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Molecular Basis of Chemotherapy and Radiotherapy Treatments Resistance in Cancer Management

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Abstract

Cancer is a leading cause of death worldwide. Surgery is the primary treatment approach for cancer, but the survival rate is very low due to the rapid progression of the disease and presence of local and distant metastasis at diagnosis. Adjuvant chemotherapy and radiotherapy are important components of the multidisciplinary approaches for cancer treatment. However, resistance to radiotherapy and chemotherapy may result in treatment failure or even cancer recurrence. Radioresistance in cancer is often caused by the repair response to radiation-induced DNA damage, cell cycle dysregulation, cancer stem cells (CSCs) resilience, and epithelial-mesenchymal transition (EMT). Understanding the molecular alterations that lead to radioresistance may provide new diagnostic markers and therapeutic targets to improve radiotherapy efficacy. Patients who develop resistance to chemotherapy drugs cannot benefit from the cytotoxicity induced by the prescribed drug and will likely have a poor outcome with these treatments. Chemotherapy often shows a low response rate due to various drug resistance mechanisms. This review focuses on the molecular mechanisms of radioresistance and chemoresistance

in cancer and discusses recent developments in therapeutic strategies targeting chemoradiotherapy resistance to improve treatment outcomes

Keywords: Cancer, Chemotherapy, Radiotherapy, Drug Resistance. DNA Damage

Introduction

Cancer, a global challenge that threatens human health, sees approximately 18.1 million new cases annually, with 9.6 million cancer-related deaths reported in 2018 For both sexes, lung cancer is the most commonly diagnosed cancer (11.6% of the total cases) and the leading cause of cancer-related death (18.4% of the total cancer deaths), closely followed by breast cancer in women (11.6%), colorectal cancer (CRC) (10.2%), and prostate cancer (7.1%) for incidence and CRC (9.2%), stomach cancer (8.2%), and liver cancer (8.2%) for mortality (Bray *et al.*, 2018). Cancer is mainly treated with a combination of surgery, chemotherapy, and radiation. As scientific research continues to make progress many drugs have been developed to improve the treatment efficiency for specific types of cancer. Radiotherapy is based on high-energy radiation to kill cancer cells and shrink tumors (Chen *et al.*, 2017). Normal tissues are relatively insensitive to radiation and are often spared during treatment. Chemotherapy is administered to inhibit the growth of cancer cells, kill cancer cells, or block cancer cell proliferation. However, clinical trials have repeatedly shown no significant increase in survival between some cancer patients who received postoperative chemoradiotherapy and those who only underwent surgery. The radiation response of a tumor, which is linked to radiosensitivity and radioresistance, is the key factor in determining the therapeutic effect (Wu *et al.*, 2015). DNA damage induced by radiotherapy eventually influences cell proliferation and changes the cell cycle, leading to apoptosis or other programmed death pathways. Chemoresistance can be classified as primary drug resistance (PDR) or multidrug resistance (MDR). PDR refers to patients who develop drug resistance only to the inducing drug and do not show cross-resistance with other drugs, whereas MDR refers to tumor cells that are resistant not only to the original antitumor drug but also to other antitumor drugs with different structures and mechanisms of action (Gillet and Gottesman, 2010); this is the primary cause of chemotherapy failure. More chemotherapy drugs than ever are clinically available for cancer patients including oxaliplatin, Taxol, cisplatin (CDDP), and 5-fluorouracil (5-FU). In general, chemotherapy

regimens for cancer are administered as monotherapy or two-drug polytherapy. Different treatment plans can be administered for different conditions to achieve the optimal therapeutic effect. In addition, radiation causes a series of physical and chemical reactions, and cells may lose their ability to divide and die. Therefore, understanding the genes that affect therapeutic resistance is useful for exploring drugs that reverse chemoand radiotherapy resistance. Two types of genes are involved in the process of cell tumorigenesis: oncogenes (such as epidermal growth factor receptor [EGFR] and human epidermal growth factor receptor 2 [HER2]), which cause normal cells to become cancerous, and tumor suppressor genes (such as p53), which inhibit cell proliferation and tumorigenesis and are often mutated in tumors (Lu, 2000). Elucidating the relationship between these genes and chemo- and radiotherapy resistance in cancer patients undergoing these treatment modalities may have profound impacts on the treatment and prevention of cancer. This review aims to expand the knowledge on the genetic mechanisms associated with radio- and chemoresistance in cancer, which may provide new ideas for the development of targeted therapy.

Molecular Mechanisms of Radioresistance in Cancer

DNA Damage Repair

Radiation therapy is known to either directly induce DNA damage via ionizing radiation (IR) or indirectly promote the absorption of high-energy wavelengths by other molecules surrounding DNA, resulting in highly reactive free radicals that can damage DNA (Azzam *et al.*, 2012).These radicals induce the formation of reactive oxygen species (ROS) and subsequent oxidative stress, and the cancer cells are eventually injured (Borrego-Soto *et al.*, 2015). To kill tumor cells, radiotherapy causes various forms of damage to intracellular DNA, such as the generation of abasic sites, single-strand breaks (SSBs) and double-strand breaks (DSBs) in DNA; DSBs are the most deleterious. In response, cancer cells activate a series of complex reactions to survive, which can lead to the cancer recurring after DNA damage. However, how do cells sense DNA damage and respond accordingly? Taking DSBs as an example, Rad24p, phosphorylated H2AX (*γ*H2AX), the NBS1/hMRE11/hRAD50 complex, Ku (Ku70/Ku80 heterodimer), mediator of DNA damage checkpoint protein 1 (MDC1), and tumor suppressor p53 binding protein 1 (53BP1) are involved in sensing DNA damage and activating downstream pathways in

