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Review article

Molecular mechanisms of mTOR-mediated cisplatin response in tumor cells

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ABSTRACT

Cisplatin (CDDP) is one of the main chemotherapeutic drugs that is widely used in many cancers. However, CDDP resistance is a frequent therapeutic challenge that reduces prognosis in cancer patients. Since, CDDP has noticeable side effects in normal tissues and organs, it is necessary to assess the molecular mechanisms associated with CDDP resistance to improve the therapeutic methods in cancer patients. Drug efflux, detoxifying systems, DNA repair mechanisms, and drug-induced apoptosis are involved in multidrug resistance in CDDP-resistant tumor cells. Mammalian target of rapamycin (mTOR), as a serine/threonine kinase has a pivotal role in various cellular mechanisms such as autophagy, metabolism, drug efflux, and cell proliferation. Although, mTOR is mainly activated by PI3K/AKT pathway, it can also be regulated by many other signaling pathways. PI3K/Akt/mTOR axis functions as a key modulator of drug resistance and unfavorable prognosis in different cancers. Regarding, the pivotal role of mTOR in CDDP response, in the present review we discussed the molecular mechanisms that regulate mTOR mediated CDDP response in tumor cells.

1. Introduction

Recent progresses in immunotherapy, radiotherapy, chemotherapy, and surgery have significantly improved the survival of cancer patients; however, there is still a high rate of therapeutic failure in these patients [1–3]. Cisplatin (CDDP) as one of the anticancer drugs triggers the DNA damage that suppresses tumor cell proliferation while induces apoptosis [4]. However, CDDP resistance is a frequent therapeutic challenge that reduces prognosis in cancer patients [5]. Regarding the CDDP side effects in normal tissues, it is required to assess the molecular mechanisms associated with CDDP resistance. Multiple processes including provoked drug efflux, detoxifying systems, DNA repair mechanisms, drug-induced apoptosis, and reduced drug uptake are involved in multidrug resistance in CDDP-resistant tumor cells [6–8]. Mammalian target of rapamycin (mTOR), as a serine/threonine protein kinase plays a pivotal role in various cellular mechanisms, such as ferroptosis, autophagy, metabolism, and cell proliferation through regulating nutrient status and growth factors [9–11]. mTOR activation by PI3K/Akt axis modulates its downstream targets such as elongation initiation factor 4E (eIF4E), binding protein-1 (4EBP1), and p70S6 kinase (S6K) that accelerate cell proliferation and protein synthesis [12–14]. PI3K/Akt/mTOR axis functions as a key modulator of drug resistance and unfavorable prognosis in different cancers, indicating their potential to be targeted in cancer therapy [15–17]. The rapamycin/sirolimus (Wyeth) and its analogues, such as AP23573 (Ariad), CCI-779/temsirolimus (Wyeth), and RAD001/everolimus (Novartis) are mTOR inhibitors which are used as anti-cancer drugs in

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numerous cancers. The mTOR inhibitors are antiprolifrative agents that can arrest cancer cells in G1 phase; however, they are not enough for tumor eradication. Inhibition of mTOR induces the efficacy of various chemo cytotoxic drugs, such as docetaxel, mitoxantrone, carboplatin, paclitaxel, doxorubicin, cisplatin, dexamethasone in different human cancers [18–21]. Over-stimulated mTOR also increases the drug resistance in tumor cells [22,23]. Therefore, all of the molecular mechanisms associated with mTOR regulation can be involved in CDDP response of tumor cells. MicroRNAs (MiRNAs) are involved in regulation of cell proliferation, invasion, and drug resistance [24,25]. MiR-100 and miR-497 reduced CDDP resistance by mTOR targeting in chondrosarcoma, lung, gastric, and ovarian tumor cells [26–29]. Regarding the pivotal role of mTOR in CDDP response, in the present review we discussed the molecular mechanisms that regulate mTOR function during CDDP response in tumor cells (Table 1)

1.1. mTOR-mediated CDDP response by regulation of apoptosis, DNA repair, and ferroptosis

It has been shown that mTOR has a key role in CDDP response by rergulation of apoptosis, ferroptosis, and DNA repair mechanisms (Fig. 1). Mcl-1 preserves cells from a variety of proapoptotic activators that stimulate the mitochondrial apoptotic pathway and subsequent drug resistance [30]. AKT pathway positively regulates Mcl-1 via CREB [31]. In contrast to MAPK pathway inhibitors, AKT inhibitors notably enhanced the cisplatin and temozolomide sensitivity. A combination of the rapamycin (mTOR inhibitor) and LY294002 (PI3K inhibitor) with the cisplatin or temozolomide increased apoptosis while inhibited tumor growth in melanoma which was associated with Mcl-1 inhibition as an antiapoptotic protein. Therefore, combinations of chemotherapeutic drugs and AKT inhibitors promoted apoptosis in melanoma cells through suppression of Mcl-1 by mTOR-modulated protein synthesis suppression [32]. Heat shock leads to the aggregation and unfolding of proteins in tumor cells. It also destroys nuclear DNA, cell cytoskeleton, and membrane and impairs lysosomes, mitochondria, ER, and the Golgi system [33,34]. Cisplatin is a well-known drug combined with hyperthermia (HT) in the therapeutic plan of numerous cancers [35]. This combination strategy decreased the p70s6k, mTOR, and Akt phosphorylation in prostate tumor cells. It also accelerated apoptosis of prostate tumor cells via synergistically suppressing the antiapoptotic IAP and Bcl-2 proteins and Akt-mTOR-p70s6k pathway [36]. MiR-1271 reduced the growth while promoted apoptosis in CDDP-treated CRC cells. There were also caspase-3 and Bax up regulations in CDDP-treated cells. MiR-1271 increased CDDP sensitivity of CRC cells via mTOR targeting [37]. IL-17 is the proinflammatory cytokine of Th17 cells that has a crucial role in inflammatory diseases including rheumatoid arthritis [38], inflammatory bowel disease [39], and development of cancers including thyroid cancer [40] and lung cancer [41]. It has crucial roles in cancer initiation and development [42–47]. IL-17 induced cell proliferation while suppressed apoptosis in CDDP treated CRC cells. IL-17 suppression and CDDP treatment acted synergistically to induce apoptosis. It also increased chemoresistance through activation of PI3K-Akt-mTOR and inhibition of Bcl-2 [48]. The endocannabinoid system (ECS) is implicated in a variety of normal cellular processes such as inflammation, pain, appetite, memory, and learning [49–51]. ECS operates via the crosstalk between the two G protein-coupled receptors (cannabinoid receptor 1 (CB1) and CB2) and cannabinoids. Tumor suppressive function of CB2 has been reported in numerous cancers [52–55]. CB2 attenuated the growth while enhanced apoptosis in BC cells via the Akt/mTOR targeting. CB2 also inhibited the p-mTOR and p-Akt, followed by Bcl2 downregulation and Bax upregulation in BC cells. Moreover, CB2 increased CDDP sensitivity in BC cells [56]. Ghrelin is a ligand for growth hormone secretagogue receptor (GHSR) that has a vital function in the differentiation and progression of various solid tumors [57]. Acylated ghrelin (AG) as the most active form of circulatory ghrelin operates via triggering secretagogue receptor type 1a (GHS-R1a). However, unacylated gherlin (UAG) form is less active and GHS-R1a-independent [58]. It has been indicated that AG induced the cell growth and CDDP-resistance in OC cells via GHS-R1a as well as some other processes including activation of PI3K/Akt, mTOR, NF-κB and inhibition of PUMA and p53. CDDP increased cell death by up regulation of p53, PUMA, and cleaved caspase-3 in OC cells that was associated with inhibition of PI3K/Akt/p-mTOR. AG was found to impair Cis-induced cell apoptosis in OC cells via the PI3K/Akt triggering and its sequential effectors NF-κB and mTOR as it prompts the expression levels of the nuclear NF-κB P65, p-mTOR, p-Akt, as well as p-PI3K [59]. E3 identified by differential display (EDD) is an E3 ubiquitin ligase that regulates cell growth and development [60,61]. EDD immunostaining was increased in low-grade and high-grade breast tumors compared to the benign breast tissues and ductal carcinoma. There was an inverse correlation between the levels of EDD expression and survival in BC patients. Loss of EDD enhanced apoptosis and impeded the survival of breast tumor cells. There was also a close correlation between these processes and the expression of proapoptotic proteins (Bax, Bak, and Bim), MOAP-1 (Bax stimulator and translocator), and caspase-7 fragmentation. Additionally, EDD inhibition up regulated MOAP-1, Bax, and BIM to induce apoptosis in BCa cells. EDD suppression restrained drug resistance via positively regulating pro-apoptotic proteins. EDD stimulated TORC1 signaling by 4EBP1 phosphorylation, fostering translation in BCa cells [62]. There was significant linc-ROR up regulation in A549/DDP cells. Linc-ROR inhibition significantly down regulated bcl-2 while up regulated BAX. Linc-ROR negatively modulated PI3K/Akt/mTOR axis. Therefore, Linc-ROR inhibition or PI3K/Akt/mTOR axis suppression enhanced CDDP sensitivity in NSCLC which suppressed cell proliferation and invasion while induced apoptosis [63].

