

Review Article

Biological landscape and nanostructural view in development and reversal of oxaliplatin resistance in colorectal cancer

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ABSTRACT

The treatment of cancer patients has been mainly followed using chemotherapy and it is a gold standard in improving prognosis and survival rate of patients. Oxaliplatin (OXA) is a third-platinum anti-cancer agent that reduces DNA synthesis in cancer cells to interfere with their growth and cell cycle progression. In spite of promising results of using OXA in cancer chemotherapy, the process of drug resistance has made some challenges. OXA is commonly applied in treatment of colorectal cancer (CRC) as a malignancy of gastrointestinal tract and when CRC cells increase their proliferation and metastasis, they can obtain resistance to OXA chemotherapy. A number of molecular factors such as CHK2, SIRT1, c-Myc, LATS2 and FOXO1 have been considered as regulators of OXA response in CRC cells. The non-coding RNAs are able to function as master regulator of other molecular pathways in modulating OXA resistance. There is a close association between molecular mechanisms such as apoptosis, autophagy, glycolysis and EMT with OXA resistance, so that apoptosis inhibition, pro-survival autophagy induction and stimulation of EMT and glycolysis can induce OXA resistance in CRC cells. A number of anti-tumor compounds including astragaloside IV, resveratrol and nobiletin are able to enhance OXA sensitivity in CRC cells. Nanoparticles for increasing potential of OXA in CRC suppression and reversing OXA resistance have been employed in cancer chemotherapy. These subjects are covered in this review article to shed light on molecular factors resulting in OXA resistance.

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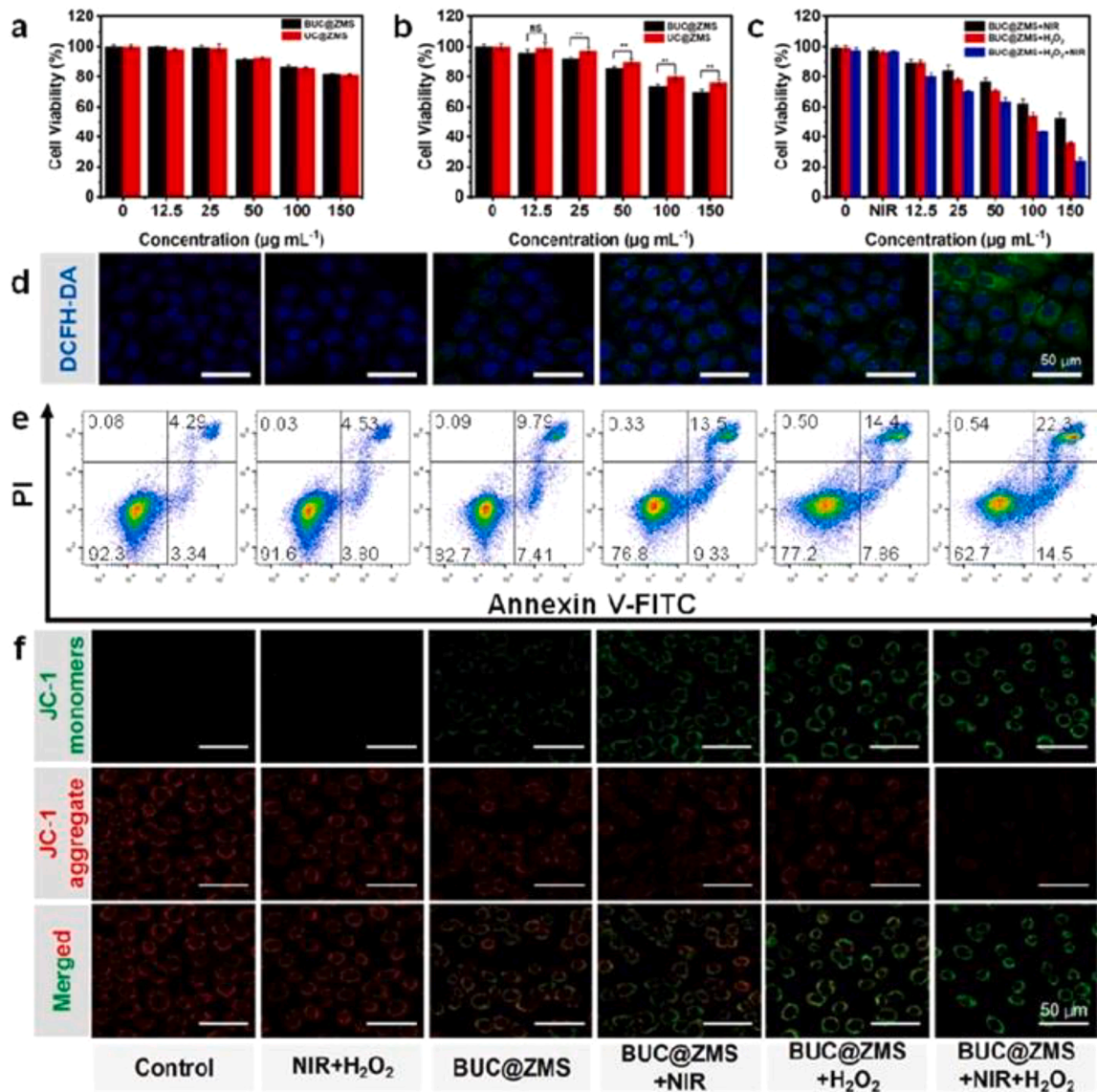


Fig. 1. a-f) The application of the nanomaterials for the treatment of cancer and their ability in suppressing tumorigenesis in the different cell lines. These nanoparticles can cause apoptosis in the tumor cells and mediate mitochondrial membrane potential loss. Reprinted with permission from Elsevier [46].

Introduction

Colorectal cancer

The third most common malignancy around the world is colorectal cancer (CRC) that has been ranked as fourth in causing death and its burden is suggested to enhance by 2030 and reach to 60% [1,2]. A combination of factors including genetic mutations, environmental factors and lifestyle changes participate in development of CRC [3]. CRC can be affected by hereditary factors and its spread and development are a slow-occurring processes that happen in step-wise manners and are known as adenoma-carcinoma sequence [4]. CRC is a highly aggressive tumor types and it is a combination of tumors of colon and rectal and about 11% of all cancer cases are related to CRC [5,6]. The mortality of CRC depends on geographical alterations and highest mortality of CRC is observed in men in Hungary and lowest incidence rate is related to females in Norway [7]. Moreover, CRC has been commonly diagnosed in men in Japan, South Korea, Slovakia and high mortality rate in Saudi Arabia, Oman and UAE [7]. Based on sequencing technology and array-based methods, CRC can be divided into types in view of molecular profile. The first group is hypermutated group and second group is

non-hypermutated groups [8]. There are a variety of risk factors for CRC such as environment, family history, age, obesity, smoking, alcohol consumption and poor physical activity [9]. The biological landscape of CRC has been of importance in recent years among other risk factors and therefore, researchers have attempted to understand function of genes and related molecular pathways in CRC progression and determining response to therapy. Silencing CDK15 suppresses carcinogenesis in CRC and its function in CRC is based on binding to PAK4 and stimulating its phosphorylation at S291 site. Upon phosphorylation of PAK4, the progression and proliferation of CRC cells increase due to induction of β -catenin signaling [10]. The metabolic reprogramming in CRC cells is regulated by molecular interactions that OTUB2 as a deubiquitinase is able to increase PKM2 activity in triggering glycolysis in CRC cells [11]. Moreover, upregulation of ENO3 promotes glycolysis in CRC cells [12]. Upregulation of DDX39B leads to overexpression of PKM2 in triggering glycolysis and metabolic reprogramming in enhancing CRC progression [13]. The 5-FU sensitivity in CRC elevates by apoptosis stimulation [14]. In an AGO-dependent manner, tRF3008A reduces FOXK1 expression to impair tumorigenesis [15]. According to the experiments, the molecular profile of CRC determines their progression and ability in proliferation and metastasis [16–18]. The biological profile of CRC has been more

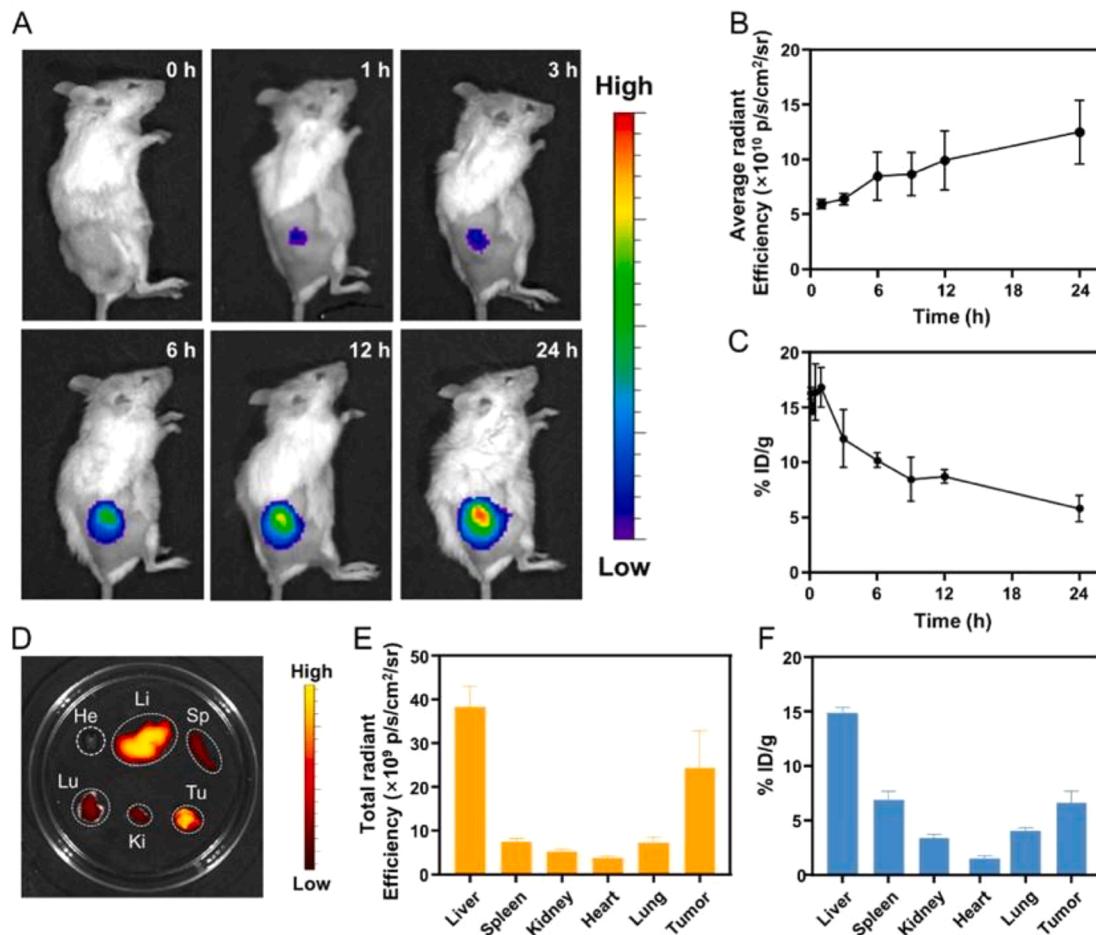


Fig. 2. A-F) Evaluating the ability of the calcium phosphate nanostructures for the imaging in vivo. Reprinted with permission from Elsevier [53].