response. As a DNA damage sensor, Rad24p forms a complex with Ddc1p and Mec3p and induced cell cycle arrest after DNA damage. In addition, the Rad24p-Rfc2p or Rad24p-Rfc5p complexes can recruit the Rad24p-Ddc1p-Mec3p complex to produce a series of cascade reactions, thereby triggering downstream kinases or effectors such as Rad53p8 (Huang and Zhou, 2020). Nonhomologous end joining (NHEJ) mediated DSBs are recognized by the Ku protein, which forms an open loop structure connected to the end of the DNA, with one side of the loop forming a scaffold that protects one surface of the DNA double helix, and the other side allowing other NHEJ factors to enter the DSB. Another approach to DNA repair, homologous recombination (HR), includes many mechanisms. HR is always activated in response to SSBs and is promoted by various proteins including the MRE11-RAD50-NBS1 (MRN) complex. In addition, the DNA damage signaling system that relies on ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) is closely related to the activation of the HR pathway (Jackson and Bartek, 2009). DNA damage sensor proteins can not only detect DNA damage but also recruit transducer proteins to provide signals to enzymes to promote DNA repair. There are four main DNA repair pathways in tumor cells: DSB repair, base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). For all these processes, multiple sensor proteins are involved such as *γ*H2AX, 53BP1, NBS1, BRCA1/2, and Ku (Huang and Zhou, 2020). There is a direct relationship between MDC1, *γ*H2AX, and 53BP1 expression and DNA breaks: the greater the number of DNA breaks, the higher the level of *γ*H2AX/53BP1 expression is. Therefore, detecting the expression levels of these sensors may serve as predictive biomarkers for determining the outcome of radiotherapy in cancer patients. For example, *γ*H2AX, which can be detected by focal immunocytochemistry or immunofluorescence staining, has been used clinically as a predictive biomarker of radiotherapy sensitivity in certain cancers. According to the theory of radiobiology, cells with a strong ability to activate DSB repair will develop radioresistance, and cells with weaker repair ability are more sensitive to the killing effect of radiation. In addition, IR activates the expression of phosphatidylinositol-3 kinases (PIKKs), including ATM, ATR, and DNA-dependent protein kinases (DNA-PKs), which have the ability to transform and amplify DNA damage signals. Finally, the components of DNA repair are recruited to the damaged site and initiate their repair activities (Raleigh DR, Haas-Kogan, 2013). Thus, when radiation induces DNA damage, the cells can either engage in successful repair promotes to survival or leave the DNA unrepaired and

eventually undergo cell death. Hence, regulating tumor cells' sensitivity to radiation by affecting the DNA damage repair mechanism has been one of the momentous research directions for improving cancer treatment.

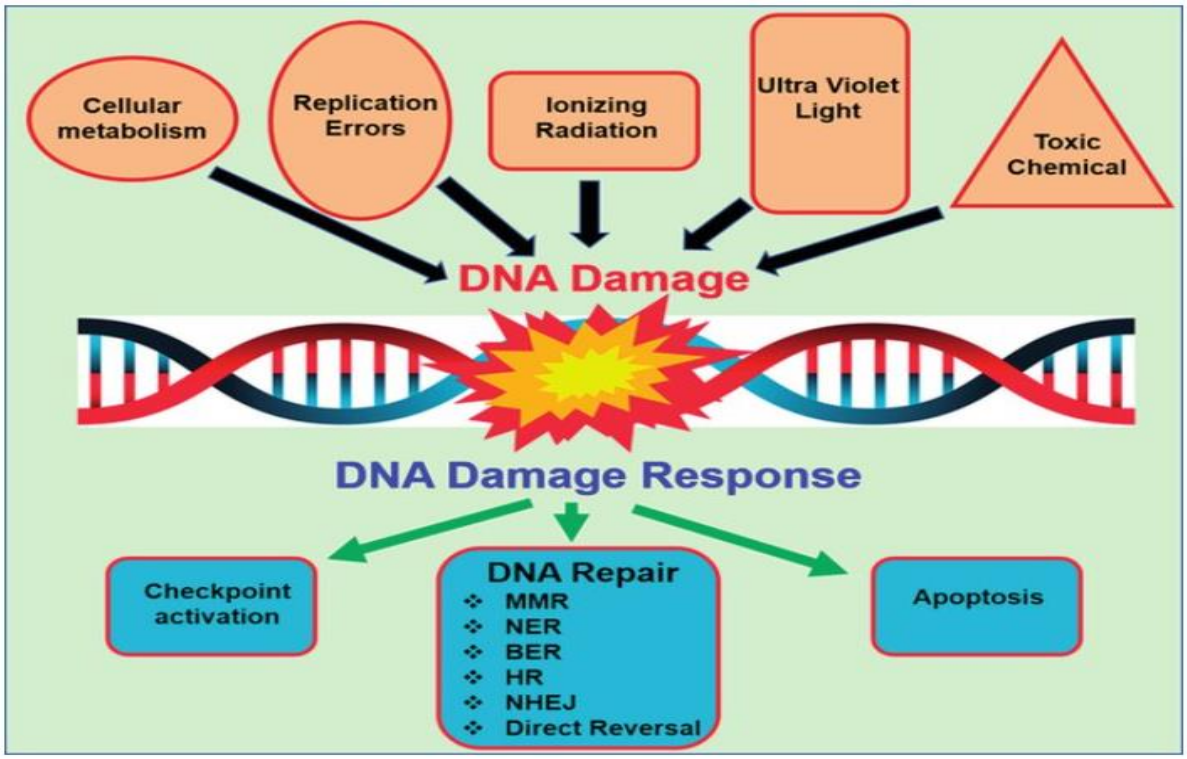

Figure 1: DNA damage, DNA damage response, and repair. Graphical illustration demonstrating the DNA damage caused by different sources and the cellular response to DNA damage