Nucleotide excision repair (NER) is the essential pathway, which removes CDDP-induced damaged DNA [64]. Xeroderma pigmentosum complementation group C (XPC) is involved in the detection of DNA damage [65]. Inhibition of XPC induces apoptosis via the up regulation of matrix metalloproteinase-1 (MMP1) and p53 transcription [66]. XPC suppression significantly increased apoptosis and decreased A549/DDP cell proliferation. XPC also activated PI3K/Akt/mTOR axis through the regulation of the essential proteins involved in this pathway. XPC up regulation was observed in CDDP-resistant A549 cells compared to parental cells. XPC inhibition down regulated p-Akt and p-mTOR to induce CDDP sensitivity [67]. NEIL3 is a class of DNA glycosylases that play a key role in DNA repair via DNA base excision repair [68]. NEIL3 preserves genomic integrity by reconstructing telomeric damage and mitotic chromosomal segregation [69]. There was an NEIL3 up regulation in NSCLC tissues, which was correlated with poor prognosis. NEIL3 increased NSCLC cell growth, migration, and CDDP sensitivity via modulating the PI3K/AKT/mTOR axis [70].

Table 1
Molecular mechanisms of mTOR during CDDP response in tumor cells.

Study	Year	Tumor Type	Samples	mTOR regulator
Xu [26]	2017	Gastric cancer	30T 30N[a] MGC-803, AGS, SGC-7901, and BGC-823 cell lines Xenograft model	miR-7 reduced CDDP resistance via suppressing mTOR
Xu [27]	2015	Ovarian cancer	41T 41N TCGA DATASET A2780, A2780/CP, SKOV3, and SKOV3/CP cell lines Xenograft model	miR-497 reduced CDDP resistance of by mTOR inhibition
Zhu [28]	2014	Chondrosarcoma	CHON-001 and C-28/I2 cell lines	miR-100 reduced CDDP resistance by downregulating mTOR
Gou [29]	2016	Epithelial ovarian cancer	SKOV3 cell line Xenograft model	miR-100 reduced CDDP resistance via suppressing mTOR
Yao [37]	2019	Colorectal cancer	30T 30N CRC SW480 cell line	miR-1271 reduced CDDP resistance via inhibiting mTOR
Sui [48]	2019	Colorectal cancer	37T 37N CRC HCT116 cell line	IL-17 induced CDDP resistance via activating the PI3K-Akt-mTOR axis
Song [56]	2023	Breast cancer	139T 139N MDA-MB-231 and MCF-7 cell lines Xenograft model	CB2 reduced CDDP resistance via suppressing the PI3K/Akt/mTOR pathway
El-Kott [59]	2019	Ovarian cancer	A2780 cell line	Acylated Ghrelin induced CDDP resistance via Activation of the PI3K/Akt/mTOR Pathway
MacDonald [62]	2019	Breast cancer	56T 14N MCF-7, T47D, SKBR3, MDA-MB-231, and MDA-MB-436 cell lines Xenograft model	EDD induced CDDP resistance via stimulating TORC1 signaling
Teng [67]	2019	Lung adenocarcinoma	A549 and A549/DDP cell lines	Downregulation of XPC reduced CDDP resistance via inhibiting AKT/mTOR axis
Huang [70]	2022	Non-small cell lung cancer	4T 4N TCGA DATASET dataset SPC-A-1, SK-MES-1, A549, and H1299 cell lines	NEIL3 induced CDDP resistance via activating the PI3K/AKT/mTOR signaling pathway
Jiang [74]	2023	Cervical cancer	HeLa and CaSki cell lines Xenograft model	DHODH inhibition reduced CDDP resistance via downregulating the mTOR activity
Jin [83]	2012	Non-small cell lung cancer	H1299 and A549 and A549/DDP cell lines	Suppressing Twist1 reduced CDDP resistance via inhibiting mTOR/S6K1
Chen [84]	2016	Lung adenocarcinoma	34T 34N A549, H1299 cell lines Xenograft model	miR-206 induced CDDP resistance via MET/PI3K/AKT/mTOR axis activation
Deng [85]	2019	Ovarian cancer	A2780 and A2780-cis EOC cell lines	BEZ235 reduced CDDP resistance via Inhibition of PI3K/Akt/mTOR
Harhaji-Trajkovic [100]	2009	Glioma, Fibrosarcoma	U251 glioma, rat C6 glioma and mouse L929 fibrosarcoma cell lines	AMPK induced CDDP resistance by mTOR pathway
Zhu [101]	2021	Lung adenocarcinoma	131T 131N A549, HCC827, NCI-H460, NCI-H1299, NCI-H1915, and H1650 cell lines	UBE2T induced CDDP resistance via the p53/AMPK/mTOR pathway
Wu [102]	2015	Lung adenocarcinoma	A549 and A549/DDP cell lines	Autophagy induced CDDP resistance by AMPK/mTOR signaling pathway activating
Liu [104]	2018	Non-small cell lung cancer	6T 6N A549/DDP cell line	miR-181 reduced CDDP resistance via suppressing the PTEN/PI3K/AKT pathway
He [106]	2022	Non-small cell lung cancer	H1299, H460, and A549 and A549/DDP cell lines Xenograft model	TRIM25 induced CDDP resistance via AKT/mTOR pathway activation
Gao [107]	2020	Laryngeal squamous cell carcinoma	107T 107N FD-LSC-1 and Tu 177 cell lines Xenograft model	circPARD3 induced CDDP resistance via PRKCI-Akt-mTOR pathway
Meng [108]	2020	Osteosarcoma	MG63, U2OS, Saos2 and OS9901 cell lines Xenograft model	miR-22 reduced CDDP resistance via inhibiting the PI3K/Akt/mTOR pathway
Qi [114]	2021	Ovarian cancer	20T 11N GEO DATASET CAOV3 and OV90 Xenograft model	TTK silencing reduced CDDP resistance by activating mTOR
Liu [117]	2023	Ovarian cancer	92T 92N SKOV3 and A2780 cell lines Xenograft model	LDLR induced CDDP resistance via activating PI3K/AKT/mTOR signaling pathway

