Hippo pathway cause carcinogenesis by encouraging tumor stem cells and proliferation, which leads to metastasis and drug resistance, common in gynecological cancers [174]. The overexpression of Ajuba protein in CC promotes CRC by upregulating its downstream mediators

Table 1
Synopsis of CRC-based signaling in CC.

Cellular signaling	Type of pre-clinical studies	Impact over hallmark	Reference
p53	*In-vivo*	Evading growth suppressor	[35,146]
PIP3K/Akt/MAPK	*In-vitro*	Evading cell death	[71,147,151,152]
EGFR	*In-vitro*	Evading cell death	[154–156]
JAK-STAT	*In-vitro*	Evading cell death	[157,165–167]
Hippo	*In-vitro*	Activating invasion and metastasis	[173,175]
SH3BP1	*In-vivo*	Resist cell death	[178]
YB1	*In-vitro*	Sustaining proliferative signaling	[52,183]

YAP and TAZ in Hippo signaling in Hela and SiHa cells [175]. There is transcriptional dependent regulation of the Hippo signaling by AJUBA [176]. Clinical research revealed a significant link between the expression of AJUBA and the expressions of YAP and YAZ in patients, as well as a favorable correlation between AJUBA and TAZ [177]. Thus, the Hippo signaling pathway may have been engaged in the AJUBA-based CRC in CC.

6.6. SH3BP1 pathway

SH3BP1, which inactivates Rac1 and its target Wave2, is required for cell motility and is hence thought to be an important regulator of cancer cell metastasis [178]. SH3BP1's specific impacts and molecular pathways in CC development, however, are still unknown. Patients with CC who have increased SH3BP1 expression have a reduced overall survival rate [179,180]. A Rac1 inhibitor, NSC 23766, could partially reverse SH3BP1's promoter action. The SH3BP1 overexpression enhances cell invasion, migration, and chemo-resistance in CC via Rac1 activity and Wave2 levels [178]. SH3BP1 enhances cell chemo-resistance in response to SH3BP1 overexpression to Rac1 activity and Wave2 protein level with CRC in CC [178]. The overexpression of SH3BP1 enhances Rac1 activity, whereas SH3BP1 knockdown inhibits Rac1 activity [178]. SH3BP1 overexpression raised Wave2 protein levels but SH3BP1 knockdown decreased Wave2 protein levels. When CC tissues were compared to cisplatin-sensitive CC tissues, the mRNA expression of SH3BP1, Rac1, and Wave2 was dramatically up-regulated by CRC [178]. Rac1 inhibitors partially counteract the pro-inflammatory impact of SH3BP1 and are substantially higher in cisplatin-resistant than cisplatin-sensitive in CC [181]. Thus, indicating that the SH3BP1/Rac1/Wave2 pathway possesses the potential for a successful therapeutic target for CC.

6.7. YB1 pathway

Box binding factor 1 (YB-1) has been linked to poor prognosis with various stages of cancer as illustrated in Fig. 6. Tumor cell development is inhibited when YB-1 expression is reduced, although the mechanism is unknown [182]. YB-1 expression is linked to the activity of E2F transcription factors, suggesting that this pathway might be used to regulate tumor cell development [183]. In the case of Hela/DDP cells, NCL (Nucleolin) protein levels were found to be higher, which consequently caused CC cell growth while lowering cisplatin susceptibility.

The overexpression of the NCL gene increased MDR1 gene expression and drug efflux. In CC, NCL was found to be highly associated with CRC. NCL had a major function in the transcription of the MDR1 gene by controlling the transcription factor YB-1. NCL appears to have a distinct function with CRC in CC, implying that it could be a feasible therapeutic target for chemoresistance [52]. In CC cells, resistance does not come from the YB1-MDR1 pathway, but rather from the overexpression of NCL, which increases cell proliferation and decreases DDP sensitivity when compared to the NCL control [52]. The YB-1 pathway in NCL overexpression cells causes a decrease in cell proliferation and an increase in sensitivity to DDP. Thus, DDP can be utilized in radiotherapy or chemotherapy during the clinical stages [52]. In CC, a summary of CRC-based signaling has been represented in Table 1.