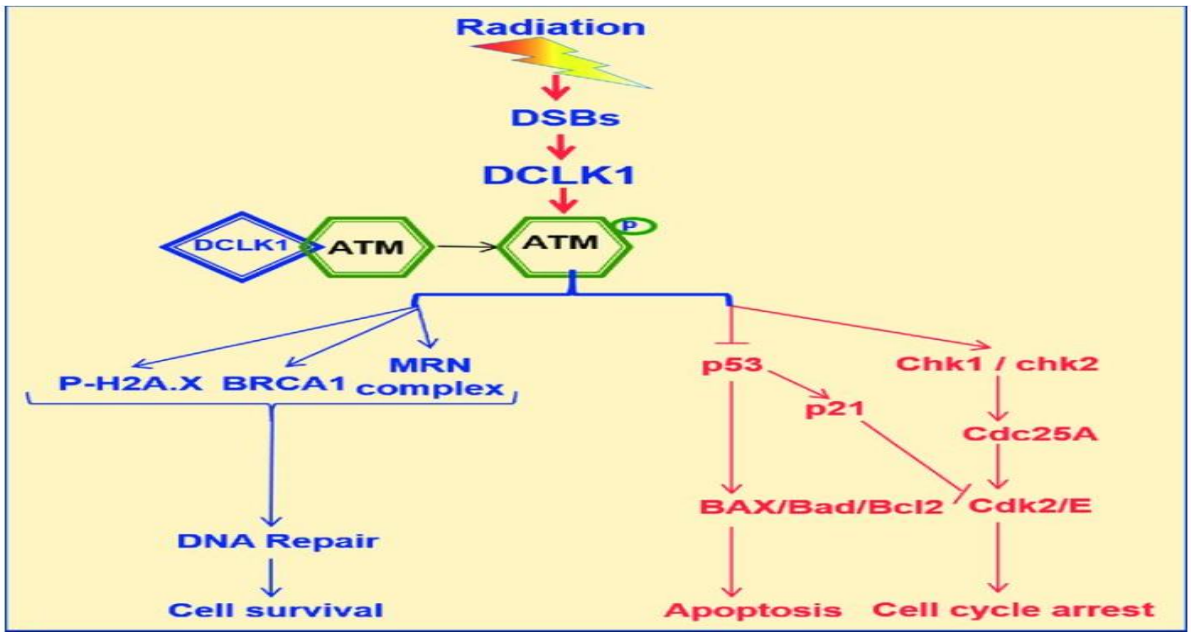

Figure 2: llustration demonstrating the regulatory role of Doublecortin-like kinase 1

(DCLK1) in DNA Damage Response (DDR) following radiation injury. DDR is primarily mediated by phosphatidylinositol-3-kinase-like protein kinase (PIKKs) members of ataxia-telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related protein (ATR)

Cell cycle Redistribution

Maintaining the integrity of the genome after DNA damage is essential for the proliferation and survival of eukaryotic cells. Upon activating a series of biochemical reactions in response to DNA damage, the cells undergo apoptosis or become senescent when the damage is too severe or continue to stay in the cell cycle for a longer period of time to enhance the DNA repair mechanism if the damage is not irreversible **(**Tembe and Henderson, 2007**).** DNA damage causes cell cycle arrest, such as the activation of the G2/M checkpoints triggered by ATM and ATR, which prevent cells from entering mitosis with damaged DNA. In cells, the MRN complex is recruited in response to DNA damage and promotes the activation of ATM and the recognition of DSBs (Marechal and Zou, 2013**).**

Cell cycle and its Regulation

The cell cycle is an ordered series of events involving cell growth and cell division that produces two new daughter cells. Cells on the path to cell division proceed through a series of precisely timed and carefully regulated stages of growth, DNA replication, and division that produce two genetically identical cells. The cell cycle has two major phases: interphase and the mitotic phase (Figure 3). During interphase**,** the cell grows and DNA is replicated. During the mitotic phase**,** the replicated DNA and cytoplasmic contents are separated and the cell divides. Watch this video about the cell cycle:

The progression of cells through the cell cycle is controlled by various checkpoints at different stages. These detect if a cell contains damaged DNA and ensure those cells do not replicate and divide. The **restriction point (R)** is located at G1 and is a key checkpoint. The vast majority of cells that pass through the R point will end up completing the entire cycle. Other checkpoints are located at the transitions between G1 and S, and G2 and M. If damaged DNA is detected at any checkpoint, activation of the checkpoint results in increased **p53** protein production. p53 is a tumour suppressor gene that stops the progression of the cell cycle and starts repair mechanisms for the damaged DNA. If this DNA cannot be repaired, it ensures the cell undergoes apoptosis and can no longer

replicate. This cycle is also closely regulated by **cyclins** which control cell progression by activating cyclin-dependent kinase (CDK) enzymes.

An example of a tumour suppressor protein is retinoblastoma protein **(Rb).** *Rb* restricts the ability of a cell to progress from the G1 to the S phase in the cell cycle. CDK phosphorylates *Rb* to *pRb,* making it unable to restrict cell proliferation, thereby inhibiting its cell growth-suppressing properties. This allows cells to divide normally.