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Tumor Type	Samples	mTOR regulator
Lu [121]	2019	Gastric cancer	KATO-III cell line Xenograft model	Suppression of CD133 reduced CDDP resistance via Inhibiting PI3K/AKT/mTOR pathway
Gong [130]	2018	Non-small cell lung cancer	H1299 and A549 and A549/DDP cell lines	Knockdown of KLF5 reduced CDDP resistance via inactivation of the PI3K/Akt/mTOR pathway
Sun [131]	2021	Non-small cell lung cancer	A549 and A549/DDP cell lines	miR-21 induced CDDP resistance via inhibiting the PI3K/AKT/mTOR/HIF-1a signaling pathway
Ren [133]	2020	Osteosarcoma	30T 30N GEO DATASET SaOS-2 and MG63 cell lines	Repressing CLEC3A reduced CDDP resistance by inhibiting the AKT1/mTOR/HIF1α pathway
Wang [141]	2019	Esophageal adenocarcinoma	48T 48N OE19 and OE33 cell lines	EMX2 reduced CDDP resistance via inhibiting AKT/mTOR/S6K axis
Liu [143]	2021	Ovarian cancer	TCGA DATASET A2780 and SKOV3 cell lines Xenograft model	ELF3 induced CDDP resistance via activating the mTOR pathway
Jiang [144]	2018	Non-small cell lung cancer	A549 and A549/DDP cell lines	Knockdown of SALL4 reduced CDDP resistance via inhibiting AKT/mTOR signaling pathway
Morelli [149]	2021	Lung cancer	A549 and A549/DDP cell lines	STAT3 induced CDDP resistance via mTOR signaling activation
Wu [150]	2021	Gastric cancer	BGC-823, MKN28, MGC803, MKN45, AGS cell lines Xenograft model	FOXD1-AS1 induced CDDP resistance via activating the PI3K/AKT/mTOR pathway
Wang [152]	2022	Ovarian cancer	76T 76N 18S CAOV3/ES2 cell line Xenograft model	miR-18-5p reduced CDDP resistance via inhibition of AKT/mTOR pathway NACC1 induced CDDP resistance via AKT/mTOR pathway activation
Yang [160]	2022	Colorectal cancer	HCT-116 and LOVO cell lines	CRNDE reduced CDDP resistance by inhibiting the Akt/mTORC1-mediated Warburg effect
Zhu [163]	2016	Cervical cancer	17R 19S[b] C4-1 and HeLa cell lines	PKM2 reduced CDDP resistance via mTOR signaling
Jiang [166]	2022	Tongue squamous cell carcinoma	42T 42N CAL27 and SCC15 cell lines Xenograft model	SNHG26 induced CDDP resistance via mTOR signaling activation
Zhao [178]	2021	Epithelial Ovarian Cancer	61T 15N HEK293T, OVCAR3, SK-OV-3, and A2780 cell lines Xenograft model	Suppression of Exo70 reduced CDDP resistance by downregulating mTOR
Jiang [185]	2021	Gastric cancer	SGC-7901, MGC-803, and HEK 293 T cell lines	miR-107 reduced CDDP resistance via inhibiting HMGA2/mTOR/P-gp pathway
Li [186]	2017	Cholangiocarcinoma	RBE and GBC-SD cell lines	miR-199a-3p reduced CDDP resistance via inhibiting mTOR pathway
Song [196]	2017	Osteosarcoma	40T 40N MG-63 and SaOS-2 cell lines Xenograft model	LPAATβ induced CDDP resistance via activating PI3K/Akt/mTOR signaling pathway
Lin [202]	2020	Nasopharyngeal Carcinoma	96T 96N C666-1 and HNE1 cell lines Xenograft model	Silencing HOXA11-AS/miR-454-3p axis reduced CDDP resistance via inhibiting the c-Met/Akt/mTOR pathway
Wang [204]	2022	Ovarian cancer	30T 30N SKOV3 and A2780 cell lines Xenograft model	PTPRZ1 reduced CDDP resistance via inhibiting PI3K/AKT/mTOR pathway
Li [212]	2016	Head and neck squamous cell carcinoma	Cal 27/UM-SCC25/UMSCC1/JHU-O28 cell lines	IKK/NF-kB induced CDDP resistance via upregulating EGFR/Akt/mTORC1 axis
Song [216]	2022	Breast cancer	MCF-7, MDA-MB-231, and MDA-MB-436 cell lines Xenograft model	RBM8A knockdown reduced CDDP resistance via inhibiting the AKT/mTOR axis
Zeng [224]	2016	Bladder cancer	T24 and 5637 cell lines	miR-222 induced CDDP resistance by activating the PPP2R2A/Akt/mTOR axis
Ye [232]	2019	Non-small cell lung cancer	25T 25N A549 and H1299 cell lines	TM4SF1 induced CDDP resistance via the DDR1/Akt/ERK-mTOR axis

[a] Tumor (T) tissues and Normal (N) margins.
[b] Resistant (R) patients and Sensitive (S) patients to CDDP.