7. Molecular therapies against cisplatin resistance

The use of cisplatin or CDDP is associated with therapeutic success in the initial stages in terms of disease stabilization and partial responses. However, chemo-resistance is developed in the majority of the tumors that were initially sensitive to CDDP [184–186]. This poses a major limitation in the use of CDDP which can be overcome by the use of nanocarriers, radiotherapy, photodynamic therapies, CRISPR/Cas9,

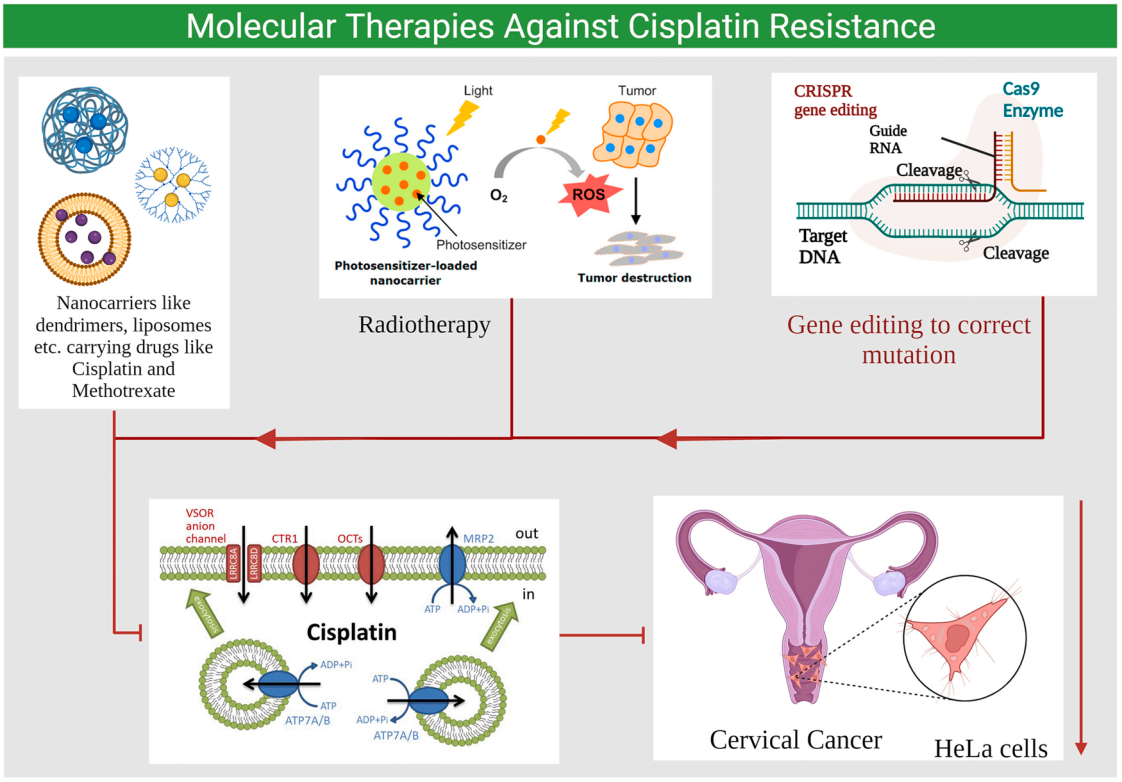

Fig. 7. Combination of CRIPSR/Cas system, miRNA, radiotherapy, and nanocarriers with cisplatin to overcome drug resistance and enhance anti-cancer activity in CC.