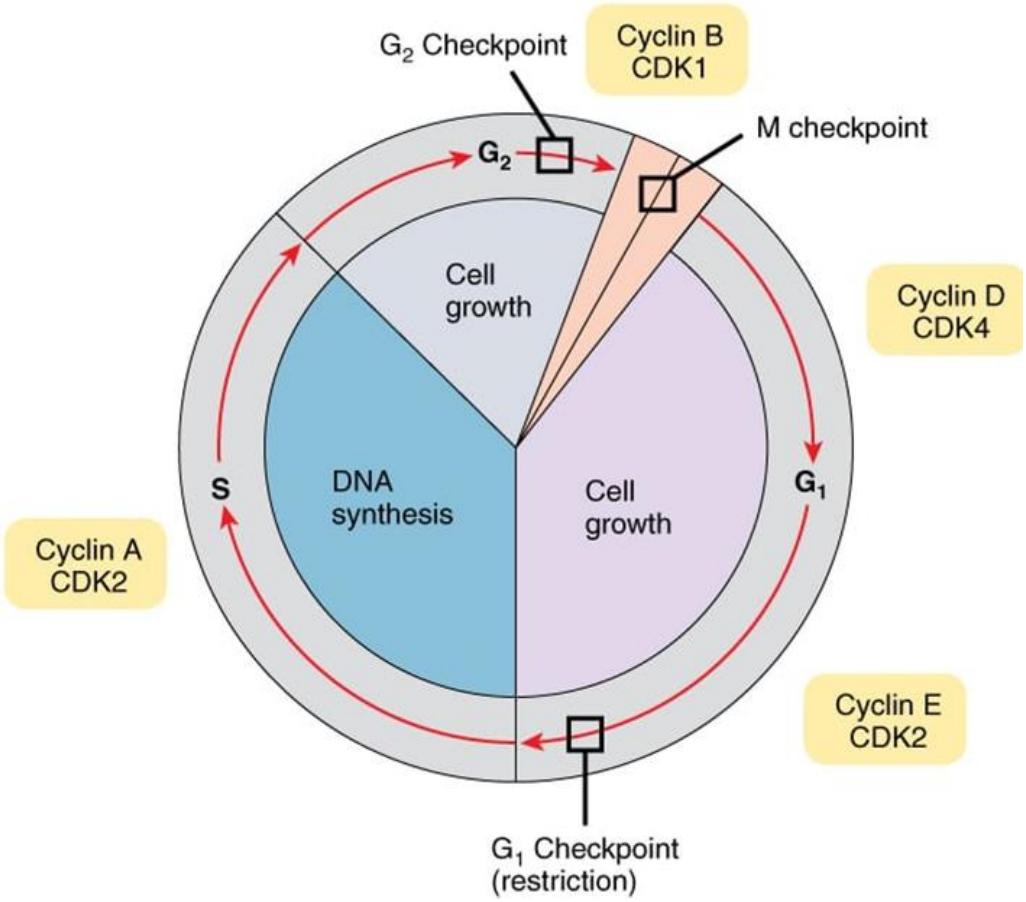

Figure 3: Cell cycle and its Regulation

Epithelial-mesenchymal Transition

Epithelial-mesenchymal transition (EMT) is the process by which epithelial cells transform into mesenchymal cells and acquire migratory abilities (Santos-Ramos *et al.*, 2017)**.** Cancer cells undergo EMT, which create a favorable microenvironment for cancer development and metastasis, and the acquisition of EMT functionality is associated with resistance to radiotherapy and poor prognosis in multiple types of malignant tumors. One of the characteristics of EMT is the loss of intercellular adhesion and decreased expression of E-

cadherin; this progressive decline is regulated by the zinc finger proteins Snail and Slug. Studies have shown that radiation activates the Wnt/*β*-catenin pathway and EMT in esophageal squamous cell carcinoma (ESCC) cells and CRC cells (Liu *et al.*, 2019)**.** According to previous research on the radiation-resistant KYSE-150RR esophageal cancer cell line, the effects of radiation exposure mostly depend on downregulation of phosphatase and tensin homolog (PTEN) expression and activation of the PK B (Akt)/Snail signaling pathway to induce EMT. Moreover, PTEN, a possible tumor suppressor gene, can enhance cell radiosensitivity by acting on phosphatidylinositol-3-kinase (PI3K) to suppress tumor proliferation and metastasis **(**McKenna and Muschel, 2003)**.**

Cancer Stem Cells

CSCs are undifferentiated cancer cells with high tumorigenicity, self-renewal ability, and multidirectional differentiation potential (Aponte and Caicedo, 2017). Reestablished proliferation of surviving CSCs leads to tumor recurrence and/or distant metastasis because of the radiotherapy resistance of these cells. Conversely, the generation of CSCs may represent a novel mechanism of resistance to radiotherapy. Various signaling molecules are activated in cancer during radiotherapy, often resulting in irreparable DNA damage and apoptosis. Radiation-induced DNA damage is generally ineffective because of the high expression of stemness genes, efficient DNA damage repair, and aberrant regulation of the cell cycle, all of which make CSCs less susceptible to radiation (Figure 1) (Anuja *et al.*, 2019).