investigated. These experiments highlight the importance of molecular pathway dysregulation in the metabolism, carcinogenesis and chemoresistance. The overexpression of IGF2BP2 promotes TFRC expression and facilitates the metabolism of iron in accelerating CRC malignancy [19]. Noteworthy, through m6A-dependent mechanism, FMR1 upregulates the stability of EGFR to enhance the tumorigenesis in colorectal cancer [20]. TNF- α upregulates USP14 expression that is vital for increasing JNK levels and developing feedback loop in promoting tumorigenesis [21]. LARP6 has potential in causing SGMS2 down-regulation to interfere with sphingomyelin synthesis in the treatment of CRC [22]. HIF-1 α enhances the tumorigenesis in CRC; the stability of HIF-1 α elevates by Myo1b in suppressing its autophagic degradation to induce angiogenesis [23]. An interesting experiment has displayed that exposure of CRC to the platinum drugs for the cancer chemotherapy enhances chance of drug resistance. Long-term application of platinum drugs and their accumulation of cancer-associated fibroblasts can stimulate chemoresistance [24]. The M2 polarization of macrophage by BST2 can be induced to enhance tumorigenesis in CRC [25]. The epigenetic changes can also accelerate the progression of cancer. LncRNA NALT1 is capable of miR-574-5p suppression to regulate PEG10 expression in facilitating CRC carcinogenesis [26]. The increase in the glucose metabolism of CRC, known as glycolysis can be stimulated by METTL16 in enhancing cancer progression [27]. Hence, current review has been allocated in understanding function of molecular landscape in CRC in controlling response to oxaliplatin (OXA).

Drug resistance development

As a third-platinum anti-tumor compound, OXA reduces tumor

progression via suppressing synthesis of DNA in cancer cells and impairing cell division and growth [28–30]. The application of OXA for CRC treatment was first confirmed in 1996 [31] and for advanced and metastatic CRC, a combination of OXA, 5-fluorouracil and leucovorin is employed. Moreover, OXA has shown anti-tumor activities against breast cancer, lung cancer and lymphoma, among others [32]. Although chemotherapy appeared as an important part in retarding cancer progression, cancers with malignant behavior are able to obtain chemoresistance. A variety of factors have been considered that participate in chemoresistance. Oncogenic factor upregulation, onco-suppressor pathway suppression, drug transporter dysregulation and others can regulate chemotherapy response. Recent experiments have emphasized on highlighting underlying mechanisms participating in chemoresistance; high metabolism of glucose in tumor-associated macrophages (TAMs) can lead to drug resistance via inducing O-GlcNAcylation of lysosomal cathepsin B [33]. Upregulation of stanniocalcin 1 results in cisplatin insensitivity in ovarian tumor via inducing PI3K [34]. ZCCHC4 as an RNA-binding protein is capable of suppressing apoptosis due to DNA damage and mediates chemoresistance [35]. Moreover, microRNAs (miRNAs) [36] and presence of feedback loops [37] can affect chemotherapy response of tumor cells. Hence, similar to other anti-cancer agents, it is possible to develop resistance to OXA chemotherapy [38,39]. For instance, upregulation of lncRNA DUBR by SP1 results in CIP2A upregulation via sponging miR-510d-5p to stimulate OXA resistance in hepatocellular carcinoma [40]. The bioengineering exosomes for co-delivery of OXA and PGM5-AS1 is of importance in suppressing drug resistance [41]. Upregulation of lncSLC01C1 in gastric tumor causes sponge of miR-211-5p and miR-204-5p to inhibit DNA damage and to mediate OXA

resistance [42]. Prevention of mitochondrial apoptosis results in OXA resistance in gastric tumor [43] and silencing lncRNA LINC01134 leads to OXA sensitivity via inducing ferroptosis in hepatocellular carcinoma [44].

Nanoparticles in tumor therapy

The recent experiments have highlighted the increasing application of nanoparticles for tumor suppression. The presence of inflammation and pro-inflammatory cytokines can significantly increase the progression of cancer and accelerate tumorigenesis. The smart MnO nanostructures are capable of downregulating TLR and NF- κ B and they impair the recruitment of macrophage to interfere with the presence of inflammation in impairing metastasis [45]. The new advances are related to the development of nanocarriers that are biomimetic and their stealth properties have been improved. The multifunctional nanostructures developed from ZnMn1-xS core-shell nanocarriers in combination with upconversion nanostructures are able to impair pancreatic cancer progression. These nanocarriers have been functionalized with cancer cell membrane to improve their properties and they have able to induce photodynamic and chemodynamic therapy to suppress pancreatic tumor (Fig. 1) [46].

There are some questions that what is the difference between microparticles and nanoparticles in the treatment of cancer? Interestingly, a recent experiment has shown that lipid microparticles have a similar potential to lipid nanostructures to deliver mRNA and impair the progression of cancer [47]. Moreover, an improvement in the cancer therapy has been obtained through application of stimuli-responsive nanocarriers such as glutathione-responsive mesoporous nanostructures that active both immune system and mediate chemotherapy in the tumor suppression [48]. Since the potential of chemotherapy in the suppression of tumor has been reduced that the main reason is the development of resistance, the application of nanostructures such as micellar nanostructures for the delivery of chemotherapy compounds has improved the potential in tumorigenesis suppression [49]. Moreover, it is of importance that nanoparticles have been developed for the therapy of specific kinds of tumor including urological tumors and they can also impair the major mechanisms of tumorigenesis such as EMT that increases cancer metastasis [50]. Moreover, plant virus and bacteriophage can be applied as nanostructures for the delivery of TLR agonist in accelerating tumor immunotherapy [51]. One of the mechanisms to induce immunotherapy is to mediate pyroptosis. The ZIF-8 nanostructures have shown potential in pyroptosis induction and TME remodelling to mediate cancer immunotherapy [52]. The nanoparticles can be developed from ions and metals to release them at the tumor site for potentiating tumor suppression. Calcium phosphate nanostructures have been embedded with disulfiram to release Cu²⁺ and disulfiram in tumor suppression (Fig. 2) [53]. The recent studies have also focused on the utilization of nature-based nanostructures for the carcinogenesis suppression. The application of chitosan nanostructures for the delivery of isolongifolene can accelerate the potential in tumor suppression and these nanocarriers have high biocompatibility in plasma [54]. The nanoparticles based on hyaluronic acid can specifically target the tumor cells overexpressing CD44 receptor [55]. The nanoparticles mediate the sustained release of drugs to facilitate their efficacy in tumor therapy. For improving this feature, the drugs could be complexed with cyclodextrins that improves the potential in cancer suppression [56]. The nanoparticles could deliver two anticancer drugs for causing synergistic cancer suppression [57]. Moreover, in order to prevent the clearance of nanostructures from the body and improve their potential in cell death induction, the nanoparticles are designed in a way to evade macrophages [58].

Oncogenic pathways and oxaliplatin chemotherapy

Regardless of cancer type, high expression level of oncogenic factors

can lead to cancer tumorigenesis and malignancy. In some cases, these factors reduce response to chemotherapy and mediate resistance. Silencing such oncogenic factors can reverse process of drug resistance development in CRC. Down-regulating KLK11 expression results in apoptosis stimulation and reduction in proliferation. Upon knock-down of KLK11, apoptosis induction due to caspase-3 upregulation occurs that increases OXA sensitivity of CRC cells [59]. YTHDF3 has been utilized as an oncogenic factor and its upregulation elevates brain invasion of breast tumor cells [60]. Moreover, it can induce degradation of lncRNA GAS5 in inducing YAP signaling and increasing tumorigenesis [61]. Similarly, YTHDF3 increases malignancy of CRC cells and it recruits eIF2AK2 and eIF3A to increase CRC progression and its overexpression is obviously observed in OXA-resistant tumor cells [62]. The phosphorylation status of molecular factors can also determine OXA response of CRC cells. Deficiency of NSF1 elevates OXA sensitivity of CRC cells and this loss of NSF1 is vital for mediating PANoptosis in vitro and in vivo. The oxidative stress caused by OXA leads to phosphorylation of NSF1 in S293 that mediates poor prognosis and low response to chemotherapy [63].

WBCR22 is another regulator of tumor progression and Merm1/WBCR22 inhibits apoptosis in increasing viability of tumor cells [64]. Moreover, high expression level of WBCR22 mediates unfavorable prognosis in cancer [65]. Therefore, it demonstrates oncogenic function in some tumors and CRC is among them. Noteworthy, the factors that inhibit WBCR22 expression are of importance in reducing CRC progression. Natural killer cells are able to increase expression level of miR-146b-5p and as a result, they reduce expression level of WBCR22 in suppressing OXA-resistant CRC cells [66]. Silencing WBCR22 does not affect cell cycle progression, but it induces apoptosis in CRC cells. Moreover, knock-down of WBCR22 increases ROS generation by OXA in CRC cells and increases their chemosensitivity [67].