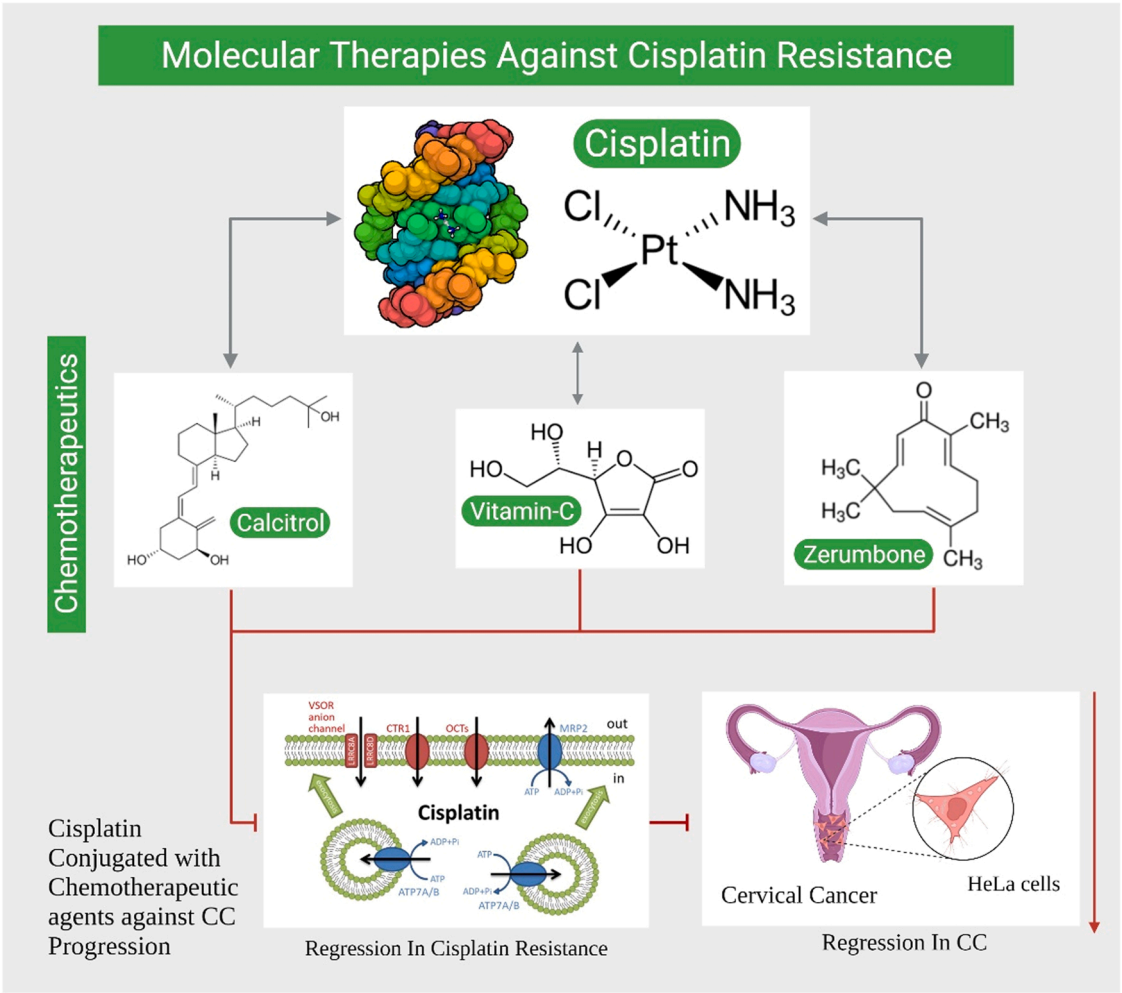

Fig. 8. Combination of chemotherapeutics with cisplatin to overcome drug resistance and enhance anti-cancer activity in CC.

Table 2
Combinatorial approaches to synergy with cisplatin to overcome CRC in CC.

Strategy	Impact	Type of pre-clinical studies	Reference
Nanocarriers	Increases antitumor efficacy by localized incorporation	*In-vitro*	[192–194]
PDT	Increases antitumor efficacy	*In-vitro*	[49,211–213]
CRISPR/Cas9	Decreases drug resistance	*In-vitro* and *in-vivo*	[203,216, 219–221, 224–227]
miRNA	Decreases drug resistance	*In-vitro*	[193,233,245]
Chemotherapeutics (Placlitaxel)	Increases antitumor efficacy	*In-vivo*	[246]
Chemotherapeutics (Calcitriol)	Decreases drug resistance	*In-vitro*	[245,253]
Chemotherapeutics (Doxorubicin)	Decreases drug resistance	*In-vitro*	[254,255]
Chemotherapeutics (Vitamin C)	Increases antitumor efficacy	*In-vitro*	[264,265]
Chemotherapeutics (Zerumbone)	Increases antitumor efficacy	*In-vivo*	[266,267]

miRNA, and combination with various other drugs and natural compounds [47]. Herein we have elucidated the clinical significance of the aforementioned therapies as illustrated in Fig. 7 and Fig. 8. Table 2 highlights the synopsis of the preclinical significance of the aforementioned strategies that aid in mitigating drug resistance and enhancing CC regression.

7.1. Nanocarriers

Nanocarriers (size <500 nm) are colloidal drug carrier systems that cause decreased toxicity, enhanced stability, specificity, and solubility accompanied by a high surface area to volume ratio. [187,188]. Drug delivery using nanocarriers is being widely accepted because of the sustained release of the drug, reliable absorption efficiency, and systemic distribution [189,190]. Through the precise administration and improved permeability or retention effect (EPR) of nanocarriers, the sensitivity of chemoradiotherapy can be increased while reducing systemic toxicity. The wide vessel wall space, poor integrity of the tissues, and abundant blood supply of solid tumors cause the preferential aggregation of nanocarriers in these sites rather than in the normal sites [191].

Dana et al. [192] developed CDDP-related liposome carrier and poly lactic-co-glycolic acids (PLGA) to reduce the toxicity and drug resistance of CDDP. Avastin, an anti-angiogenic drug was conjugated using a double emulsion solvent evaporation approach (L-PLGA-Cis-Avastin) that depicted a greater binding capacity and improved potential for cellular uptake. Wang and Liang et al. [193] in a similar investigation conjugated CDDP, miRNA-1284, and CD59 and loaded this conjugate in liposomes (CD/LP-miCDDP) to cause increased apoptosis by 6.9-fold higher maintenance of encapsulated drug in circulating blood was

seen along with a decrease of 8-fold in the clearance rate. By entrapping CDDP non-aggregated folic acid-conjugated gelatin nanoparticles, a cellular uptake rate of 81% has been observed as compared to 51% in CDDP plain gelatin nanoparticles [194].