Ferroptosis is an iron-related programmed cell death that is triggered by reactive oxygen species (ROS) and lipid peroxidation [71]. Dihydroorotate dehydrogenase (DHODH) is a vital modulator of the de novo pyrimidine synthesis positioned in the inner membrane of mitochondria. DHODH represses ferroptosis via inhibition of ubiquinone to ubiquinol in a GPX4 or FSP1 independent manner. DHODH depletion hinders intracellular pyrimidine nucleotide reservoirs, followed by cell cycle arrest and chemosensitivity in tumor cells [72,73]. Inhibition of DHODH negatively regulated the cell proliferation while increased ferroptosis-induced cell death in cervical cancer. Additionally, DHODH suppression promoted cisplatin sensitivity of cervical cancer (CC) cells via ferroptosis. There was a significant downregulation of mTOR pathway which induced ferroptosis in CC cells upon cisplatin and DHODH inhibition combined therapy [74].

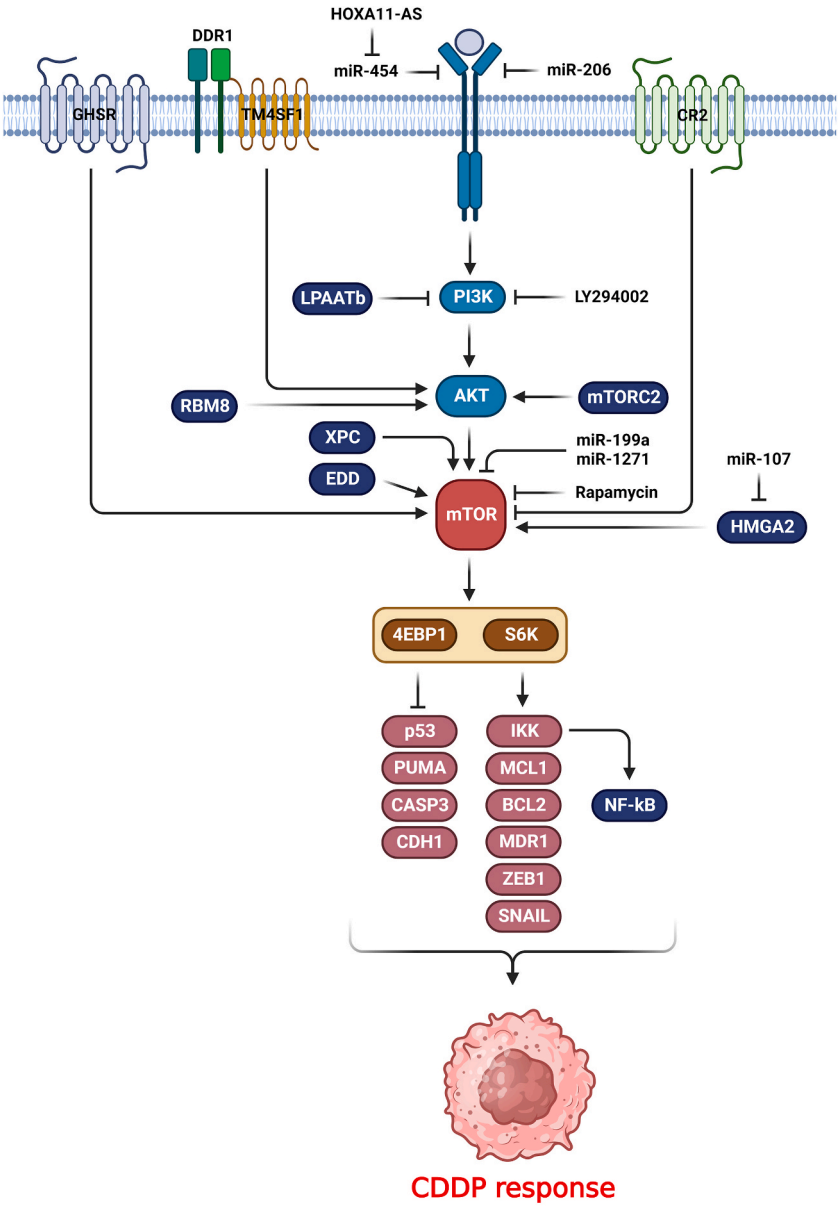

Fig. 1. mTOR is involved in CDDP response via regulation of apoptosis, ferroptosis, EMT, DNA repair, drug efflux, and structural proteins. (Created with BioRender.com).

1.2. mTOR-mediated CDDP response by regulation of EMT process

Epithelial-to-mesenchymal transition (EMT) is a cellular mechanism in which epithelial cells acquire mesenchymal features during embryogenesis and tumor progression. This mechanism is featured by promoting migration ability, attenuating cell–cell adhesion, and decreasing cell polarity [75]. There is a correlation between drug resistance and EMT-like cancer cells [76,77]. A close interaction has been detected between EMT mechanism and PI3K/AKT/mTOR axis [78]. It has been reported that mTOR has a key role in CDDP response by regulation of EMT process (Fig. 1). Downregulation of the epithelial molecules E-cadherin and upregulation of mesenchymal markers including zinc-finger E-box binding homeobox 1 (ZEB1), Vimentin, Slug/Snai2, and Snail/Snai1 elevates cell invasion, motility, and chemoresistance [79]. Zinc-finger proteins (e.g., Zebs/SIP1, Zeb1, Slug, and Snail) and basic helix-loop-helix factors (E47 and Twist) can modulate the EMT process [80]. Twist promotes EMT through overexpression of mesenchymal markers (vimentin, N-cadherin, and fibronectin) and epithelial cell marker (E-cadherin) downregulation, followed by tumor metastasis and aggressiveness [81,82]. Inhibition of Twist1 increased cisplatin sensitivity in lung cancer cells via restraining ATP that activated AMPK, suppressed mTOR/S6K1, and down regulated Mcl-1 [83]. There were reduced levels of miR-206 in resistant lung cancer cell lines. MiR-206 sensitized cisplatin-resistant cells and restrained the mesenchymal characteristics by MET targeting. In addition, suppression of

miR-206 increased CDDP resistance and EMT morphology via MET/PI3K/AKT/mTOR axis activation, and subsequent overexpression of Snail, ZEB1, and MDR1 in CDDP-resistant cells [84]. There was a significant association between triggering the PI3K/Akt/mTOR axis and promoting EMT and CSC markers in chemoresistant EOC cells. E-cadherin downregulation and N-cadherin/Vimentin upregulation were discovered in cisplatin-resistant EOC cells. BEZ235 alone or combination treatment significantly restrained EMT and repressed CSC markers via inhibition of PI3K/Akt/mTOR signaling in cisplatin-resistant EOC cells compared with cisplatin alone or control. Combination therapy ameliorated apoptosis, proposing that BEZ235 sensitized cisplatin-resistant cells by PI3K/Akt/mTOR signaling suppression [85].