UPF1 is a mRNA-surveillance factor and it accounts for nonsense-mediated decay of mRNAs containing premature stop codons [68]. The dysregulation of UPF1 has been confirmed in cancers. Aberrant expression of UPF1 in CRC is in favor of developing drug resistance in tumor cells. The zinc finger of UPF1 interacts with Toprim of TOP2A to elevate phosphorylation of TOP2A in a SMG1-dependent manner. Then, UPF1 increases cancer progression and preserves stemness in triggering OXA resistance in CRC cells [69]. These studies highlighted that fact that increase in progression of tumor cells can lead to development of OXA resistance in CRC. Sometimes, the story is related to accumulation of drug in cancer cells and some tumor cells may be able to increase efflux of drugs from them to increase chemoresistance. P-glycoprotein (P-gp) is a drug transporter and a member of ABC family. It has been located on the surface of cells and its hyperactivity can lead to development of drug resistance [70]. The upregulation of P-gp has been responsible for development of chemoresistance in CRC. Silencing CAC1 down-regulates P-gp and MRP-1 expression levels in increasing 5-fluorouracil sensitivity in CRC [71]. Notably, P-gp has demonstrated close association with OXA resistance in CRC. When expression level of P-gp decreases, the sensitivity of CRC cells to OXA enhances. miR-506 down-regulates MDR1/P-gp expression through inhibition of Wnt/ β -catenin to promote OXA sensitivity in CRC cells [72]. Upregulation of PI3K/Akt results in activation of NF- κ B signaling to mediate OXA resistance via increasing P-gp expression. However, Zui Jin Wan suppresses PI3K/Akt/NF- κ B axis in reducing P-gp expression and suppressing OXA resistance in CRC [73]. Moreover, high expression level of stanniocalcin 2 has been responsible for development of OXA resistance in CRC and it is mediated via increasing P-gp expression and activity [74].

The cancer progression is a result of interactions among various molecular pathways and each interaction can affect a hallmark of cancer such as proliferation, metastasis and even resistance to therapy. FKBP3 has been considered as a regulator of tumor progression in which its overexpression enhances tumor growth via increasing promoter activity of HDAC2 [75]. Moreover, administration of melatonin reduces FKBP3

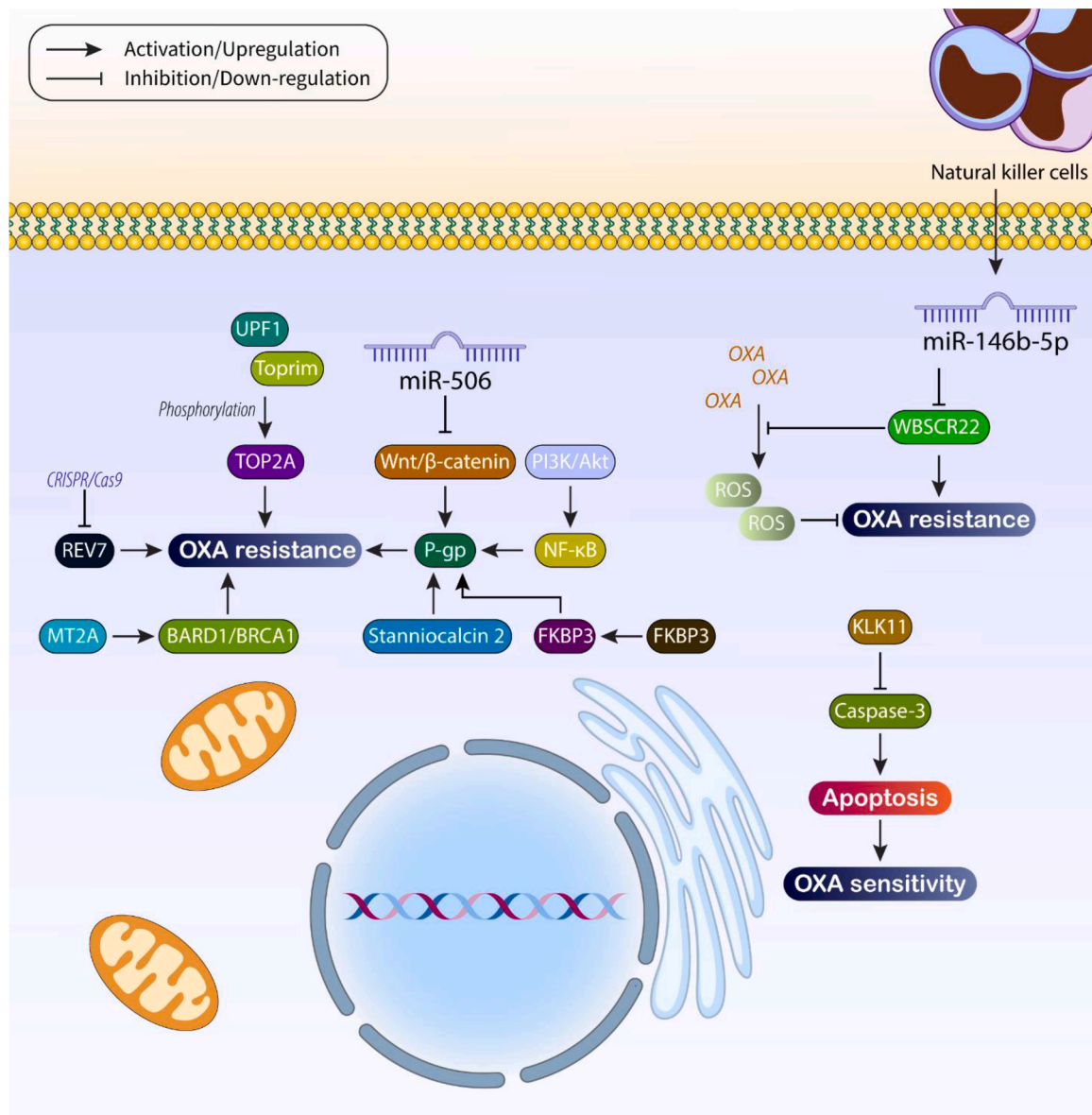


Fig. 3. The role of oncogenic pathways in oxaliplatin resistance. Since the dysregulation of molecular pathways commonly occurs in the CRC, the studies have shown that upregulation of these pathways such as KLK11 can prevent apoptosis through caspase-3 downregulation to reduce drug sensitivity. Moreover, reduction in the levels of P-gp and increase in the activity of P-gp can cause drug resistance.

expression in suppressing tumorigenesis [76]. In CRC cells, high expression level of FKBP3 reduces sensitivity to OXA chemotherapy and its knock-down promotes drug sensitivity of tumor cells. Moreover, FKBP3 is able to increase expression level of HDAC2 in mediating OXA resistance in CRC cells. Silencing FKBP3 decreases HDAC2 expression, down-regulates P-gp activity and Akt expression, and stimulates PTEN signaling in enhancing OXA sensitivity [77]. KIF18b is a member of kinesin superfamily and it modulates microtubule-related movement. Hence, migration, mitosis and transportation are regulated by KIF18b [78]. Recent studies have shown oncogenic function of KIF18b that stimulates β -catenin [79]. Moreover, KIF18b promotes expression level of CDCA8 in facilitating pancreatic cancer progression [80]. Therefore, KIF18b demonstrates oncogenic function and noteworthy, it can mediate drug resistance in human cancer [81]. In CRC cells, SP-1 recruits DNMT3b to induce methylation of PARPBP promoter in reducing its expression level. However, upregulation of KIF18b prevents recruitment of DNMT3b to PARPBP promoter in inducing OXA resistance in CRC cells [82]. These studies demonstrate that development of OXA

resistance in CRC is a result of interaction among various molecular pathways. When expression level of MT2A increases, it stimulates OXA resistance in CRC cells. Silencing MT2A increases OX sensitivity of CRC cells. MT2A increases BARD1/BRCA1 in inducing OXA resistance in CRC cells [83]. Moreover, some of the oncogenic factors are able to induce resistance to more than one chemotherapy agent. For instance, high expression level of REV7 can result in drug resistance in CRC and its down-regulation by CRISPR/Cas9 system is of importance in reversing 5-fluorouracil and OXA resistance in tumor cells [84]. Therefore, various molecular pathways are able to mediate OXA resistance in CRC (Fig. 3).

Onco-suppressor pathways and oxaliplatin chemotherapy

The previous section revealed that oncogenic pathways demonstrate upregulation in CRC and they can increase malignancy of CRC cells in developing OXA resistance. On the other side, there are onco-suppressor factors that increase OXA sensitivity of CRC cells. Although main

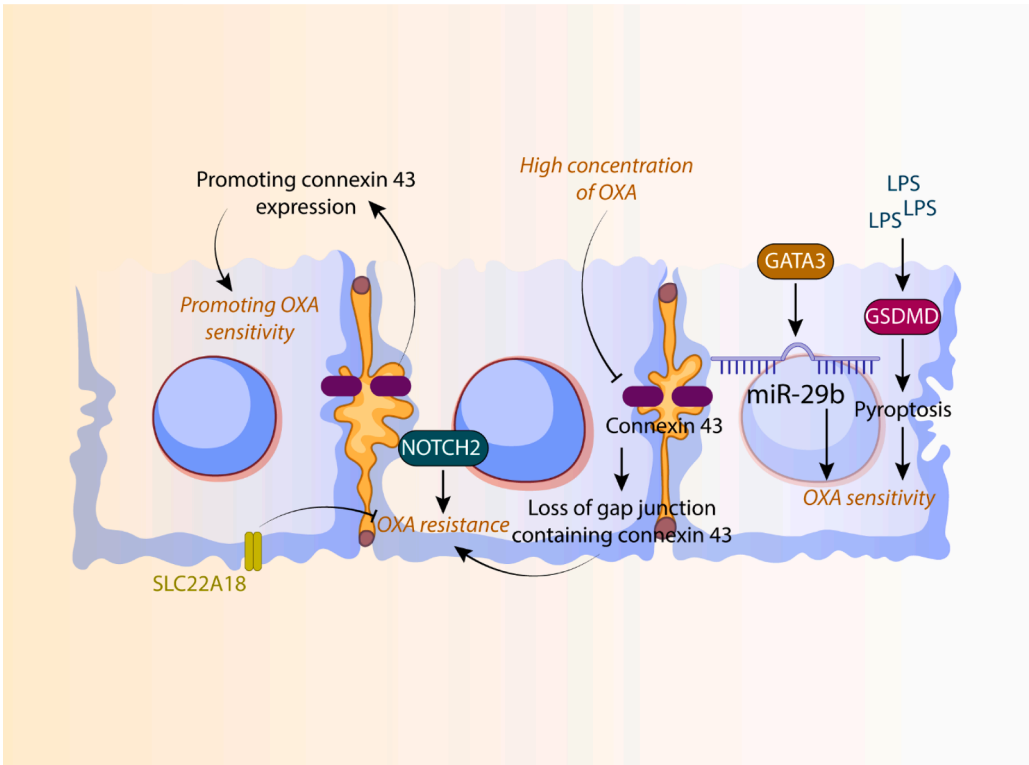


Fig. 4. Onco-suppressor pathways in reducing oxaliplatin resistance. The overexpression of SLC22A18 and NOTCH2 induces drug resistance, while enhancing connexin 43 levels accelerates drug sensitivity. Moreover, pyroptosis induction by GSDMD causes drug sensitivity and the overexpression of miR-29b by GATA3 accelerates the response to chemotherapy.