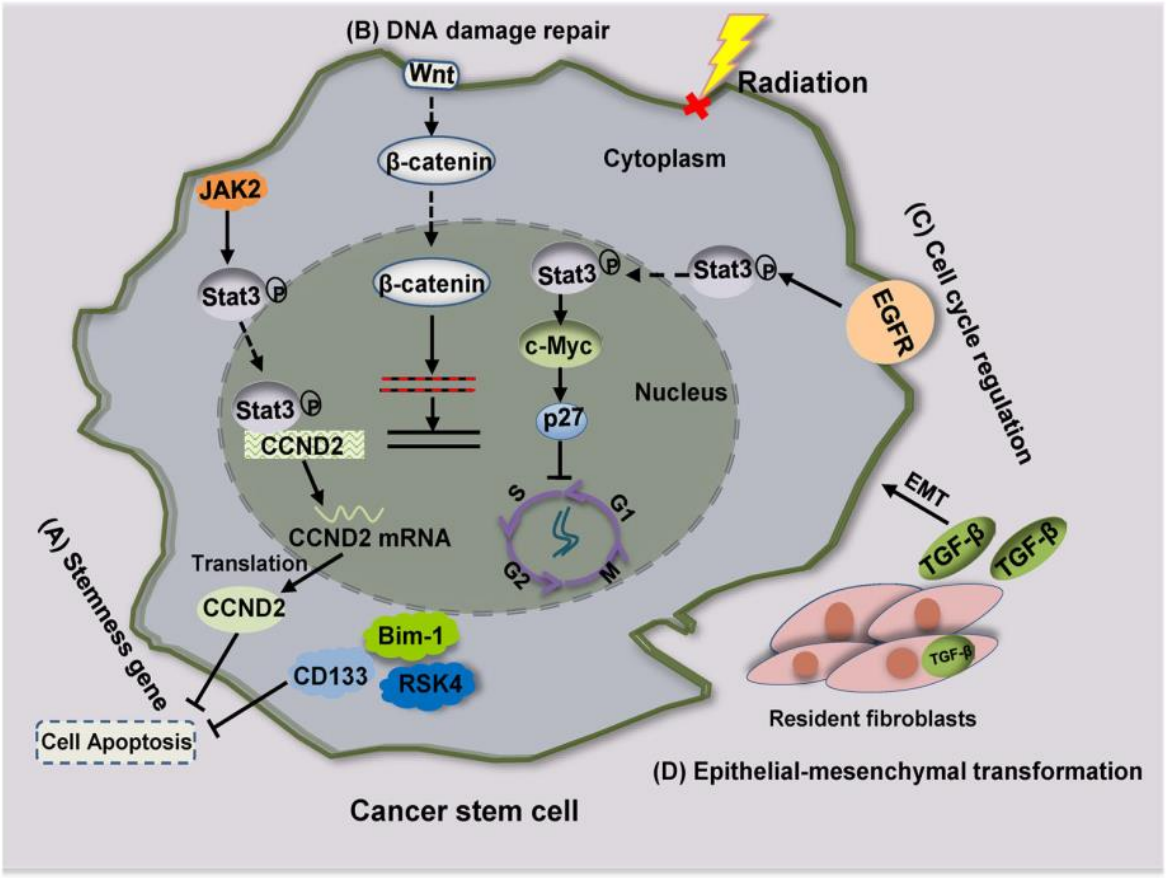

Figure 4: The abnormality of genes contributes to the formation of radiation resistance in CSCs. (A) High expression of Bim-1, RSK4, CD133, and JAK2 induces cancer cells resistance to radiation. (B) Activation of the Wnt/*β*-catenin signaling pathway not only enhances DNA damage repair in CSCs but also promotes the EMT, which induces radioresistance. (C) EGFR/Stat3/c-Myc/p27 pathway contributes to the cell quiescence and lead to abnormal cell cycle in cancer. (D) TGF-*β* secreted by resident fibroblasts promotes the EMT of CSCs, which may decrease radiosensitivity

Multiple Signaling Pathways Promote Cell survival and Proliferation

DNA damage and the oxidative emergency response caused by irradiation activate specific signaling pathways in cells. Apoptosis or survival signaling pathways may be activated depending on the degree of DNA damage. Studies have shown that the Wnt/*β*-catenin pathway, NF-*κ*B pathway, Akt/cyclin D1/CDK4 survival signaling pathway, and autophagy are associated with radiological resistance in cancer (Su *et al.*, 2015).

Autophagy mediates the degradation of dysfunctional organelles and promotes the turnover of long-lived proteins via a highly conserved process. The activation of the

autophagy pathway serves as a survival and adaptive mechanism that provides metabolic support in the presence of cellular stressors (such as exposure to radiation), thus, limiting the efficacy of radiation therapy (Nam *et al.*, 2013).

Activated NF-*κ*B signaling regulates its downstream target genes, such as cyclin D1 and c-Myc, mitigates apoptosis and induces the proliferation, invasion, and metastasis of tumor cells as well as their resistance to radiotherapy and chemotherapy.