1.3. *mTOR-mediated CDDP response by regulation of autophagy*

Autophagy is a cellular mechanism in which lysosomes destroy damaged organelles and macromolecules in eukaryotic cells. It has a critical role in normal cells by regulation of organelle renewal and cell metabolism [86,87]. Autophagy has a critical role in chemoresistance as it removes destructed parts of the cells within autophagosomes, maintaining homeostasis of cells. It preserves cell balance during the production, destruction, and subsequent recycling of crucial molecules upon nutrient deprivation [88,89]. Autophagy is stimulated in response to different therapies in solid tumors, and is involved in metabolic adaptation pathways such as repressing drug-mediated apoptosis and preserving the viability of tumor cells [90,91]. Autophagy is a critical regulator of CDDP-resistance in tumor cells [92,93]. mTOR is a pivotal serine/threonine kinase that is involved in CDDP response by regulation of autophagy (Fig. 2). AMPK/mTOR pathway critically regulates cellular autophagy [94]. Oxidative stress, endoplasmic reticulum (ER),

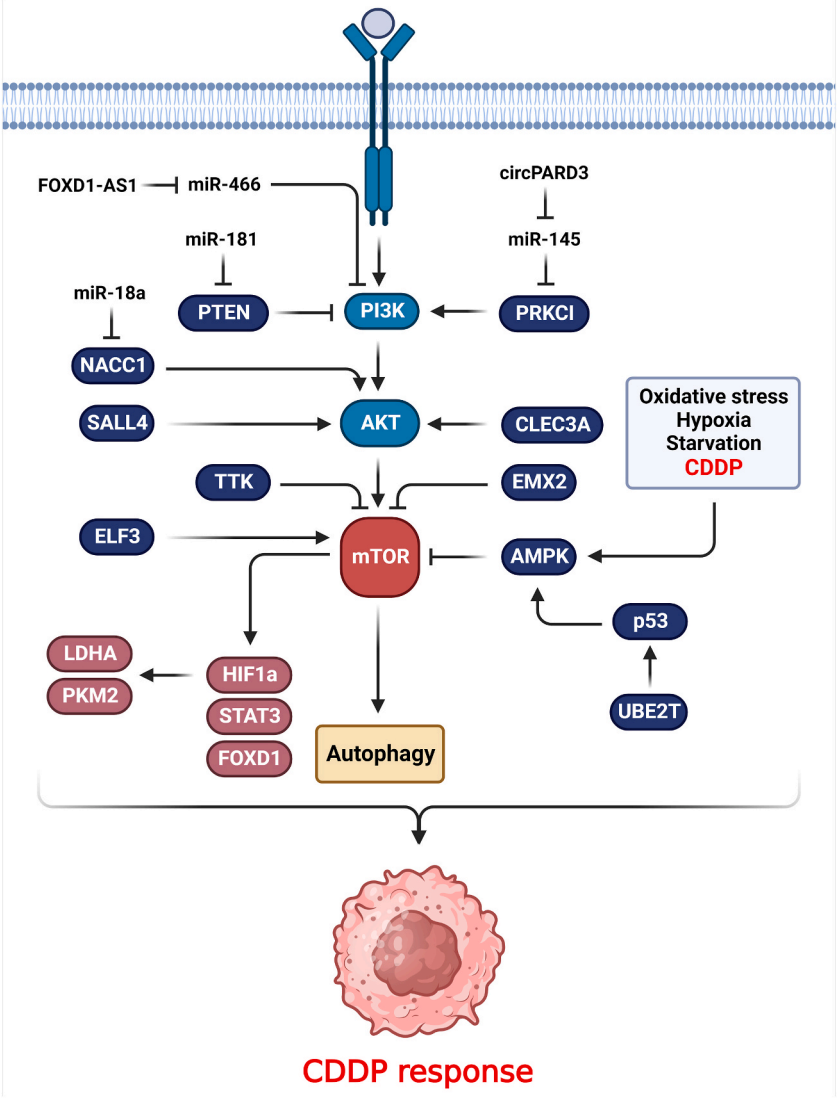

Fig. 2. mTOR is involved in CDDP response via regulation of autophagy and transcription factors. (Created with BioRender.com).

stress hypoxia, and starvation induce autophagy following nutrient energy sensor AMP kinase (AMPK) stimulation and mTOR suppressing [95,96]. AMPK facilitates the autophagy process as it is a pivotal energy sensor of cells [97]. Cellular and environmental stress conditions trigger AMPK following an intensified AMP/ATP ratio that suppresses ATP-requiring processes, while initiating ATP-generating degradative pathways [98]. AMPK promotes autophagy by inhibiting the mTOR as an important autophagy repressor [99]. CDDP trigerred the autophagy in glioma cells via the AMPK/mTOR axis. AMPK also interrupted the CDDP-mediated Bax/Bcl-2 ratio elevation in these cells. Additionally, AMPK reinforced the expression of beclin-1 to induce autophagy in CDDP-treated fibrosarcoma and glioma cells. There was a correlation between CDDP-induced AMPK activation and reduced phosphorylation of S6K. Therefore, CDDP ameliorated autophagy via mTOR inhibition in glioma cells [100]. Ubiquitin-conjugating enzyme E2T (UBE2T) promoted autophagy in NSCLCs via regulation of p53/AMPK/mTOR pathway. Additionally, the multigene panel including autophagy genes and UBE2T effectively predicted drug sensitivity and prognosis in NSCLC patients [101]. AMPK/mTOR pathway induced CDDP-mediated autophagy in lung tumor cells. Increased AMPK phosphorylation, upregulated Beclin-1 and LC3B, and decreased mTOR phosphorylation were observed in CDDP-treated lung tumor cells [102].

PTEN activates autophagy by reversing the inhibitory impact of PI3K/PKB on autophagy [103]. There was downregulation of miR-181 in cisplatin-resistant NSCLC compared with normal patients which was followed by LC3 and ATG5 inhibition in CDDP-resistant NSCLC cells. MiR-181 also suppressed tumor spread and cell growth while increased apoptosis and autophagy via targeting the PTEN/PI3K/AKT/mTOR axis in CDDP-resistant NSCLC cells [104]. PTEN as an inhibitor of PI3K/AKT/mTOR pathway can be degraded by the NEDD4-1 induced polyubiquitination [105]. A crosstalk between TRIM25 and PTEN has been reported that orchestrated the K63-related polyubiquitination of TRIM25, leading to AKT/mTOR activation. Additionally, suppression of TRIM25-induced PTEN ubiquitination increased the chemosensitivity in NSCLC cells [106]. CircPARD3 functioned as an autophagy inhibitor that was upregulated in LSCC tissues. CircPARD3 induced cell proliferation and chemoresistance in LSCC cells by suppressing autophagy. CircPARD3 suppressed autophagy via miR-145-5p/PRKCI axis that triggered Akt-mTOR pathway [107]. MiR-22 increased CDDP-sensitivity in MG63 and MG63/CDDP cells via inhibiting autophagy. MiR-22 and CDDP down regulated the PI3K, Akt, and mTOR. Consequently, miR-22 reduced chemoresistance and suppressed CDDP-mediated autophagy through the PI3K/Akt/mTOR signalling pathway [108].