emphasis has been focused on oncogenic factors, some of the researches have been directed towards understanding function of onco-suppressor factors in increasing OXA sensitivity in CRC. Connexin 43 (Cx43) has been defined as a sensitizer of chemotherapy in CRC cells. For instance, upregulation of Cx43 mediates paclitaxel sensitivity in CRC [85]. Moreover, kanglaite increases Cx43 expression and down-regulates NF-κB in promoting Taxol sensitivity of tumor cells [86]. Furthermore, Cx43 suppresses Akt signaling in increasing efficacy of photodynamic therapy in impairing CRC progression [87]. High concentration of OXA decreases Cx43 expression, while promoting Cx43 expression is of importance in promoting OXA sensitivity of CRC cells via gap junctional communication function [88]. Loss of gap junction containing Cx43 leads to OXA resistance in CRC [89], confirming that Cx43 has onco-suppressor function and can increase OXA sensitivity in CRC. SLC22A18 is another factor that contributes to OXA sensitivity in CRC that its down-regulation leads to overexpression of ERK in triggering OXA resistance in CRC [90].

Exposure of CRC cells to stress can cause cell death and increase in OXA sensitivity. Low expression level of GSDMD is observed in CRC cells and mediates poor prognosis. Exposure to lipopolysaccharide (LPS) leads to upregulation of GSDMD and subsequent stimulation of pyroptosis in promoting OXA sensitivity [91]. Enhancing expression level of onco-suppressor factors is of importance in mediating OXA sensitivity in CRC cells. High expression level of H3K27me3 leads to OXA sensitivity, and when expression level of H3K2me3 occurs, induction of NOTCH2 expression occurs to promote OXA resistance and progression of CRC cells [92]. Hence, the optimal strategy is to increase expression level of onco-suppressor factors in treatment of CRC and mediating OXA sensitivity. GATA3 pre-mRNA degradation by KIAA1429 results in progression of tumor cells [93]. GATA3 decreases cancer growth and it can function as an independent prognostic factor [94]. Restoring GATA3 expression interferes with OXA resistance in CRC. GATA3 increases expression level of miR-29b to reverse OXA resistance in CRC, and

Table 1		
The regulation of oxaliplatin resistance in colorectal cancer.		
Molecular pathway	Remark	Ref
FOXCl/miR-31-5p/LATS2	FOXCl increases miR-31-5p expression to down-regulate LATS2 in triggering drug resistance	[96]
Cyr61/Bcl-xL	Cyr61 promotes Bcl-xL expression in chemoresistance development	[97]
PKM2 GLS1	Silencing PKM2 and GLS1 increases drug sensitivity	[98]
EIF4A2/c-Myc	EIF4A2 increases c-Myc expression in inducing chemoresistance	[99]
DHX9/Circ-CCDC66	DHX9 is upregulated by OXA and increases circ-CCDC66 expression in chemoresistance	[100]
S100A10	Upregulation of S100A10 decreases OXA sensitivity	[101]
B7-H3	Suppressing B7-H3 impairs OXA resistance in CRC	[102]
SIRT1/miR-20b-3p/DEPDC1	SIRT1 reduces miR-20b-3p expression in upregulating DEPDC1 and mediating chemoresistance	[103]
CHK2	Upregulation of CHK2 increases DNA repair to mediate drug resistance	[104]
GRP78/CD24	Silencing GRP78 down-regulates CD24 expression in inducing drug resistance	[105]

knock-down of GATA3 enhances tumor growth and volume (Fig. 4) [95]. According to these studies and Table 1, a variety of factors are considered as regulators of OX sensitivity in CRC and in these cases, down-regulation of oncogenic factors and upregulation of anti-tumor factors are suggested.

Non-coding RNAs and oxaliplatin chemotherapy

microRNAs

miRNAs are a class of short non-coding RNAs consisting of 17-25 nts and they directly bind to 3'-UTR of mRNAs to degrade mRNA or prevent



chemotherapy and radiotherapy [119,120]. Upregulation of SIRT1 can lead to development of OXA resistance in CRC cells. However, increasing miR-29b expression leads to SIRT1 down-regulation in enhancing ROS generation and inducing JNK phosphorylation to impair OXA resistance in CRC [121]. miR-488 is a new emerging therapeutic target in CRC that suppresses MAPK signaling in reducing CRC progression [122]. miR-488 reduces CRC malignancy via down-regulating PHF8 [123]. miR-488 has been considered as a regulator of OXA resistance in CRC. miR-488 decreases expression level of PFKFB3 to suppress glycolysis and OXA resistance [124]. A similar function is followed by miR-200b-3p in regulating OXA resistance in CRC. Expression level of mi-200b-3p decreases in OXA cells and tissues, and restoring its expression promotes OXA sensitivity. miR-200b-3p reduces expression level of TUBB3 to induce apoptosis and to suppress proliferation and invasion of CRC cells in increasing OXA sensitivity [125]. The exact function of some of the miRNAs is not certain and therefore, it can increase complexity of tumor progression. miR-107/103 is an inducer of metastasis in CRC via decreasing DAPK and KLF4 levels [126], while another experiment reveals that miR-107 suppresses CRC progression via down-regulating TFR1 expression [127]. It has been reported that miR-107 reduces CAB39 expression, while DCA increases CAB39 expression. Upregulation of miR-107 leads to development of OXA resistance in CRC cells [128].

Exosomes are minute membrane vesicles that their average diameter is less than 100 nm and they can be released by a variety of eukaryotic cells [129,130]. Exosomes have been interested in recent years due to their function in different diseases and ability in transferring bioactive molecules, especially genetic materials [131,132]. Exosomal miR-208b can be secreted by CRC cells and then, it decreases mRNA level of PDCD4 to increase Treg cell expansion in triggering OXA resistance in tumor cells [133]. Moreover, exosomal miR-46146 reduces expression level of PDCD10 in triggering OXA resistance in CRC [134].

Long non-coding RNAs

The non-coding RNA part of genome has been always of interest for researchers and it was found that these RNAs can have important regulatory functions in cells. The long non-coding RNAs (lncRNAs) have more than 200 nts in length and they do not encode proteins, but they regulate gene expression at transcriptional and post-transcriptional levels [135,136]. lncRNAs have been important regulators of drug resistance [137] and their expression level changes during CRC progression [138,139]. Increasing evidence has evaluated function of lncRNAs in regulating OXA resistance in CRC. Notably, the expression level of lncRNAs such as LINC00973 changes after chemotherapy in CRC cells [140]. LINC00525 is involved in mediating OXA resistance in CRC. LINC00252 promotes stemness of CRC cells and it is associated with poor prognosis. LINC00525 increases levels of ELK3 via miR-507 down-regulation to prevent apoptosis and to enhance stemness in triggering OXA resistance in CRC cells [141]. lncRNA MCF2-AS1 shows oncogenic function and it can increase growth, invasion and glucose metabolism of tumor cells [142]. Moreover, the function of lncRNA MCF2-AS1 in promoting CRC progression is mainly mediated via sponging miRNAs [143,144]. A recent experiment has demonstrated that high expression level of lncRNA MCF2-AS1 can lead to development of OXA resistance in CRC cells. lncRNA MCF2-AS1 shows upregulation in CRC and reduces response of tumor cells to chemotherapy. lncRNA MCF2-AS1 reduces miR-105 expression to upregulate IL-1 β in triggering OXA resistance in CRC cells [145]. lncRNA BLACAT1 is another oncogenic factor [146] that can sponge miRNAs [147] and it regulates tumor hallmarks such as growth, invasion and glycolysis [148]. The upregulation of BLACAT1 has been associated with OXA resistance in CRC. BLACAT1 increases CREB1 expression via miR-519d-3p sponging to increase CRC progression and to mediate OXA resistance in tumor cells [149]. It is also worth mentioning that expression level of lncRNAs can be increased by upstream mediators. IRF-1 is able to increase expression

Table 2
The role of non-coding RNAs in regulating OXA resistance in CRC.