The flexible properties of amphoteric liposomes aid to overcome the membrane-mediated barriers to chemotherapeutic drug delivery [195]. The minimized time of systemic administration and enhanced penetration of drug via EPR effect through lipophilicity in the amphoteric liposomes [191]. The combination of the lipid component with pro-drugs of conjugates of phospholipid tails (2 T), podophyllotoxin (P), and the analog (N) causes improved drug stability and localized incorporation of the drugs in CC cells [196]. A lipid vector reduces the side effects associated with CDDP causing enhanced local and systematic uptake.

Compared to systemic chemotherapy, the implantation of localized drug delivery devices into tissue as site-selective drug delivery systems showed great promise for treating cancer in specific areas [197]. Local drug delivery systems have recently received a lot of attention due to their benefits of enhancing local drug concentrations and minimizing adverse effects in cancer treatment [198]. However, the majority of localized drug delivery systems expose a tumor site to a specific drug for an insufficient amount of time, resulting in an inadequate therapeutic dose. In contrast, a variety of implantable formulations have been developed in recent years that exhibit continuous drug release over an extended period of time, even for several months, without any visible burst release [199,200]. Among localized implants, drug-loaded electrospun fiber mats with distinctive qualities such as high specific surface area, high drug capacity, and ease of production and handling have been reported as promising methods for implantable local cancer treatment [201]. Many potent anticancer drugs, such as doxorubicin, paclitaxel, and cisplatin, have been electrospun into nanofibers, resulting in increased tolerance and antitumor activity [201–203].

Using biocompatible Poly(L-lactide) polymer, a layer of oxaliplatin-loaded fibers was inserted into a multilayered fiber matting system through a sequential electrospinning process. Implantable nanofiber mats containing dichloroacetate and oxaliplatin demonstrated synergistic combination chemotherapy against cervical cancer *in vitro* and *in vivo*[204].

Solid lipid nanoparticles (SLN) are innovative nanoparticulate systems made up of an amphiphilic surfactant and a biocompatible lipid core. SLN are gaining attention as novel colloidal drug carriers because they combine the benefits of polymeric nanoparticles, fat emulsions, and liposomes while avoiding some of their drawbacks. The SLN has the additional advantages of high drug payload, easy modification of the drug release profile, large-scale synthesis, and preservation of the drug from chemical degradation [205,206]. In an effort to improve the efficacy of cisplatin while simultaneously lowering its toxicity and increasing its therapeutic index, microemulsion of cisplatin with stearic acid have been incorporated into SLN of soy lecithin [207].

7.2. Low-dose cisplatin with photodynamic therapy and radiotherapy

The limitations associated with the application of CDDP such as the toxicity and CDDP resistance can be overcome to obtain sufficient therapeutic efficacy by combining photodynamic therapy (PDT) or radiotherapy with low dose CDDP. CDDP predominantly promotes apoptosis and its combination with PDT results in a higher percentage of dead cells. A photosensitizing agent that localizes tumors requires metabolic synthesis of a pro-drug that, when administered in PDT proceeded by the agent being activated by a specific wavelength of light. This is used for the treatment of tumors in varied conditions [208–210]. PDT is targeted, and non-invasive, and damage to the surrounding healthy tissues is avoided [211]. The combination of CDDP with ionizing X-ray radiation leads to enhanced DNA damage. Upon irradiation, the single-strand and double-strand breaks are observed in the DNA of tumor cells. When the cells were intercalated with platinum molecules such as CDDP, an enhancement in the number of single and double-stranded DNA breaks was observed [49]. However, the treatment with pelvic radiotherapy along with weak CDDP has proved to be accompanied by considerable acute toxicity [212]. The cytotoxic and apoptotic death of CC cells can be significantly enhanced with a combination of PDT drugs like photofrin or indocyanine green (ICG) and CDDP.

An *in vitro* experiment conducted by de Freitas et al. was found that methylene blue-photodynamic therapy (MB–PDT) followed by CDDP treatment for 24 h and CDDP for 6 h followed by Photogem–photodynamic therapy (PG–PDT) was the best treatment for the eradication of tumor cells of CC. More than 90% of the tumor cells were eliminated in these conditions [213]. The combination of PDT and CDDP, facilitated by Photogem or methylene blue, possesses a low mutagenic potential and is therefore safe for clinical practice treatments for CC [214]. FEN1 is overexpressed in HeLa cells, according to Li et al. and the expression can be further raised by IR. FEN1 inhibition increases IR and when combined with CDDP sensitivity in CC cells, and this impact is mainly because of the disruption of repair mechanisms of DNA damage caused by FEN1 inhibition, which leads to cancer cell death [215].