TTK protein kinase (TTK) serves as a dual specificity serine/threonine kinase is involved in regulation of spindle assembly checkpoint (SAC) [109–111]. SAC is a surveillance mechanism during mitosis that ensures the accurate segregation of chromosomes thus preserving genome stability [112]. Additionally, TTK regulates DNA repair, cytokinesis, chromosomal alignment, and mitotic checkpoint production [113]. There was a significant TTK upregulation in HGSOC and CDDP-resistant ovarian tumor cells. Inhibition of TTK promoted the cisplatin cytotoxicity via mTOR/autophagy axis. The loss of TTK also suppressed the autophagy pathway followed by decreasing tumor growth while enhancing cisplatin sensitivity. Therefore, TTK repressing mitigated ovarian cancer development via suppressing autophagy and triggering mTOR [114]. Low-density lipoprotein receptor (LDLR) attaches with LDL and translocates it into cells via endocytosis as a membrane mosaic molecule [115,116]. There was LDLR up regulation in OC cells and its downregulation inhibited cell proliferation and autophagy via PI3K/AKT/mTOR pathway. LDLR was up regulated and autophagy was induced in CDDP-resistant OC cells [117]. Conventional chemotherapy and radiotherapy are usually unable to ablate the CSCs and subsequent tumor recurrence due to the ability of highly expressing extrusion pumps and DNA repair mechanisms in CSCs [118,119]. CD133/p85 interaction triggeres the PI3K/AKT pathway and promoted tumorigenesis in glioma stem cells [120]. CD133 has been indicated to accelerate cell proliferation and autophagy while decreased apoptosis and cisplatin efficiency. Additionally, PI3K/AKT/mTOR pathway and apoptosis-related protein increased CD133-induced cisplatin resistance. Hence, CD133 increased the cisplatin resistance of GC cells via PI3K/AKT/mTOR pathway [121]. PDZ-binding kinase (PBK) is a mitogen-activated protein kinase kinase (MAPKK) family member that facilitated autophagy in ovarian cancer (OC) cells via mTOR pathway triggering following ERK1/2 phosphorylation. There was a correlation between PBK expression and cisplatin resistance, metastasis, and unfavorable prognosis in high-grade serous ovarian carcinoma (HGSOC) patients. PBK decreased the sensitivity of OC cells to cisplatin and induced autophagy by the ERK/mTOR axis. EVI1 up regulated the PBK to induce CDDP resistance in HGSOC cells via autophagy induction [122].

1.4. Transcription factors associated with mTOR-mediated CDDP response

Tumors have different strategies to develop drug resistance including providing an acidic microenvironment to increase tumor proliferation and aerobic glycolysis to supply energy [123]. Hypoxia is a well-known mechanism that is involved in numerous tumoral processes, such as drug resistance, angiogenesis, apoptosis, and growth [124]. Hypoxia-induced chemoresistance is a critical issue in tumor therapy [125]. Transcription factors have a key role in CDDP reponse by regulation of AKT/mTOR axis (Fig. 2). Hypoxia-inducible factor-1α (HIF-1α) regulates cell proliferation, apoptosis, and glycolysis upon hypoxic condition [126]. HIF-1α-mediated glycolysis critically increased the chemoresistant of NSCLC cells [127]. Krüppel-like factor 5 (KLF5) plays a core part in different processes in human cancers, such as cell growth, differentiation, death, and tumor progression [128]. KLF5 functioned as an upstream effector of HIF-1α in hypoxic tumors [129]. KLF5 developed hypoxia-mediated cisplatin resistance via triggering the PI3K/Akt/mTOR axis in NSCLC cells. The loss of KLF5 inhibited hypoxia-mediated cisplatin resistance via suppressing HIF-1α-associated glycolysis by PI3K/Akt/mTOR inhibition [130]. PI3K/AKT axis served as an intermediate factor in tumor cells, as it modulates the Myc and HIF-1α or is regulated by the Ras and Src. MiR-21 suppressed the PI3K/AKT/mTOR/HIF-1α axis, followed by LDHA and PKM2 inhibition, and subsequently decreased glycolysis in CDDP resistant NSCLC cells [131]. The c-type lectins belong to the c-type lectin receptors (CLR) family, which is involved in cell migration and differentiation. CLRs have the c-type lectin-like domains which can recognize specific carbohydrates and can detect and bind to lipids, carbohydrates, and proteins [132]. There

was CLEC3A up regulation in OS tissues that was correlated with lymph node invasion and TNM stage. CLEC3A inhibition also suppressed OS cell proliferation while induced their CDDP sensitivity via the AKT1/mTOR/HIF1α axis. CLEC3A inhibition significantly down regulated HIF-1α and reduced its nuclear transportation [133].

Empty spiracles homeobox 2 (EMX2) belongs to the Homeobox gene family, that participates in cell growth and differentiation [134]. EMX2 exerts regulatory functions in mammalian reproduction, the stereociliary array positioning of sensory hair cells, hair cell maturation, neurogenesis, and cortical development [135–140]. EMX2 downregulation has been identified to be correlated with EMT in EAC, and EMX2 inhibited EMT by targeting AKT in the AKT/mTOR/S6K axis. Additionally, EMX2 inhibition was associated with p-S6K1, p-mTOR, and p-AKT upregulation in the tumor tissues. Therefore, EMX2 increased the CDDP sensitivity of EAC cell lines [141]. ELF3 is a member of the ETS family of transcription factors [142]. ELF3 levels were increased in OC, which was correlated with a poor overall survival rate. ELF3 decreased chemosensitivity and induced OC progression via the up regulation of mTOR axis [143]. Sall4 as a developmental transcription factor preserves the self-renewal. Inhibition of Sall4 reduced cell growth while promoted CDDP-mediated apoptosis via AKT/mTOR suppression in NSCLC cells [144]. STAT3 is a transcription factor which regulates cell survival and angiogenesis [145]. STAT3 is activated by various protein kinases, cytokines, and growth factors [146] and constitutive activation of STAT3 maintains malignant behavior in various cancers [147]. STAT3 activation by the mTOR allows its maximal activation [148]. The up regulation of mTOR pathway has been associated with chemotherapy resistance in A549 lung cancer tumor cells. STAT3 promoted EMT and increased CDDP resistance. Therefore, the combination of STAT3 inhibitors, cisplatin, and rapamycin was suggested as an effective strategy in the treatment of lung cancer [149]. FOXD1-AS1 up regulated PI3K/AKT/mTOR axis via miR-466 sponging and subsequent release of PIK3CA, which led to 4E-BP1 activation via hyperphosphorylation. 4E-BP1 activation increased eIF4E and eIF4G interaction and up regulated FOXD1 protein, which increased CDDP resistance. FOXD1-AS1 induced CDDP resistance via the regulation of the FOXD1 protein translation [150]. Nucleus accumbens-associated protein 1 (NACC1) is involved in cancer-related mechanisms, including chemoresistance, cytokinesis, and stemness [151]. hMSC-EVs contained miR-18a-5p suppressed cell migration in OC cells by NACC1 targeting. AKT/mTOR axis had a negative and positive association with miR-18-5p and NACC1, respectively. NACC1 activated the AKT/mTOR pathway in OC. hMSC-Evs derived miR-18a-5p mitigated OC cell growth, migration, aggressiveness, CDDP-resistance, and tumorigenesis in OC cells [152].