Molecular pathway	Remark	Ref
Circ-0032833/miR-125-5p/MSI1	Circ-0032833 knock-down increases miR-125-5p expression in MSI1 down-regulation and enhancing OXA sensitivity	[167]
Circ-0082182/miR-326/NFIB	Circ-0082182 increases NFIB expression through miR-326 inhibition in OXA resistance	[166]
Circ-CD44/miR-330-5p/ABCC1	Circ-CD44 increases ABCC1 expression by miR-330-5p inhibition in OXA resistance	[168]
Circ-FBXW7/miR-18b-5p	Circ-FBXW7 reduces miR-18b-5p expression in ameliorating drug resistance	[169]
Circ-PTK2/miR-136-5p/YTHDF1	Circ-PTK2 increases YTHDF1 expression through miR-136-5p inhibition in drug resistance development	[170]
CiRS-122/miR-122/PKM2	CiRS-122 increases PKM2 expression through miR-122 sponging in glycolysis induction and mediating OXA resistance	[171]
c-Myc/miR-27b-3p/ATG10	c-Myc suppresses miR-27b-3p expression to upregulate ATG10 in autophagy induction and mediating drug resistance	[172]
miR-325/HSPA12B/PI3K/Akt/Bcl-2	miR-325 reduces expression level of PI3K/Akt by interacting with HSPA12B to reduce Bcl-2 expression in mediating drug sensitivity	[173]
miR-1254/MEGF6	miR-1254 transfection decreases apoptosis, increases MEGF6 expression and mediates drug resistance	[174]
miR-124/CAPN2	miR-214 decreases protein levels of CAPN2 in increasing drug sensitivity	[175]
miR-133b/DOT1L	miR-133b reduces expression level of DOT1L in increasing OXA sensitivity	[176]
miR-543/PTEN/Akt/mTOR	Dichloroacetate decreases miR-543 expression to induce PTEN signaling in inhibition of Akt/mTOR and mediating drug sensitivity	[177]
miR-106a/FOXQ1	miR-106a reduces expression levels of FOXQ1 in promoting OXA sensitivity	[178]
miR-483-3p/FAM171B	miR-483-3p reduces FAM17B expression in elevating OXA sensitivity	[179]
miR-138/PDK1	miR-138 reduces expression level of PDK1 in reversing OXA resistance	[180]
miR-33a-5p	miR-33a-5p presence in extracellular vesicles is a biomarker for response to OXA	[181]
miR-135b/FOXO1	miR-135b reduces FOXO1 expression in drug resistance development	[182]
miR-96/TPM1	miR-96 decreases TPM1 expression in chemoresistance	[183]
miR-34a/TGF- β /Smad4	miR-34a inhibits macroautophagy via suppressing TGF- β /Smad4	[184]
miR-140/MRE11	miR-140 induces MRE11 down-regulation and ameliorates OXA treatment	[185]
miR-15a-5p/SIRT4	miR-15a-5p reduces SIRT4 expression to increase cancer progression and to mediate OXA resistance	[186]

level of lncRNA PVT1-214 in CRC cells and this leads to miR-128 down-regulation in enhancing tumor progression and inducing resistance to OXA chemotherapy [150].

Circular RNAs

The presence of circular RNAs (circRNAs) was confirmed more than four decades ago by electron microscopy [151–155] and advances in bioinformatics analysis and high-throughput sequencing led to recognition of more circRNAs [156–158]. The generation of circRNAs can be mediated by exon skipping and direct back-splicing that their structure is a closed loop and lacks polyadenylated tail [159–161]. Recent studies have demonstrated important function of circRNAs in CRC [162–164]. Circ-0079662 has been associated with development of OXA resistance in CRC due to sponging miR-324-5p to increase HOXA9 expression [165]. The studies mainly have focused on the miRNA sponge by circRNAs in regulating OXA resistance in CRC. Circ-0082182 reduces miR-326 expression to increase levels of NFIB in enhancing malignancy of CRC cells and triggering OXA resistance [166]. Moreover, silencing oncogenic circRNAs increases OXA sensitivity of CRC cells. Reducing

circ-0032833 enhances OXA sensitivity of CRC cells and this is mediated via promoting miR-125-5p expression to down-regulate MSI1 [167]. The circRNAs also demonstrate a close association with drug transporters in tumor cells that should be highlighted. Circ-CD44 promotes expression level of ABCC1 via miR-330-5p down-regulation to reduce apoptosis and increase proliferation and metastasis of CRC cells that are of importance in triggering OXA resistance [168]. Similar to miRNAs, circRNAs can be found in exosomes and therefore, their uptake by cancer cells can be enhanced. Exosomal circ-FBXW7 can reduce miR-18b-5p expression to ameliorate OXA resistance in CRC cells (Fig. 5) [169]. According to these studies, circRNAs are important regulators of OXA chemotherapy in CRC cells. Table 2 summarizes role of non-coding RNAs in regulating OXA resistance in CRC.

Molecular mechanisms and oxaliplatin chemotherapy

Apoptosis

The final aim is to reduce survival rate of tumor cells after chemotherapy for improving prognosis of patients. The anti-tumor agents that induce apoptosis significantly reduce viability of cancer cells. However, tumor cells are also able to develop resistance to apoptosis and can active anti-apoptotic proteins for supporting themselves. In previous sections, it was mentioned that drug transporters can reduce accumulation of OXA in mediating resistance in CRC cells. Noteworthy, upregulation of ABCG2 can also affect a molecular mechanism known as ER stress. High expression level of ABCG2 functions as an oncogenic factor during ER stress [187] via inducing phosphorylation of PERK and eIF2 α [188]. NF- κ B upregulation leads to increase in expression levels of ABCG2 to inhibit ER stress-mediated apoptosis in CRC cells and to induce OXA resistance [189]. It seems that upregulation of NF- κ B can prevent apoptosis in CRC cells and increases their survival rate. The high expression level of SPRK1 is observed in CRC cells and it promotes Akt expression to induce NF- κ B signaling in preventing apoptosis and reducing sensitivity of tumor cells to OXA chemotherapy [190]. The incorporating OXA in nanoparticles can increase apoptosis induction in CRC cells. For instance, PEGylated liposomal nanocarriers containing OXA are able to stimulate apoptosis in CRC cells via increasing Fas/FasL levels and caspase-8 upregulation [191]. Moreover, suppression of cellular Prion protein by melatonin is of importance in enhancing apoptosis in OXA-resistant CRC cells [192]. Therefore, inhibition of oncogenic pathways related to apoptosis inhibition in CRC cells is of importance in enhancing OXA sensitivity of tumor cells.

Autophagy

Autophagy is another molecular mechanism that its function in cancer and drug resistance has been of interest in recent years. Autophagy is a programmed cell death mechanism similar to apoptosis that is modulated in cells, and its function is to provide homeostasis in cells. One of the complexities about autophagy is its dual function in cancer and a number of its regulators including AMPK, mTOR, PI3K, Beclin-1 and ATGs have been recognized [193–195]. Autophagy determines response of cancer cells to chemotherapy. For instance, there is NNK in tobacco smoking stimulates autophagy via β 2-AR/Akt loop to mediate stemness and drug resistance [196]. SOCS5 modulates Bcl-2-regulated autophagy in affecting temozolomide resistance [197]. The regulation of autophagy has been of importance in affecting progression of CRC cells. Inhibition of pro-survival autophagy is of importance in promoting apoptosis and cell death in CRC [198]. Withanolide is able to regulate β -catenin signaling in mediating apoptosis and autophagy in CRC cells [199]. Moreover, graphene oxide increases ROS levels to stimulate apoptosis and autophagy via ULK1 upregulation in reducing CRC progression [200]. The current section focuses on the function of autophagy in regulating OXA resistance in CRC.

HMGB1 has been defined as an important regulator of CRC

progression and its upregulation decreases OXA response in tumor cells. High expression level of HMGB1 is associated with stimulation of MEK/ERK axis in autophagy induction. In this case, function of autophagy is oncogenic and it increases OXA resistance in CRC cells. Silencing HMGB1 may inhibit autophagy in enhancing OXA sensitivity of CRC cells [201]. The function of chemotherapy agents is to induce cell death and this is vital for reducing survival rate of tumor cells. Exposure of CRC cells (Caco-2 cells) to OXA is associated with cell death induction through enhancing ROS generation and mediating ER stress. Stimulation of pro-survival autophagy is of importance in protecting CRC cells against cell death mediated by OXA through ER stress and ROS over-generation. Silencing ATG5 or Beclin-1 as inducers of autophagy results in increased cell death and ROS overgeneration in CRC cells [202]. According to these studies, suppression of pro-survival autophagy is of importance in enhancing OXA sensitivity of CRC cells. ASPP2 is another factor that can also regulate OXA response of CRC [203]. Accumulating data demonstrates oncogenic function of ASPP2 in human cancer; so that, its low expression promotes YAP expression to increase endometrial cancer progression [204]. Low expression of ASPP2 leads to recruitment of aPKC/GLI1 pathway in enhancing metastasis of gallbladder tumor cells [205]. Interestingly, ASPP2 can enhance drug sensitivity via reducing XIAP expression [206]. ASPP2 demonstrates a close association with autophagy in CRC cells. High expression level of ASPP2 leads to autophagy inhibition that is of importance in increasing OXA-mediated cell death in CRC cells [203]. In fact, exposure of CRC cells to OXA chemotherapy leads to pro-survival autophagy induction. Restoring ASPP2 expression is of importance in apoptosis induction via preventing OXA-mediated autophagy in tumor cells [207]. It appears that a number of factors can lead to development of OXA resistance in CRC. Dysregulation of p53, induction of cytoprotective autophagy and increase in stemness can jointly lead to development of OXA resistance in CRC cells [208].

In case that autophagy has cytoprotective function, its reversal to autophagic cell death can be followed. PAPEI nanoparticles harboring LDHA-siRNA suppress M2 polarization of macrophages and change autophagy to a pro-death mechanism in increasing OXA efficacy in cancer suppression [209]. The use of photosensitizers for increasing chemosensitivity of tumor cells has been of importance. Hypericin is a photosensitizer that stimulates ER stress in stimulating cytotoxic autophagy and enhancing OXA sensitivity of CRC cells [210]. Moreover, high expression level of keratin 18 and its phosphorylation can lead to autophagy induction and mediating OXA sensitivity in CRC cells [211]. These studies demonstrate that autophagy is an important regulator of OXA sensitivity/resistance in CRC cells [212,213].

Glycolysis

The ATP generation in tumor cells is mediated by a mechanism known as glycolysis or Warburg effect [214] that suppressing glycolysis can mediate apoptosis in drug resistant-tumor cells and therefore, targeting glycolysis is a promising strategy in reversing drug resistance [215]. PTBP1 is a RNA-binding protein and it is a splicing factor that regulates biological mechanisms [216]. Studies have revealed potential of PTBP1 as an oncogenic factor that its expression reduces by circ-RHOBTB3 in preventing lung metastasis in CRC [217]. Alternative microexon splicing by PTBP1 and RBFOX2 leads to metastasis in CRC [218]. Moreover, PTBP1 stimulates alternative splicing of coractin in promoting CRC malignancy [219]. PTBP1 demonstrates a positive association with glycolysis in colon tumor cells. PTBP1 increases expression level of PKM2 to induce glycolysis in mediating OXA resistance in colon cancer. Silencing PTBP1 or PKM2 as a downstream can increase chemosensitivity [220]. Moreover, decrease in mitochondrial DNA content can lead to glycolysis induction in promoting survival rate of CRC cells and subsequent resistance to OXA chemotherapy [221]. In addition to PKM2 that is an important enzyme in glycolysis mechanism, it has been reported that HK2 is also involved in glycolysis induction.