7.3. CRISPR/Cas9

Chemo-sensitivity of tumor cells can be regulated by microRNAs that play a crucial role in differentiation, development, and carcinogenesis [216–218]. The gene expression regulated by miRNAs causes degradation or translation repression of mRNAs by binding to their 3′-UTRs causing miR-214 down-regulation in CC tissues. miR-214 ectopic expression can inhibit cellular growth, proliferation, invasion, and migration in HeLa CC cell lines [219–221]. miR-214, in CC, plays an essential role in regulating cell proliferation, cell invasion, metastasis, apoptosis, and angiogenesis [222,223]. In an experiment conducted by Wang, F. et al. a significant reduction in cell survival was observed. By the combined use of miR-214 and CDDP, an increase in the sensitivity towards cisplatin was observed by causing inhibition of the effect of Bcl2l2, an anti-apoptotic protein, in HeLa cells. The over-expression of caspase-8, caspase-9, caspase-3, and Bax were induced by miR-214, and apoptosis was also induced indicating that miR-214 induced cell apoptosis through altered Bax/Bcl2l2 ratio via intrinsic apoptosis pathway [224]. In a similar study conducted by Sen et al. miR-214 was knocked out in C33A, CaSki, and HeLa cells by the CRISPR system for increased apoptosis in CC cells. The miR-214 was CRISPR knocked out overexpressed in the 3 different cell lines. Cell viability was determined upon treatment with CDPP and a decreased sensitivity of the cells towards the drugs was observed in miR-214 knockout (CP) while miR-214 overexpression showed CDDP sensitivity increase [225]. In a study conducted by Pirouzfar et al. [226] used CRISPR/Cas9 technology to target MLL5 along with CDDP to evaluate its effect on the viability and apoptosis of HeLa CC cells apoptosis and viability. The P53 levels increased significantly and the cell viability reduced along with an increase in apoptosis of the HeLa cells. When used in combination with chemotherapy, CRISPR/Cas9-mediated knockout of MLL5 and E6 may benefit the HPV16/18 positive CC treatment. The HPV16 E6/E7-CRISPR/Cas9 could specifically and the sensitivity of cells is enhanced effectively towards CDDP in both *in vitro* and *in vivo* [227].

7.4. miRNA

MicroRNAs (miRNAs) are used to monitor the response to chemotherapy in cancer patients that regulate the expression of their targets post-transcriptionally [228]. The 3′ untranslated regions (3′UTR) are bound by miRNAs on the mRNA causing degradation of the mRNA molecule for full complementarity or preventing translation in partial complementarity [229]. The up-regulation of miR-7–5p causes therapeutic failure in CC cells. SiHa and HeLa CC cells saw an increase of miR-7–5p in *in vitro* investigation. MiR-7–5p targets both B-cell

lymphoma 2 (*BCL2)* and poly ADP-ribose polymerase 1 (*PARP-1*). The PARP-1 repression stops resistant cells from undergoing apoptosis and the BCL2 down-regulation ensures the availability of energy by autophagic process [230]. This causes inhibition of apoptosis and contributes to moderating the mechanisms of DNA repair.