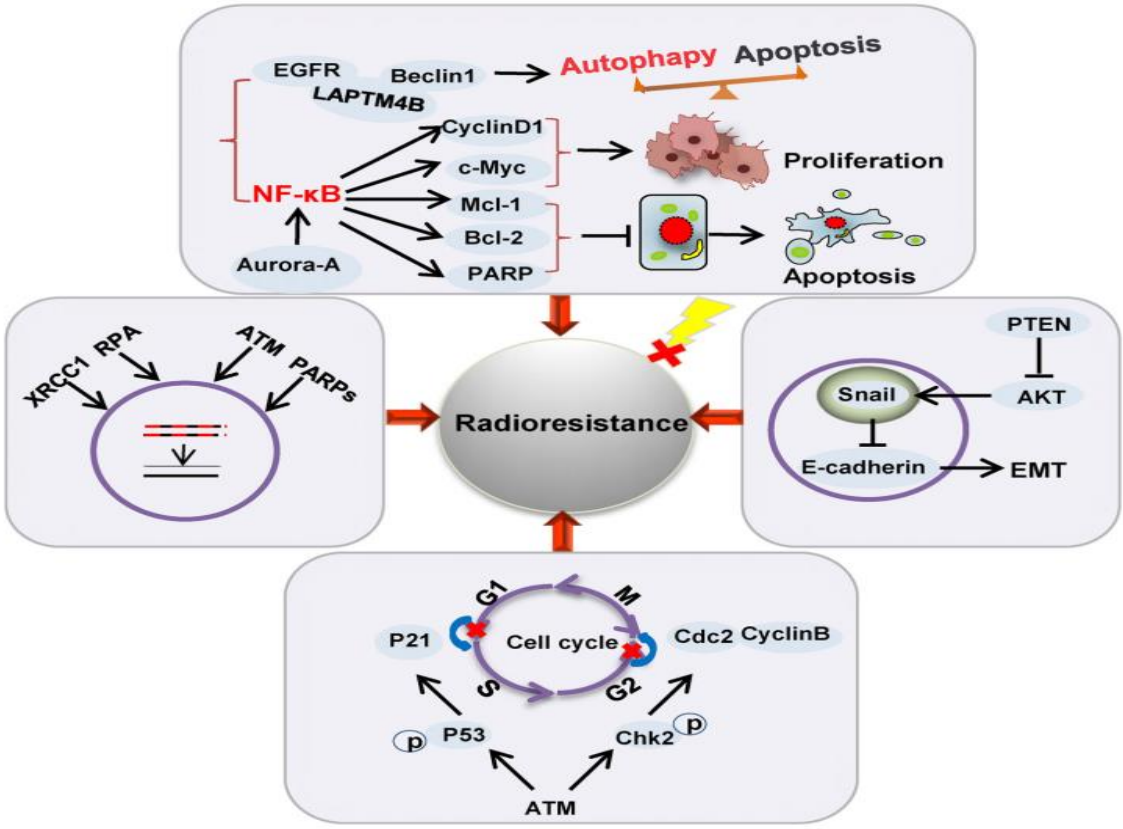

Figure 5: Roles of genes in radioresistant cancer cells. Enhanced DNA damage repair, cell cycle redistribution, EMT, and activation of signaling pathways that promote survival and proliferation contribute to forming radioresistance in cancer.

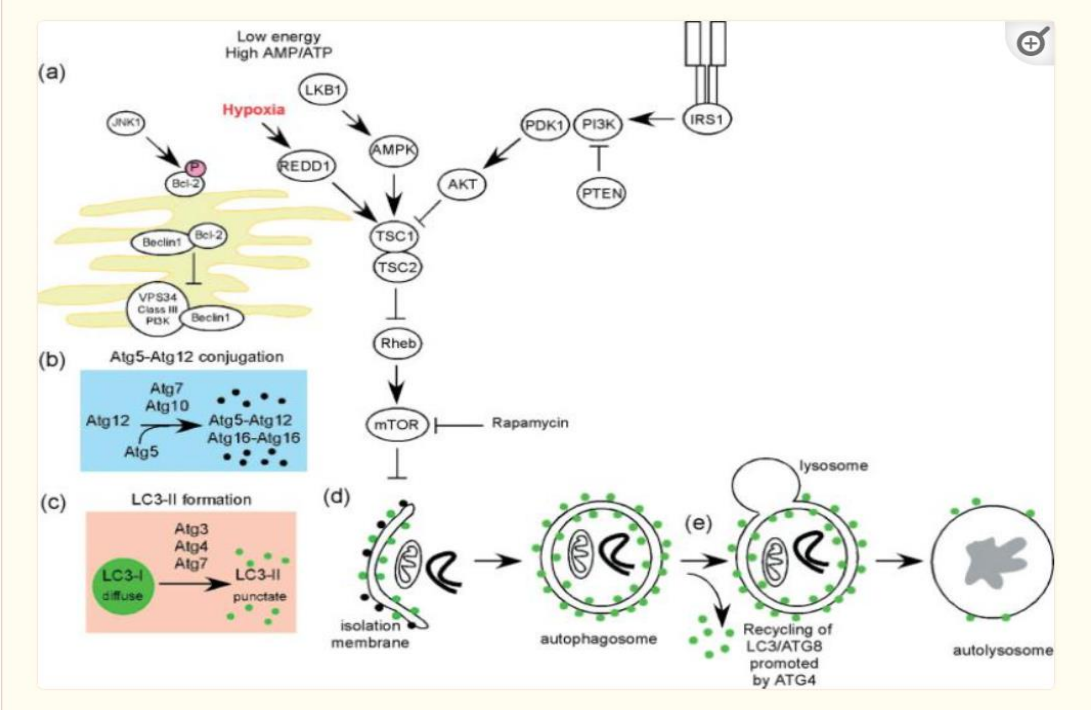

Figure 6: Autophagy Pathway

Molecular Mechanisms of Chemoresistance in Cancer

Classes of Cytotoxic Drugs

Alkylating agents

Alkylating agents were among the first anti-cancer drugs and are the most commonly used agents in chemotherapy today. Alkylating agents act directly on DNA, causing cross-linking of DNA strands, abnormal base pairing, or DNA strand breaks, thus preventing the cell from dividing. Alkylating agents are generally considered to be cell cycle phase nonspecific, meaning that they kill the cell in various and multiple phases of the cell cycle. Although alkylating agents may be used for most types of cancer, they are generally of greatest value in treating slow-growing cancers. Alkylating agents are not as effective on rapidly growing cells. Examples of alkylating agents include chlorambucil, cyclophosphamide, thiotepa, and busulfan.

Antimetabolites

Antimetabolites replace natural substances as building blocks in DNA molecules, thereby altering the function of enzymes required for cell metabolism and protein synrhesis. In other words, they mimic nutrients that the cell needs to grow, tricking the cell into

consuming them, so it eventually starves to death. Antimetabolites are cell cycle specific. Antimetabolites are most effective during the S-phase of cell division because they primarily act upon cells undergoing synthesis of new DNA for formation of new cells. The toxicities associated with these drugs are seen in cells that are growing and dividing quickly. Examples of antimetabolites include purine antagonists, pyrimidine antagonists, and folate antagonists.

Plant Alkaloids

Plant alkaloids are antitumor agents derived from plants. These drugs act specifically by blocking the ability of a cancer cell to divide and become two cells. Although they act throughout the cell cycle, some are more effective during the S- and M- phases, making these drugs cell cycle specific. Examples of plant alkaloids used in chemotherapy are actinomycin D, doxorubicin, and mitomycin.