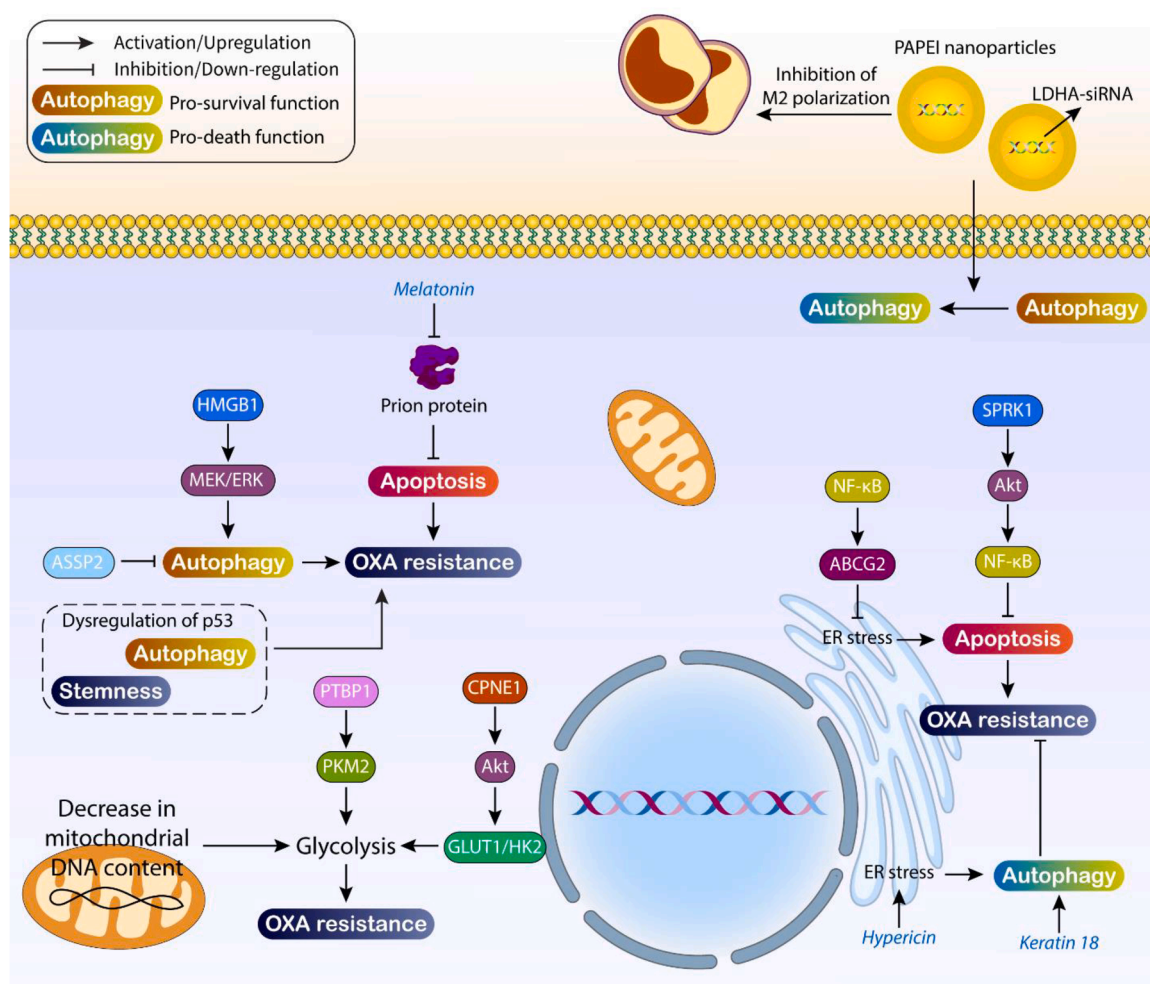


Fig. 6. Apoptosis, autophagy and glycolysis in oxaliplatin chemotherapy colorectal cancer. The inhibition of prion protein by melatonin can increase apoptosis to mediate drug sensitivity. The autophagy induction enhances drug resistance, while it is suppressed by ASSP2. Moreover, HMGB1 stimulates protective autophagy in drug resistance development. Upregulation of glycolysis by PKM2 and increase in stemness can cause drug resistance.

Upregulation of CPNE1 results in induction of Akt signaling to promote GLUT1/HK2 levels in glycolysis and OXA resistance in CRC (Fig. 6) [222].

Pharmacological compounds and oxaliplatin chemosensitivity

Several kinds of anti-cancer agents have been used in treatment of CRC and the final aim of using these compounds have been to induce apoptosis and decreasing proliferation and invasion of cancer cells. Anti-tumor compounds follow two ways in CRC therapy that include increasing potential of OXA in cancer therapy and reversing drug resistance. For instance, curcumin has been employed in increasing potential of OXA in CRC suppression. A combination of curcumin and OXA stimulates cell cycle arrest at S and G2/M phases and also, they increase expression of Bax, caspase-3, PARP and reduce Bcl-2 and survivin levels in triggering apoptosis and synergistic treatment of CRC [223]. Luteolin is a flavonoid and a bioactive compound that can be found in fruits and vegetables, and it is capable of impairing CRC tumorigenesis in mice [224,225]. Luteolin increase miR-384 expression to down-regulate PTN in reducing CRC progression [226]. A combination of luteolin and OXA promotes p53 and PARP expression levels, and suppresses HO-1 and AMPK in reducing CRC progression [227]. In addition, luteolin has been beneficial in increasing OXA sensitivity of CRC cells. Luteolin increases expression level of PPAR γ to upregulate OCTN2. Then, affinity of OCTN2 towards OXA increases and it can

promote accumulation of OXA in CRC cells. The ability of luteolin in increasing OCTN2 expression is related to enhancing PDZK1 and PDZK2 to increase OXA sensitivity of CRC cells [228]. Ursolic acid is another regulator of CRC progression that its administration has been of importance in reducing tumorigenesis. Ursolic acid increases miR-4500 expression and suppresses JAK2/STAT3 axis in apoptosis induction in CRC cells [229]. Moreover, ursolic acid reduces ZEB1 expression in suppressing metastasis of CRC [93]. Ursolic acid has been of importance in enhancing OXA sensitivity of CRC. Ursolic acid increases ROS and apoptosis, and reduces growth rate of CRC cells in enhancing OXA sensitivity [230]. A variety of molecular pathways are affected by ursolic acid in regulating OXA sensitivity in CRC. Ursolic acid suppresses growth of CRC cells and stimulates apoptosis. Moreover, ursolic acid reduces expression levels of Bcl-xL, Bcl-2, Survivin, increases levels of caspase-3, -8, -9 and suppresses KRAS, BRAF, MEK1/2, ERK1/2, JNK, Akt, MAPK, PI3K/Akt and NF- κ B. Therefore, combination of ursolic acid and OXA is beneficial in interfering CRC progression [231].

Tanshinone II (Tan IIA) is the bioactive compound of Danshen [232] and it is popular due to its antioxidant, anti-inflammatory and anti-tumor activities. Tan IIA is able to stimulate ferroptosis in tumor cells via p53-induced SLC7A11 down-regulation [233]. Moreover, Tan IIA is beneficial in reversing OXA resistance in CRC. Poor expression of miR-30b-5p is observed in CRC cells that are resistant to OXA chemotherapy. Increasing miR-30b-5p by Tan IIA impairs biological behavior of CRC cells and reduces OXA resistance via down-regulating AVEN

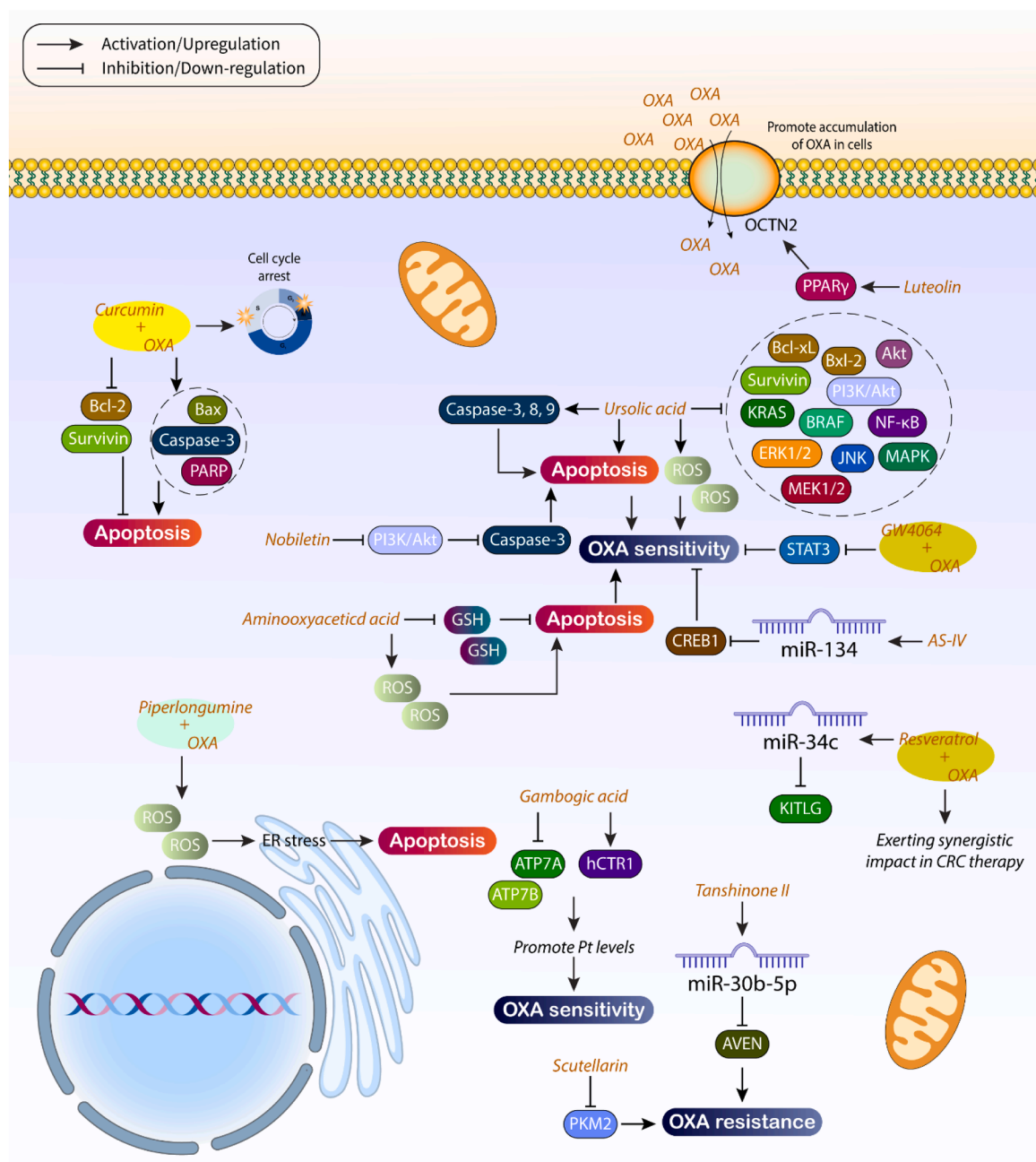


Fig. 7. Regulation of oxaliplatin sensitivity in colorectal cancer by anti-tumor compounds. The different anti-cancer compounds mainly increase ROS generation to induce cell death and they downregulate GSH to prevent support for tumor cells. Moreover, co-application of OXA with resveratrol, nobiletin and GW4064 can impair tumor progression and increase drug sensitivity.