There is a significant downregulation of miR-218 in cancer tissues as compared to non-cancerous tissues [231,232]. This down-regulation is also seen in CC where it acts as a tumor-suppressor miRNA HeLa and SiHa cells with CDDP resistance show significant downregulation of MiR-218. miR-218 restoration in cells decreases cell proliferation and assists in cell chemosensitivity towards CDDP [43]. The sensitivity of CC cells to CDDP is enhanced by the miR-1284 upregulation and consequent *HMGB1* targeting [233]. Wang et al. targeted CC cells with CD59sp-conjugated miRNA-1284/cisplatin-loaded liposomes caused greater cell death than CDDP monotherapy [193]. The expression of miR-214 is inversely correlated with the upregulation of BCL2L2 (BCLW) in CC tissues [224]. The cellular sensitivity to CDDP can be increased by miR-214 transfection into HeLa and C-33A cells via downregulation of *BCL2L2* and upregulation of Caspase-9 and caspase-8 to induce apoptosis that leads to CDDP sensitivity. Lui et al. have shown overexpression of TBX1 in SiHa and Hela cells inhibited their invasion, migration, and proliferation in CC. In CC cells overexpressing TBX1 through binding to miR-6727–5p directly causes chemosensitivity and apoptosis of cells via upregulated AKT and MAPK signaling pathways leading to increased CDDP. Furthermore, the mimic of miR-6727–5p inhibited the expression TBX1 whereas an inhibitor of miR-6727–5p increased it. This research shows that TBX1, a miR-6727–5p target gene, works as a tumour suppressor in CC, suggesting that TBX1 could be a potential target for therapy of CC [234]. Esfandyari et al. showed that the overexpression of miRNA-143 induces apoptosis by CDDP and enhance the susceptibility to lower dosage of CDDP by regulating the expression of genes related to apoptosis such as caspase-9, Bax, and Bcl-2 by overexpression of miRNA-143 [235]. After CDDP treatment, Shi et al. found that overexpression of miR-144 by binding with the 3′-UTR of LHX2 lowered cell viability, triggered cell death, and hindered cell migration and invasion in CC. The expression of LHX2 was reduced at both the mRNA and protein levels when miR-144 was overexpressed. The biological effects of miR-144 in CC cells were partially eliminated after LHX2 was restored. In CC cells, miR-144 overcomes CDDP resistance by increasing cell death and reducing invasion by targeting LHX2 [236]. In a study by Wang et al. the expression of miR-584 in CC cell lines and tissues was shown to be significantly lower than in healthy control samples. In HeLa cells, overexpression of miR-584 suppressed glioma-associated oncogene 1 (GLI1) expression and consequently decreased invasion, migration, and cell proliferation, and triggered death. Silencing miR-584 in CaSki cells caused antagonastic impact. Overexpression of GLI1 in HeLa cells that are overexpressing miR-584 completely reversed the inhibitory impact induced by miR-584. CDDP sensitivity was improved by miR-584 by boosting apoptosis that is induced by chemotherapy. Thus, miR-584 was found to be a tumor suppressor miRNA and could be a new target gene for treatments for CC in the future [237]. Chen et al. showed enhanced expression of miR-499a in CC caused a proliferation of cells, invasion, migration, and formation of colonies whereas miR-499a inhibition possessed antagonistic effects. miR-499a is a primary target of the Y box 6 sex-determining region. The carcinogenic impacts of miR-499a in CC were mediated by SOX6 downregulation produced by miR-499a. In the xenograft model mouse of CC, suppressing miR-499a could improve anticancer effects of CDDP. miRNA-499a may thus play a part in the growth of CC and could be used as a targeted therapy [238]. Yang et al. discovered that CDDP-resistant SiHa and HeLa CC cells have higher levels of miR-7–5p. Elevated miR-7–5p expression prevented DNA repair via modifying the expression of poly (ADP-ribose) polymerase 1 (PARP-1), decreased energy consumption, and promoted autophagy by suppressing Bcl-2 expression. This data suggested that miR-7–5p maintained homeostasis in CDDP therapy by enhancing the generation of energy and decreasing the consumption of energy. Thus, causing a protective impact in CC cells challenged with CDDP as miR-7–5p, decreased energy consumption by reducing PARP-1 expression and enhanced generation of energy by suppressing Bcl-2 expression [239]. In a study by Chen et al. in CC miR-1284 was found to be down-regulated. The total rate of survival of patients with reduced levels of miR-1284 was poor. miR-1284 overexpression inhibited invasion and proliferation while promoting apoptosis. Furthermore, increased miR-1284 expression increased the susceptibility of CC cells to CDDP. The effects of miR-1284 on the development and chemosensitivity of CC cells were reversed by HMGB1 as targeting HMGB1 through miR-1284 improves the sensitivity of CC cells to CDDP [240]. Yang et al. exhibited unregulated miR-497/TKT axis has substantial consequences in the CC cellular response to CDDP, and so targeting this axis could be a viable method to increase CC chemosensitivity [241]. In a similar study, Jiang et al. exhibited that miR519d3p was shown to be lower in CDDP-resistant CC cells than in HeLa and CaSki cells in hypoxic conditions. The overexpression of miR519d3p lowered the IC50 value in HeLa/CDDP and CaSki/CDDP cells and suppressed PI3K/AKT signaling pathway through expression of HIF2 protein. Thus, under hypoxic conditions, miR519d3p/HIF2 axis improved CDDP resistance in CC cells by inhibiting the PI3K/AKT signaling pathway [242]. Li et al. exhibited miR-29b expression decreased in CC but when treated with CDDP the expression of miR-29b was considerably increased leading to repression of angiogenesis, EMT and invasion of CC cells *in vitro*. Suppression of miR-29b prevented CDDP-induced epithelial characteristics, cell migration, and angiogenesis in CC cells, implying that the miR-29b/STAT3 axis is involved in cisplatin chemotherapy in CC [243]. Zhang et al. discovered that rs1292037 (A > G) locus of the miR-21 gene is linked to chemoresistance to CDDP and paclitaxel; consequently, modulating patient prognosis in CC. Furthermore, G allele at the rs1292037 (A > G) gene raises the chance of preoperative chemoresistance to CDDP plus paclitaxel and is a negative prognostic factor for CC patients [244].