Antitumor Antibiotic

Antitumor antibiotics are cell cycle nonspecific. They act by binding with DNA and preventing RNA (ribonucleic acid) synthesis, a key step in the creation of proteins, which are necessary for cell survival. They are not the same as antibiotics used to treat bacterial infections. Rather, these drugs cause the strands of genetic material that make up DNA to uncoil, thereby preventing the cell from reproducing. Doxorubicin, mitoxantrone, and bleomycin are some examples of antitumor antibiotics.

Cisplatin Resistance

Cisplatin, a widely used first-line chemotherapeutic drug for cancer, is one of the most effective chemotherapeutic agents for various malignancies (e.g., testicular cancer and ovarian cancer) (Enzinger and Mayer, 2003). For example, when surgery is combined with cisplatin-based neoadjuvant chemotherapy, the survival rate of esophageal cancer patients can be significantly improved by 5 years. However, drug resistance varies widely among cancer patients, and some patients tend to develop chemoresistance to cisplatin and other chemotherapeutic drugs. Cisplatin cross-links with DNA to form cisplatin adducts, which subsequently interfere with the basic processes of DNA replication and transcription and ultimately induce apoptosis (Kelland, 2007). Resistance to cisplatin in the clinical treatment of cancer may lead to treatment failure, and this resistance is determined by a variety of factors. EGFR, a tyrosine kinase receptor, is a major regulator of signaling pathways involved in cell survival, migration, and tissue regeneration. Clinical studies have shown

that among patients treated with neoadjuvant cisplatin, nonreactive patients more frequently have tumors with EGFR overexpression, suggesting that EGFR is a key factor in chemoresistance to cisplatin. Aside from EGFR overexpression, cisplatin resistance is acquired through several other mechanisms.

Attenuated drug accumulation is usually observed in cisplatin-resistant cell lines **(**Friboulet *et al*., 2013)**.** Copper transporter receptor 1 (CTR1) has been suggested to promote the uptake of cisplatin, and the other two copper transporters, p-type ATPase copper transporting alpha (ATP7A) and ATPase copper transporting beta (ATP7B), have also been found to be related to the export of cisplatin from cells In particular, CTR1, the major copper influx transporter, has been shown to play a significant role in platinum resistance. The researchers examined CTR1 mRNA expression levels in 15 patients with stage III/IV ovarian cancer and found a positive correlation between CTR1 mRNA expression levels and the efficacy of platinum drugs in patients. Studies have found that antioxidant 1 copper chaperone (ATOX1) may affect the accumulation of cisplatin in cells by mitigating the expression level of CTR1 via ubiquitination modification **(**Safaei *et al*., 2009)**.** Therefore, researchers suggest that the expression of CTR1 protein in tumor cells is closely related to the emergence of cisplatin resistance in tumor patients. The lower the expression of CTR1 in cells is, the lower the accumulation of platinum-based drugs and the worse the treatment effect in patients. In cisplatin-resistant cells, the expression of ATP7A and ATP7B proteins is upregulated, and overexpression of these proteins can promote cisplatin export from cells, thus, resulting in acquired drug resistance **(**Dmitriev, 2011)**.** In addition, clinical studies have shown that ATP7B expression levels can be used to predict the sensitivity of ovarian and endometrial cancers to cisplatin reatment. However, other reports in human ovarian cancer cell lines have stated that cisplatin resistance may be primarily due to reduced drug uptake. In addition, MDR-associated protein 2 (MRP2) may be the main protein used to export drugs from cisplatin-resistant cells, and its expression level may be used to predict the susceptibility of tumor cells to platinum-based therapies **(**Liedert *et al*., 2003)**.** Multidrug resistance 1 (MDR1) protein plays a major role in the forced export of cisplatin.

When cisplatin is hydrolyzed in the cytoplasm, it binds to sulfur-containing molecules, such as glutathione (GSH), metallothionein, and other proteins containing cysteine residues, which confines cisplatin to the cytoplasm and prevents it from entering the nucleus to bind DNA. Therefore, an increase in intracellular sulfur-containing molecules may lead to

cisplatin resistance. Increased GSH expression has been observed in many cisplatin-resistant tumor models and has been further confirmed in clinical studies **(**Xi *et al*., 2013)**.** Similar to the reaction of GSH, metallothionein can bind to and inactivate cisplatin, and increases in metallothionein expression level are positively correlated with cisplatin resistance in prostate, lung, ovarian, and cervical cancer.

Fluorouracil Resistance

5-FU, a pyrimidine derivative in which the hydrogen in the fifth position of uracil is replaced with fluorine, is a firstline chemotherapy agent for esophageal cancer and is commonly used chemotherapy agent for other solid tumors. The treatment outcomes of individuals with esophageal cancer treated with 5-FU differs; therefore, overcoming drug resistance and improving the efficacy of this class of anticancer drugs have become crucial obstacles in cancer treatment. As a thymidylate synthase (TS) inhibitor, 5-FU is metabolized into 5-fluorouracil deoxynucleotide (5F-dUMP) in the cell, which inhibits deoxythymidylate synthase, preventing the methylation of deoxyuridylate (dUMP) to deoxythymidylate (dTMP), and ultimately affects DNA synthesis (Koberle *et al*., 2010). Moreover, 5-FU can be converted into a 5-FU nucleoside in vivo, which is incorporated into RNA as a pseudometabolite, to interfere with protein synthesis; therefore, it impacts cells at multiple stages. Resistance to 5-FU is a multifactorial event that may be due to changes in transport mechanisms, metabolism, apoptosis, and cell cycle dynamics (Mader *et al*., 1998). Understanding the underlying mechanisms of 5-FU resistance in cancer is an essential step to predict and overcome 5-FU chemoresistance to improve patient survival.