expression [234]. Nobiletin (NOB) is a polymethoxyflavone that is derived from roots of Citrus fruits and its usage in cancer therapy has shown an increase due to regulation of various molecular pathways. Nobiletin can be used in treatment of CRC and increasing sensitivity of tumor cells to OXA chemotherapy that is attributed to suppressing PI3K/Akt/mTOR axis to induce apoptosis via increasing expression levels of Bax and caspase-3 in mediating OXA sensitivity [235]. It is also worth mentioning that some of the anti-tumor compounds such as niclosamide not only promote anti-tumor activity of CRC, but also reduce side effects of chemotherapy [236]. However, the most well-known mechanism for OXA sensitivity by anti-tumor compounds is triggering apoptosis in tumor cells [237].

Aminoxyacetic acid (AOAA) has been considered as another factor in regulating OXA sensitivity of CRC cells. AOAA increases ROS

generation and decreases GSH activity to induce apoptosis and to promote OXA sensitivity of CRC cells [238]. Similarly, MS275 and SBHA as HDAC inhibitors are able to induce apoptosis in elevating OXA sensitivity of CRC [239]. Moreover, a combination of GW4064 and OXA reduce STAT3 expression to increase cytotoxicity of OXA on CRC cells [240]. The synergistic impact that can occur between OXA and other anti-tumor compounds is related to oxidative stress regulation. A combination of piperlongumine and OXA is beneficial in increasing oxidative stress, mediating mitochondrial dysfunction and activating endoplasmic reticulum-mediated apoptosis [241]. Hence, if a factor causes increased proliferation of OXA cells, it can mediate resistance to OXA chemotherapy. PKM2 is an enzyme of glycolysis that its over-expression stimulates glucose metabolism in increasing tumor proliferation and mediating OXA resistance. Scutellarin administration results

in down-regulation of PKM2 to reverse OXA resistance in CRC cells [242].

Astragaloside IV (AS-IV) is a new introduced anti-tumor compound and this naturally product compound inhibits M2 polarization of macrophages via AMPK signaling inhibition in lung tumor [243]. AS-IV inhibits fibrosis and suppresses hepatocellular carcinoma development via regulating Nrf2/HO-1 and Smad3C/3L pathways [244]. The administration of AS-IV has been beneficial in increasing expression level of lncRNA TRHDE-AS1 to interfere with growth and invasion of tumor cells [245]. Administration of AS-IV has been beneficial in increasing OXA sensitivity of CRC cells. AS-IV promotes expression level of miR-134 to down-regulate CREB1 in EMT inhibition and enhancing OXA sensitivity of CRC cells [246]. Noteworthy, anti-tumor compounds are able to regulate expression level of non-coding RNAs in affecting OXA sensitivity of CRC cells. Zuo Jin Wan increases expression level of miR-200s via MALAT1 down-regulate to suppress JNK signaling in apoptosis induction, proliferation inhibition and OXA sensitivity in CRC cells [247]. Resveratrol is another compound that has been used in disease and cancer therapy, and nano-scale delivery systems have been employed in increasing its bioavailability and therapeutic index. Resveratrol administration has been beneficial in CRC suppression via miR-34c overexpression to down-regulate KITLG, and its combination with OXA is of importance in exerting synergistic impact in CRC therapy [248]. According to these studies, the process of OXA resistance in CRC can be reversed or delayed using anti-tumor compounds that is mainly due to their ability in apoptosis induction and regulating molecular pathways related to drug resistance development (Fig. 7).

Nanostructures and oxaliplatin delivery

Since OXA resistance has been a problem and one of the reasons has been using high concentration levels of OXA, nanostructures have been employed for targeted delivery of OXA to prevent resistance and to increase its therapeutic index. Hyaluronic acid (HA)-modified chitosan nanoparticles have been developed for delivery of OXA in targeted CRC therapy. Oral administration of OXA-loaded nanoparticles of 10 mg/kg was used for treatment of tumor-bearing mice. The HA-chitosan nanoparticles delivered 1.99 and 9.36 microg of L-OHP/g to the tissues of colon and cancer, respectively upon 12 h after treatment. These nanoparticles increased potential of OXA in CRC suppression and reduced adverse impacts [249]. The reason of modification by HA is that it can increase tumor-targeting ability of nanostructures by binding to CD44 receptor. HA is a linear polysaccharide that has D-glucuronic acid and N-acetylglucosamine linked by β -1,3-glycosidic and β -1,4-glycosidic bonds [250]. HA is able to interact with CD44v6 and it is one of hallmarks of CRC stem cells that elevates viability, growth and drug resistance [251–253]. The thin-film hydration was used to prepare liposomes for delivery of OXA and they were modified with HA. These nanostructures increased targeted delivery of OXA and promoted apoptosis and necrosis in CRC cells [254]. In order to increase potential in treatment of CRC, studies have focused on co-delivery of OXA with other anti-tumor compounds in CRC therapy. The carboxymethyl chitosan (CMCS) nanostructures were employed for delivery of OXA and resveratrol in CRC therapy. They demonstrated encapsulation efficiency of 60% for OXA with particle size of 190 nm, while resveratrol-loaded CMCS nanostructures showed encapsulation efficiency of 65% with particle size of 164.2 nm. The combination of nanoparticles demonstrated higher cytotoxicity compared to using only one of them in reducing CRC progression [255]. Another factor that can be used for surface modification of nanostructures is folic acid that can bind to folate receptor underwent overexpression on the surface of CRC cells [256,257]. Folic acid-grafted solid lipid nanostructures have been used for OXA delivery with encapsulation efficiency of 49.2%, and particle size of 146.2 and 158.8 nm. They released drug in a prolonged manner and enhanced cytotoxicity in CRC therapy [258]. These studies demonstrate that use of nanostructures is of importance in enhancing

Table 3
Nansostructure-mediated oxaliplatin delivery in colorectal cancer suppression.

Nanovehicle/nanocomposite	Remark	Ref
Polymeric nanoparticles	Hyperthermia induction by nanostructures increases their sensitivity to chemotherapy	[262]
Immunohybrid nanostructures	Oxaliplatin immunohybrid nanoparticles induce apoptosis and exert synergistic impact	[263]
Iodine nanoparticles	Oxaliplatin-loaded nanostructures induce apoptosis and demonstrate radio-sensitization impact	[264]
Folic acid-coated nanoparticles	Increasing capacity after coating with folic acid	[265]
Metal-organic framework	Stimulation of apoptosis, reducing tumor malignancy and preventing chemoresistance	[266]
Antibody-conjugated superparamagnetic and PLGA nanoparticles	A combination of phototherapy and chemotherapy, along with increasing immunotherapy capacity	[267]
Immunohybrid nanoparticles	Sustained drug release and targeted delivery (anti-CD133 antibody) of oxaliplatin	[268]
Lipid nanoparticles	95 nm particle size and 71% encapsulation efficiency for oxaliplatin	[269]
Hyaluronic acid-zein core-shell nanoparticles	Preventing degradation of drug in serum	[270]
iRGD-modified red blood cell membrane nanostructures	Increased uptake and promoting cytotoxicity	[271]
	Increasing internalization in oxaliplatin tumor cells via endocytosis	
	Cell cycle arrest and apoptosis induction	
	Enhanced cellular uptake of oxaliplatin using CD44 receptor	
	High cytotoxicity and combination therapy with curcumin	
	Co-delivery of oxaliplatin and juglone in reducing tumor progression in vitro and in vivo	
	Reducing cell viability and increased accumulation of drug at tumor site	

potential of OXA in CRC suppression.

One of the most important aspects of using nanostructures is their capacity in suppressing chemoresistance in CRC. Cholesterol-coated PLGA nanostructures can deliver OXA and retinoic acid to CRC cells. Treatment of cancer cells with nanoparticles reduced their viability rate and they induced apoptosis. Moreover, Retinoic acid- and OXA-loaded cholesterol-coated PLGA nanoparticles were beneficial in suppressing metastasis and chemoresistance in CRC cells [259]. Based on these studies, one of the important ways in reversing OXA resistance in CRC is co-delivery with anti-tumor compounds. Interestingly, since biological studies have highlighted the role of molecular pathways in OXA resistance, there have been efforts in delivery of OXA with genetic tools in reversing drug resistance. Small interfering RNA (siRNA) is one of the genetic tools that have been widely employed in cancer gene therapy and improving its internalization in tumor cells has been obtained using nanostructures. A recent experiment has developed DNA nanostructures composed of PLGA-PEG, DOTAP and siRNA-ATP7A in CRC therapy and overcoming chemoresistance. The delivery of siRNA by nanostructures to tumor cells led to down-regulation of ATP7A to induce apoptosis and to elevate OXA sensitivity of CRC cells [260]. In another effort, PEG-PAMAM nanostructures have been used for co-delivery of siRNA-ASPEN and OXA in CRC therapy that nanoparticles demonstrated particle size of 100 nm and they promoted internalization into tumor cells. Moreover, systemic administration led to improvement in animal model bearing tumors and after reducing gene expression, they promoted sensitivity of CRC cells to OXA chemotherapy (Table 3, Fig. 8, Fig. 9) [261].