7.5. CDDP with chemotherapeutics

7.5.1. CDDP and paclitaxel

Paclitaxel preferentially binds to microtubules during mitosis. The reorganization of the network of microtubules is inhibited by the resulting stabilization of microtubules. The use of paclitaxel against breast cancer, lung cancer, ovarian cancer, melanoma, and neck as well as head cancer has been observed to be effective [245]. The combination of CDDP with paclitaxel has been experimented upon and found to be effective with the response rate of CDDP and paclitaxel combination to be better (36%) as compared to the cisplatin group alone in CC (19%) [246].

7.5.2. CDDP and calcitriol

Vitamin D in its activated form results in the formation of calcitriol, the most active form, whose gene expression is regulated by specifically binding to certain vitamin D receptors (VDR). Specific nucleotide sequences are bound to a ligand for activation and dimerization with retinoid X receptor (RXR) called the vitamin D response elements (VDREs) [247]. Several tumor cell types have vitamin D target genes such as c-Myc oncogene, p21, c-Jun N-terminal kinase (JNK), E-cadherin, insulin-like transforming growth factor family, and their receptors [248,249]. Calcitriol enables the promotion of cell differentiation, promotes apoptosis, and regulates the cell cycle. It also acts as an anti-inflammatory factor within the TME [250]. Squamous cell carcinoma can be treated with a combination of CDDP and vitamin D [251] and colon cancer [252]. The HL-60 cells on pre-treatment with calcitriol for 72 h increased their sensitivity to the anti-proliferative effect *in vitro* of cisplatin, genistein, or doxorubicin causing a massive decrease in the inhibitory dose 50% values after the pre-treatment for tumor regression in CC [245,253].

7.5.3. CDDP and doxorubicin

Doxorubicin (DXB) is a chemotherapeutic derived from the *Streptomyces peucetius* bacterium. It is a part of the anthracycline group that hinders topoisomerase 2 activity causing retardation of CC cells [254]. The use of doxorubicin (DXB) and CDDP leads to enhanced amounts of reactive oxygen species and superior cell killing activity [245]. An *in-vitro* study revealed that a combination of DXB and CDDP, when loaded in nano-gels, led to superior cell killing activity with reduced toxicity. Thus, combinational therapy proved to be effective for multidrug-resistant tumors in CC with CRC [255].

7.5.4. CDDP and vitamin C

Vitamin C is a water-soluble antioxidant that possesses the properties of detoxification and acts as an active reducing agent. Several endogenous and exogenous compounds are metabolized by vitamin C [256]. Vitamin C has potential anti-cancer properties as well [257,258]. The efficiency of numerous chemotherapeutic drugs such as cisplatin has been enhanced by the combination of vitamin C [259,260]. The p53 gene, responsible for inducing apoptosis is stabilized by vitamin C [261]. One of the possible reasons for the inbuilt resistance to chemotherapeutic drugs could be the altered p53 pathway. This is mostly by mutation of the p53 gene, downregulation of p14ARF, or upregulation of MDM2 [262]. Reddy et al. found that vitamin C is essential in the stabilization of the p53 gene that causes termination of apoptosis on exposure to cancer cells deficient in p53 to ionizing radiation and DNA damaging agents. Accumulation of p53 sensitizes the action of cisplatin towards the induced arrest of the cell cycle [263]. An increase in the levels of p53 protein enhances the cancer cell susceptibility via combination treatment of vitamin C with CDDP causing apoptosis of CC cells through overexpression of the p53 gene [264,265]. The results obtained in studies and experiments conducted on the combinational drug therapy of CDDP and vitamin C have shown promising results and further studies on them are being conducted to improve their efficacy of it.

7.5.5. CDDP and zerumbone

Zerumbone (ZER) is a dietary compound (naturally occurring) that possesses anti-cancer properties derived from species of *Zingiberaceae*. When CC cells were conditioned to a combination of CDDP and zerumbone, it caused apoptosis of cell growth via arrest of the cell cycle in the G2/M phase and inhibiting the secretion levels of IL-6 and IL-6 receptors in cancer cells in the murine model [266]. The combinational therapy is effective in curing cervical intraepithelial neoplasia in female BALB/c mice and the study is being extended further to treat CC in humans [267].