1.5. mTOR-mediated CDDP response by regulation of glycolysis

Glucose oxidation is the essential cellular energy production pathway in normal cells. Glucose undergoes glycolysis to produce pyruvate, which enters mitochondria to produces ATP via the tricarboxylic acid cycle [153]. However, pyruvate does not enter into the mitochondria and is converted to lactic acid in tumor cells [153]. Although, Glycolysis produces less ATP compared to oxidative phosphorylation, glycolysis intermediates supply the required energy for rapid cell proliferation [154]. Lactic acid increases the extracellular matrix acidity, a major component of the tumor microenvironments (TME) [155]. Acidic TME induces radiotherapy resistance and tumor metastasis [156,157]. Moreover, the swift conversion of pyruvate into lactate, followed by its release from the cell, has the potential to hinder the immune, thereby promoting tumor progression [158,159]. Suppression of CRNDE reduced lactic acid, ATP and HK2, LDHA, PKM2 and GLUT1 expression in HCT-116 cells. Suppression of CRNDE also induced apoptosis and CDDP sensitivity in HCT-116 cells while inhibited their proliferation, which may be related to inhibition of the Warburg effect. Suppression of CRNDE down regulated p-mTOR, p-Ak, p-S6K, and p-S6 while up regulated EIF-4E and p-4EBP-1. CRNDE increased lactic acid and ATP and glucose uptake which mTOR and Akt suppression counteracts, showing that CRNDE promoted the Warburg effect in HCT-116 cells via the Akt/mTORC1 axis [160]. Pyruvate kinase M2 (PKM2) is a pivotal regulator of Warburg effect in cancer metabolism. The required energy for cell growth in highly glycolytic tumor cells is provided by the Pyruvate to ATP and lactic acid transformation in oxidative conditions [161]. PKM2 upregulation has been found in numerous cancers and was critical for tumor proliferation [162]. It has also participated in metabolic reprogramming as well as chemotherapy response. mTOR induced the PKM2 expression by upregulating the c-Myc. Although, the overexpression of PKM2, c-Myc, HIF-1α, and mTOR were correlated with a positive CDDP-based NACT response, there was down regulation of these molecules in treated cervical cancer tissues compared with non-treated ones. Inhibition of PKM2 decreased the CDDP-sensitivity in cervical tumor cells, implicating the critical role of PKM2 in enhancing the CDDP-sensitivity. Additionally, suppression of mTOR reduced PKM2 expression. PKM2 inhibition down regulated p-AKT, p-S6K, and mTOR. HIF-1α up regulation was significantly correlated with good chemotherapy response in cervical cancer and there was a significant response to CDDP in highly glycolytic tumor cells [163]. PGK1 is an essential enzyme in the glycolysis which is implicated in initiation of DNA replication and autophagy [164]. PGK1 has a crucial role in chemoresistance [165]. There was significant SHNG26 up regulation in TSCC tissues in comparison with normal margins that was associated with poor prognosis. SNHG26 induced TSCC cell proliferation, EMT, and CDDP resistance. SNHG26 promoted Akt/mTOR axis via binding to PGK1 and suppression of its ubiquitination [166].

1.6. mTOR-mediated CDDP response by regulation of cisplatin efflux

Drug efflux is considered as one of the main cellular processes that can be regulated by mTOR to maintan the tumor cells toward CDDP treatment (Fig. 1). Up regulation of drug efflux pumps reduce drug concentration to promote platinum resistance [167–169]. Although, the exact molecular mechanism of cisplatin-loaded lysosome exocytosis has not been indicated, lysosomal exocytosis accelerates the lysosome-accumulated platinum [170]. Exocyst regulates the secretory vesicles binding to the plasma membrane via the interaction of PIP2 in the plasma membrane and the Exo70 part of the exocyst [171,172]. Exo70 also increases cell spread and polarized lysosome release at the immune synapse in various cancers [173–177]. There was an increased cisplatin resistance in EOC

cells following exocytosis-induced cisplatin efflux by Exo70. Phosphorylation of AMPK and mTOR dephosphorylation is mediated by cisplatin increased autophagy-lysosome destruction of Exo70 in EOC cells. Therefore, rapamycin as a common stimulator of autophagy suppressed mTOR phosphorylation to induce Exo70 degradation that decreased cisplatin resistance in EOC cells [178]. CDDP-mediated lysosomal biogenesis and mitophagy form a mitochondrial-lysosomal interaction to promote CDDP resistance in HCC cells. CDDP and PI3K/mTOR inhibitor combinational therapy depleted CDDP-mediated mitochondrial-lysosomal interaction, which resulted in increased CDDP sensitivity in HCC cells [179]. Multidrug resistance protein 1 (MDR1) is an ATP-binding cassette (ABC) transporter protein that has a pivotal role in resistance to chemotherapeutic drugs through drug efflux mechanism [180]. The mTOR modulated drug resistance of tumor cells via MDR1 [181–183]. AT-hook structure of HMGA2 attaches to the chromatin-enriched AT sequences to regulate DNA conformation, related proteins, and gene transcription [184]. Exosomal miR-107 decreased drug resistance in GC cells by HMGA2/mTOR/MDR1 axis [185]. MiR-199a-3p enhanced CDDP sensitivity via suppression of mTOR pathway and down regulation of MDR1 in cholangiocarcinoma cells [186]. MUC1 belongs to the transmembrane heterodimer glycoproteins family that is found in normal prostate, breast, and lung. MUC1 glycosylation and upregulation was also observed in many tumors that were correlated with unfavorable prognosis [187]. The two subunits of MUC1 including the extracellular N-terminal subunit (MUC1-N) and transmembrane C-terminal subunit (MUC1-C) are formed via autocleavage that provide a stable heterogenous dimer at the cell membrane. It has been found that the cytoplasmic domain of MUC1-C is separated and exerts an oncogenic role [188]. MUC1-C triggers the ERK and PI3K/AKT pathways and is translocated to the nucleus through β-catenin [189]. There was a notable association between MUC1-C expression and unfavorable prognosis in CDDP-treated UC patients. MUC1-C stabilized the xCT protein expression and upregulated ABCB1/MDR1 in long-term-exposure CDDP-resistant UC cells. MUC1-C was up regulated in CR cells and phosphorylated the AKT-mTOR-S6K1 pathway. Therefore, PI3K-AKT-mTOR regulated the MDR1 expression via MUC1-C targeting in urothelial tumor cells [190]. Lysophosphatidic acid acyltransferase β (LPAATβ) is a transmembrane protein that modulates osteosarcoma cell proliferation [191,192]. LPAATβ converts the lysophosphatidic acid (LPA) into phosphatidic acids (PA) including the Raf-1 and mTOR pathways [193–195]. There was LPAATβ overexpression in CDDP-treated osteosarcoma patients. Downregulation of LPAATβ reduced the expression levels of MDR1, GST, and MRP1. Inhibition of LPAATβ stimulated the PI3K/Akt/mTOR signaling axis in CDDP-resistant cells. Therefore, LPAATβ decreased the CDDP sensitivity via stimulating PI3K/Akt/mTOR in osteosarcoma cells [196].