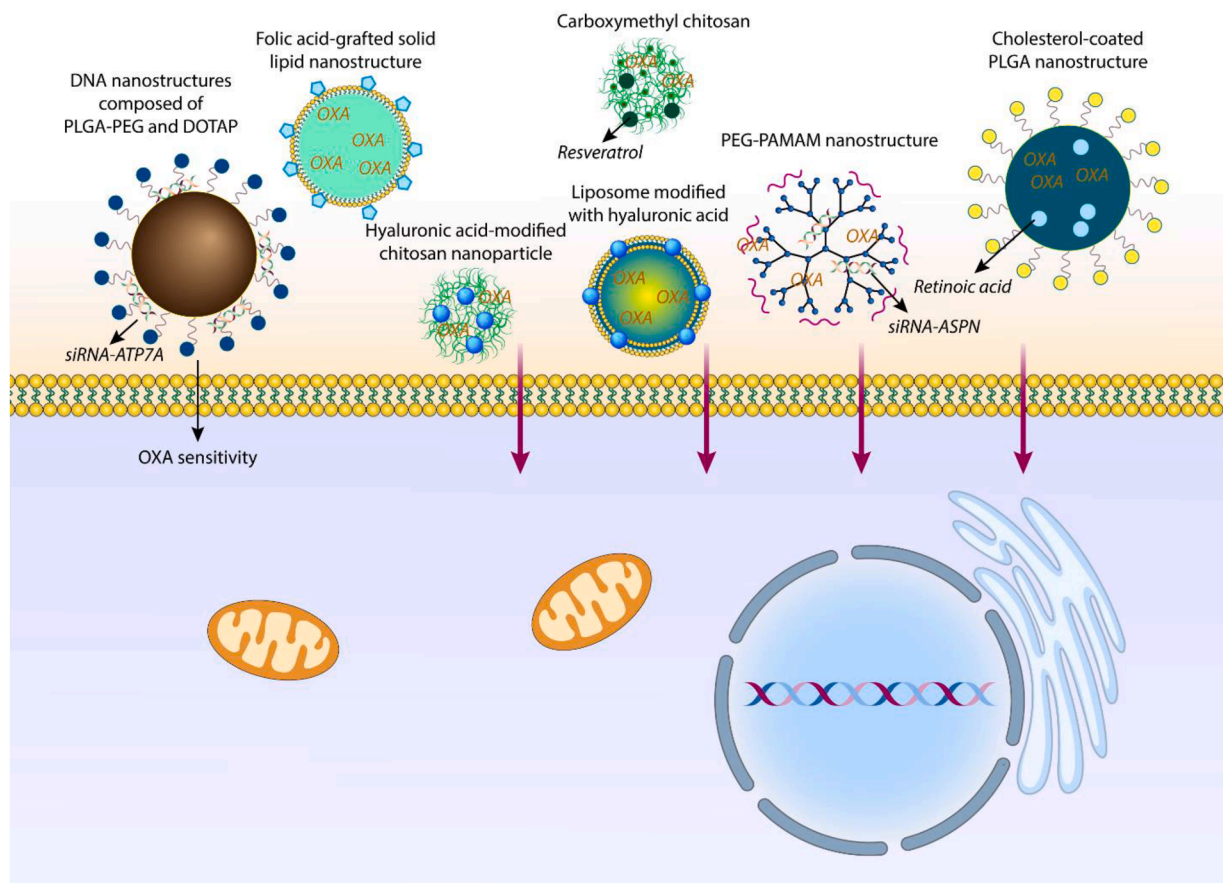


Fig. 8. The role of nanostructures in oxaliplatin delivery for treatment of colorectal cancer. The first advantage is that nanoparticles significantly increase the accumulation of drug in the tumor cells. Moreover, they can mediate co-delivery, especially with genetic tools such as siRNA to increase chemosensitivity. The nanoparticles can be modified with ligands such as folic acid to increase targeting ability.

Conclusion and remarks

Since colorectal cancer is among the most common tumors and affecting high number of people around the world, its repression using chemotherapy is a promising method. OXA is among the most common chemotherapy drugs in suppression and removal of CRC and therefore, strategies for understanding its resistance development and therapeutic approaches should be designed. The increase in expression level of tumor-promoting factors and reduction in onco-suppressor factors can mediate OXA resistance. Apoptosis inhibition and pro-survival autophagy induction mediate development of OXA resistance in CRC. The dysregulation of epigenetic factors is considered as an important factor in development of OXA resistance that current review focused on the role of miRNAs, lncRNAs and circRNAs. In addition to apoptosis and autophagy that can regulate OXA resistance, increase in glycolysis mediates OXA resistance in CRC. However, this is not the end of story and pharmacological compounds as well as anti-cancer agents have been utilized in CRC removal, apoptosis induction and increasing OXA sensitivity. The nanoparticles, especially functionalized nanostructures can mediate targeted delivery of OXA to suppress CRC progression and increase sensitivity. The current studies clearly demonstrate that the development OXA resistance can occur in OXA as a result of apoptosis inhibition, protective autophagy induction, acceleration of proliferation and metastasis. Moreover, the drugs and nanostructures have been utilized in OXA sensitivity. However, there are a number of limitations that should be considered. The first thing is that the relationship between EMT and CRC progression in the development of OXA resistance requires more investigation. Moreover, the other cell death mechanisms including necroptosis, ferroptosis, pyroptosis and immunogenic cell

death and their association with the development of OXA resistance and regulation by molecular pathways requires more investigation. Furthermore, regarding the application of small molecule drugs and phytochemicals, they need targeted delivery that application of nanostructures is suggested. Noteworthy, lipid- and natural-based nanoparticles could be used for the delivery of such compounds in the clinical level and for the treatment of cancer patients. However, the large manufacturing of the nanoparticles still requires more advances and it is hard to control the physico-chemical features of nanoparticles in the large scale.

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CRediT authorship contribution statement

Mehrdad Hashemi: Conceptualization. **Nastaran Esbati:** Visualization, Investigation. **Mohsen Rashidi:** Conceptualization. **Sadaf Gholami:** Data curation, Writing – original draft. **Rasoul Raesi:** Data curation, Writing – original draft. **Seyed Shahabaddin Bidoki:** Data curation, Writing – original draft. **Mohammad Ali Sheikh Beig Goharrizi:** Investigation, Visualization. **Yasamin Sadat Mousavi Motlagh:** Investigation, Visualization. **Ramin Khorrami:** Validation. **Alireza Tavakolpournegari:** . **Noushin Nabavi:** Writing – review & editing. **Rongjun Zou:** Validation. **Leila Mohammadnahal:** Supervision. **Maliheh Entezari:** Supervision. **Afshin Taheriazam:** Supervision, Writing – review & editing. **Kiavash Hushmandi:** Supervision.

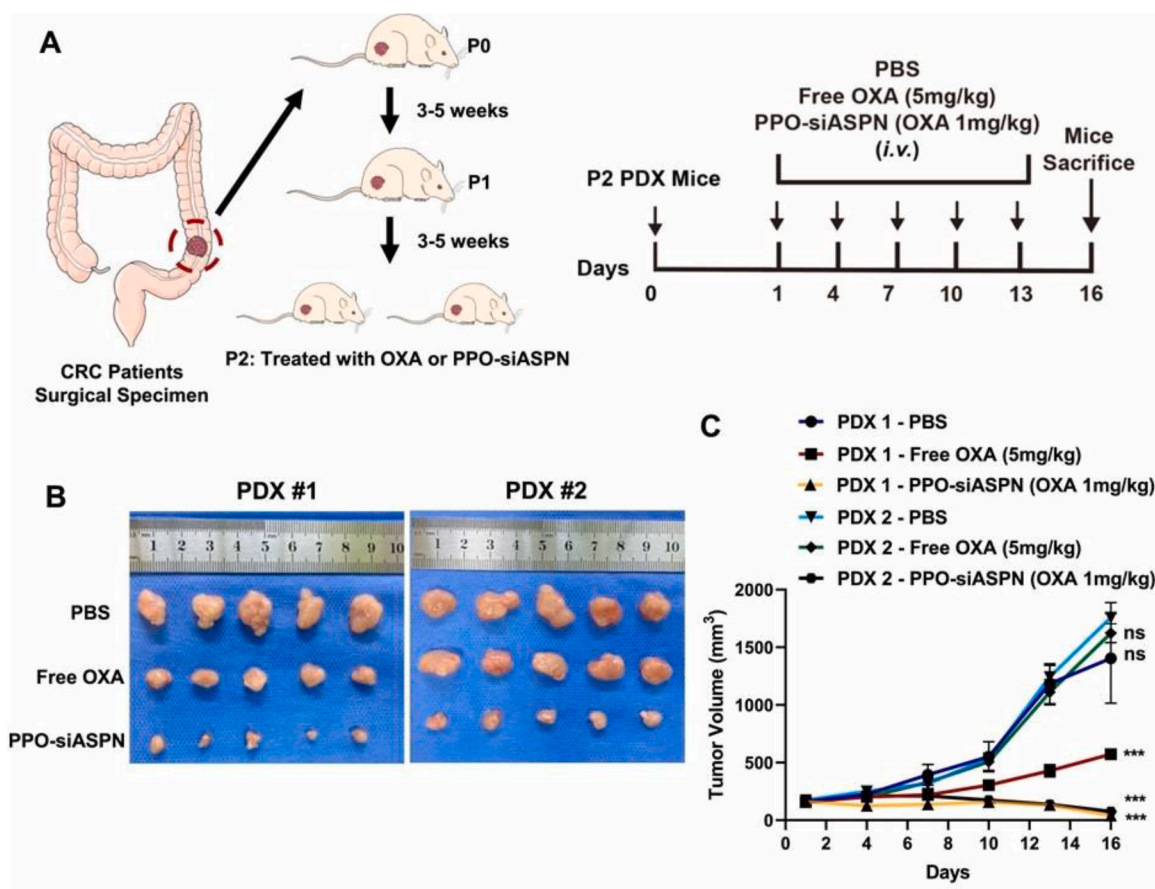


Fig. 9. A-C) The application of the PEG-PAMAM nanoparticles for the co-delivery of OXA and siRNA to suppress drug resistance and increasing CRC suppression. Reprinted with permission from Elsevier [261].

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.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.tranon.2023.101846](https://doi.org/10.1016/j.tranon.2023.101846).

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