7.5.6. Irinotecan plus cisplatin neoadjuvant chemotherapy (NACT)

Although irinotecan with CDDP neoadjuvant chemotherapy (NACT) could not enhance overall survival, it did lower the number of patients who needed post-operative radiation. When compared to the usage of paclitaxel with cisplatin for cervical cancer, NACT comprised of irinotecan with CDDP demonstrated equivalent efficacy but higher toxicity, however, the toxicity was manageable [268].

7.6. CDDP and peptides

Due to an excess of anionic molecules, bacteria and cancer cells both have an electronegative surface that differentiates them from their healthy mammalian counterparts [269,270]. Cisplatin was first discovered to prevent the growth of *E. coli* bacteria before being recognized as an efficient anticancer treatment [38]. This supports the observation that the majority of anticancer drugs have antibacterial action [271].

Antimicrobial peptides are components of innate immunity present in all classes of life [270,272,273]. Because of their electrostatic interactions with the negatively charged bacterial membrane, cationic peptides might exhibit antiproliferative effects targeted to cancer cells [274]. Resistance in cancer cells should be more difficult to establish with lytic peptides that act by physically disrupting key structural elements of the cellular membrane [275]. Therefore, drug combinations that target distinct cellular targets and diverse structural classes are among the most promising techniques for the treatment of cancers that have become resistant to conventional treatments [276].

For example, the antimicrobial peptide tachyplesin I, isolated from hemocytes of the horseshoe crab, *Tachypleus tridentatus*, could enhance the cell-killing effects of cisplatin, reducing its effective concentration and nonspecific toxicity on cultured HL-60 and HEK293T cells [277].

Similarly, shrimp anti-lipopolysaccharide factor peptide, only found in marine chelicerates (horseshoe crabs) and crustaceans, enhanced the antitumor activity of cisplatin *in vitro* and inhibits HeLa cells growth in nude mice compared to cisplatin treatment only [278].

The hemocyanin-derived peptide, B11, from *Litopenaeus vannamei*, inhibits the proliferation of cancer cells by causing mitochondrial dysfunction and inducing apoptotic cell death [279]. The membrane-destabilizing, or membranolytic, properties of these antimicrobial peptides can facilitate the intracellular diffusion and passive transport of otherwise less permeable small molecule drugs [280].

8. Conclusion and Future perspective

In summary, cisplatin has shown significant clinical effectiveness in patients with diverse forms of CC; yet, cisplatin chemoresistance has been the principal hurdle to its clinical implementation. According to different preclinical and clinical research, CRC is a complex biological process regulated by intrinsic signaling pathways of CC cells that are susceptible not just to drug stimuli but also to responses from the TME. As discussed in this review, CC cells induce CPR via a variety of mechanisms viz. reduced intracellular accumulation of cisplatin, increased repair of damaged DNA, inactivation of apoptotic pathways, activation of EMT, and other alterations such as changing the expression of genes involved in drug response. One of the most difficult aspects of addressing this clinically important concern is the activation of multiple resistance mechanisms, indicating the multifaceted nature of CPR. Thus, developing therapeutic approaches that precisely imitate the complicated TME of CC cells and establishing a strategy for devising viable cisplatin resistance treatment is critical. However, while looking for effective treatment targets, it should be important to remember that the discovery of suitable biomarkers indicating CRC in CC cells is of equal significance. Furthermore, the designing of nanocarriers that improve the administration of cisplatin might be extremely beneficial in the fight against CRC. Various efficient cisplatin-based nanocarriers therapeutics, for instance, are undergoing clinical trials. As CRC in CC cells has always been the consequence of several influential physical and biological factors, combinatorial treatment strategies that target multiple processes contributing to this phenomenon need to be explored preferentially in the long run.

This review has presented with itself novel combinatorial approaches that when combined with cisplatin aid to mitigate drug resistance and enhance CC regression. More studies focused on these combinatorial approaches will provide a path to developing new immunotherapies to solve the long-lasting issue concerning CRC. Moreover, the cascades of signaling network enlisted will not only provide insights on developing therapeutic target sites for drug discovery in near future but also may act as novel biomarkers for CC detection. The understanding of CC metabolism with CRC will pave a path to developing novel therapeutics or inhibitors to target the pathways.

Ethics approval and consent to participate

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and materials

Not applicable.

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Authors' contributions

The manuscript was conceptualized and written by RB. TD, LK, SK, RS, MG and SM collected the information, drafted manuscript, and analyzed it. NKJ participated in figure preparations. NKJ, BV, KKK, JMPdlL, and AD critically revised the manuscript and finalized it. Manuscript was finally corrected, modified and supervised by NKJ, JMPdlL, and AD for the submission. JMPdlL significantly involved in project administration and funding acquisition. All authors participated in writing, editing, and proofread. All authors have read and approved the final version of the manuscript for submission to this journal.

Consent for publication

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