1.7. Structural proteins

Apart from the mentioned cellular processes that regulate mTOR-mediated CDDP response, various structural and membrane receptors are also involved in this process (Fig. 1). Receptor tyrosine kinases (RTKs) including vascular endothelial growth factor receptors (VEGF) and epidermal growth factor receptors (EGFR) have pivotal functions in tumor development by promotion of PI3K/AKT/mTOR axis [197]. C-Met is a RTK that stimulates the PI3K/AKT/mTOR/MDM2 axis while restraining GSK3β and BAD, thus inducing cell proliferation [198,199]. The c-Met/AKT/mTOR pathway repression sensitizes resistant nasopharyngeal carcinoma cells to DDP via downregulating MDR1 [200,201]. The c-Met inhibition reduced bortezomib resistance of myeloma cells through Akt/mTOR inhibition and triggering apoptosis. HOXA11-AS modulated the cisplatin resistance of NPC by targeting the miR-454-3p/c-Met. HOXA11-AS inhibition also downregulated the c-Met/Akt/mTOR axis by miR-454-3p up regulation that enhanced apoptosis and DDP-sensitivity in NPC cells [202]. PTPRZ1 exerts the oncogenic role via integration with MET proto-oncogene [203]. There was PTPRZ1 down regulation in OC tissues and DDP-resistant cell lines. PTPRZ1 reduced the mTOR and AKT phosphorylation, indicating the regulatory role of PTPRZ1 in the cisplatin resistance of OC cells via the PI3K/AKT/mTOR axis [204]. mTORC1 is the main AKT target that promotes RNA translation by 4E-BP1 and S6K phosphorylations [205,206]. NF-κB is activated by its upstream kinase that contains IKKα, IKKβ, and IKKγ/NEMO subunits. IKKs phosphorylate IκBα for its degradation, causing NF-κB nuclear translocation to regulate target gene expression [207–211]. EGFR/Akt regulated mTORC1 activation of IKK/NF-κB that up regulated the EGFR is a positive feedback. IKK/NFκB was involved in cell proliferation and CDDP resistance in which IKK inhibition improved CDDP sensitivity in HNSCC cells [212].

RNA-binding motif protein 8A (RBM8A) belongs to the RNA-binding motif protein family which not only modulates cell growth, metastasis, and death but also participates in different signaling pathways and plays a pivotal role in tumor initiation and progression [91,213–215]. RBM8A enhanced CDDP resistance and cell proliferation in breast cancer (BC). RBM8A expression was correlated with LNM and TNM stages in BC patients. Suppression of RBM8A inhibited the AKT/mTOR axis in breast tumor cells [216]. PPP2R2A is a PP2A regulatory subunit B family member that is implicated in intracellular mechanisms, such as cell cycle, cell signaling, protein synthesis, apoptosis, and metabolism [217–219]. Akt is a subunit of PP2A that is correlated with miR-222-induced suppression of PPP2R2A [220–223]. MiR-222 increased the cell growth and mitigated CDDP-mediated cell death via the PPP2R2A/Akt/mTOR pathway in bladder tumor cells [224]. Integrin alpha-5 (ITGA5) and ITGB1 are structural proteins that regulate cellular adhesion through MAPK, AKT, and FAK signaling pathways [225]. ITGA5 induced LSCC tumor development via ephrin-B2 (EFNB2). Moreover, there was a significant stimulation of mTORC1-ITGA5-EFNB2 in LSCC, which was associated with poor prognosis. ITGA5 suppression also increased the CDDP sensitivity in LSCC cells. Therefore, dysregulated mTORC1 critically regulated the initiation of LSCC, and the ITGA5-EFNB2 axis had a great potential to be a therapeutic target in mTORC1-related LSCC patients [226].

Transmembrane-4 L-six family member-1 (TM4SF1) belongs to the small plasma membrane glycoproteins that modulate cell mobility and growth [227]. TM4SF1 has a close cross talk with discoidin domain receptor 1 (DDR1) during metastasis of pancreatic cancer and breast cancer [228,229]. DDR1 is an important effector of the AKT/mTOR pathway that is implicated in the chemoresistance of numerous tumors [230,231]. TM4SF1 modulated chemosensitivity and apoptosis via the DDR1-regulated AKT/mTOR. There was TM4SF1 upregulation in lung cancer tissues and cell lines that was correlated with unfavorable prognosis. Loss of TM4SF1

sensitized NSCLC cells to paclitaxel and cisplatin. Inhibition of TM4SF1 negatively regulated DDR1 to reduce Akt and ERK phosphorylation. Therefore, the interaction of TM4SF1 and ERK/Akt-mTOR and DDR1 promoted the chemosensitivity in NSCLC cells [232].

2. Conclusions

CDDP is a widely used chemotherapeutic drug in different cancers. However, CDDP resistance is frequently observed in cancer patients that results in poor prognosis. Therefore, it is required to assess the molecular mechanisms associated with CDDP reponse in tumor cells to improve prognosis among cancer patients. mTOR is a hub protein kinase in several signaling pathways that has key roles in CDDP response. Therefore, in the present review we discussed the molecular mechanisms associated with mTOR mediated CDDP response in tumor cells. mTOR has been reported to be associated with CDDP resistance and poor prognosis in different cancers. mTOR mediated CDDP response was also regulated by non-coding RNAs, MAPK signaling, transcription factors, and structural proteins. In this regard, various cellular processes such as apoptosis, autophagy, and drug efflux were regulated by mTOR during the CDDP response in tumor cells. This review highlights the mTOR as a key regulator of CDDP response and therapeutic target in cancer biology.

CRediT authorship contribution statement

Amirhosein Maharati: Writing – original draft, Methodology. **Yasamin Rajabloo:** Writing – original draft. **Meysam Moghbeli:** Writing – review & editing, Visualization, Validation, Supervision, Project administration, Conceptualization.

Data availability statement

Data will be made available on request. For requesting data, please write to the corresponding author.

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