Apoptosis is a mechanism of cell death commonly induced by chemotherapy, and the failure to initiate apoptosis represents a significant characteristic of chemoresistant tumor cells. As a member of the tryptophan-aspartic acid repeat protein (WD40) family, receptor for activated C kinase 1 (RACK1) is a necessary participant in transcription and translation events and regulates binding protein activity. In a recent study, RACK1 was identified as an oncogene in ESCC that promoted cell proliferation (Nakajima and Kato, 2013). Overexpression of RACK1 could promote 5-FU chemoresistance, while downregulation of RACK1 enhanced cell sensitivity to induce apoptosis. Moreover, RACK1 was found to modulate the activity of Akt, and phosphorylated Akt can increase the expression of Bcl-2), which is an antiapoptotic member of the Bcl-2 family. The balance between Bcl-2 family

proteins is vital to the regulation of apoptotic pathways, and Bim is a proapoptotic protein member of Bcl-2 family (Gomez-Bougie *et al.*, 2005).

Thymidylate synthase inhibition (TS) is a key enzyme in the metabolism of folic acid and a target enzyme of 5-FU. It can promote the conversion of intracellular dUMP to dTMP, which is the only source of new thymidylic acid in cells. Genetic variations in TS functions can alter the toxicity and efficacy of 5-FU, as indicated by a significant correlation between TS expression and survival of esophageal cancer patients (Kimura *et al.*, 2011). Low mRNA expression of TS may indicate a strong response to chemotherapy and longer survival than those of patients with high TS mRNA expression.

Multidrug Resistance

Currently, MDR during chemotherapy is believed to be the main reason for the limited clinical efficacy of chemotherapy. Tumor cells resist drugs through a variety of mechanisms, including reduced drug absorption, increased drug efflux, activation of detoxification systems and the DNA repair response, and prevention of drug-induced apoptosis (Figure 3) (Wei *et al.*, 2010). The progress of research on MDR related to esophageal cancer is presented in this section.

Enhancing the capacity of transport proteins

Many membrane proteins, including ABC transporters, play key roles in the efflux of chemotherapeutic drugs, which leads to drug resistance because of a decrease in the effective concentration. High transport capacity is attributed to increased expression of MDR-associated protein (MRP), P-glycoprotein 1 (P-gp) encoded by the MDR1 gene (also known as ABCB1), low-density lipoprotein receptor-related protein (LRP), and breast cancer resistance protein (BCRP) in cancer (Kunjachan *et al.*, 2013). At present, it is known that MDR leads to multidrug-resistant malignant tumors such as leukemia, multiple myeloma, gastric cancer, esophageal cancer, lung cancer, breast cancer, and colorectal cancer. In recent years, many studies have suggested that the MDR1 and MRP genes are highly expressed in advanced tumor cells, which is caused by changes in the expression and amplification ability of the genes during the development of disease. Eid *et al.* (1998) showed that patients with advanced testicular cancer have high expression of MDR1 and poor prognosis, suggesting that MDR1 not only mediates drug resistance but is also related to the malignant biological phenotypes (Eid *et al.*, 1998). Approximately 80% of the MDR1 and MRP genes are expressed in lung cancer naïve to chemotherapy and in 10% in cases

after chemotherapy treatment, which indicates that there is indeed increased expression of endogenous and acquired MDR1 and MRP genes in cancer cells. These data suggest that overexpression of MDR1 and MRP genes has some intrinsic connection with MDR and the malignant behaviors of tumor cells (Chen and Tiwari, 2011). Moreover, the expression level of P-gp in cancer tissues remains relatively low after disease progression and could be used to predict drug response during treatment.

Enhanced detoxification of glutathione S transferases (GSTs)

GSTs are essential enzymes for catalyzing glutathione binding reactions and eliminating exogenous toxins from cells. The GSTs associated with tumor tissues include GST-*a*, GST-*μ*, and GST-*π*. GST-*π* is one of the most relevant isoforms related to chemoresistance, as indicated by the increased expression of GST-*π* in drug-resistant esophageal cancer cells (Tang *et al*., 2013). Currently, the mechanism by which GST-*π* promotes MDR of esophageal cancer cells is thought to include the following aspects. First, GST-*π* catalyzes glutathione, which is combined with different negatively charged organic substances to form sulfhydryl compounds, inactivating the drug. Second, GST-*π* proteincatalyzes nitrosourea antitumor drugs to remove the nitro group and dampen their pharmacological effect. Finally, GST-*π* protein eliminates the oxides produced by adriamycin in the human body and promotes its sponging of cellular toxins to protect the cells (Joshi *et al*., 2005).

p53 and Ras

Mutations in both oncogenes and tumor suppressor genes have been reported to result in MDR in some cancers Recent studies have reported that MDR1 expression is correlated with the expression of mutant p53 in well differentiated prostate cancer tissues, and its expression in poorly differentiated prostate cancer tissues is high (Gurpinar and Vousden, 2015). Mechanistically, investigation into the regulation of the p53 gene on the promoter of the MDR1 gene suggested that mutant p53 protein significantly induces transcriptional activation and expression of the MDR1 gene, thus, enhancing drug resistance. Ras, a vital oncogene, plays a role in signaling to promote cell growth and differentiation. The function of Ras protein activation in MDR in multiple cancers has been demonstrated, although the mechanism varies. First, Ras protein can promote drug resistance in cancer by enhancing the protein expression of MDR1 (Chin *et al*., 1992). Second, activated Ras protein can facilitate cell proliferation and inhibit apoptosis via signal transduction, and its expression is positively correlated with treatment response. Third, activated Ras protein can increase

GST to enhance its detoxification activity and cause MDR in cancer. It was found that mutated p53 and Ras genes could significantly activate the promoter of the MDR1 gene in drug-resistant NH3HT3 cells (Chin *et al.*, 1992). Therefore, the oncogene Ras and tumor suppressor gene p53 are auxiliary players in the MDR of tumors.

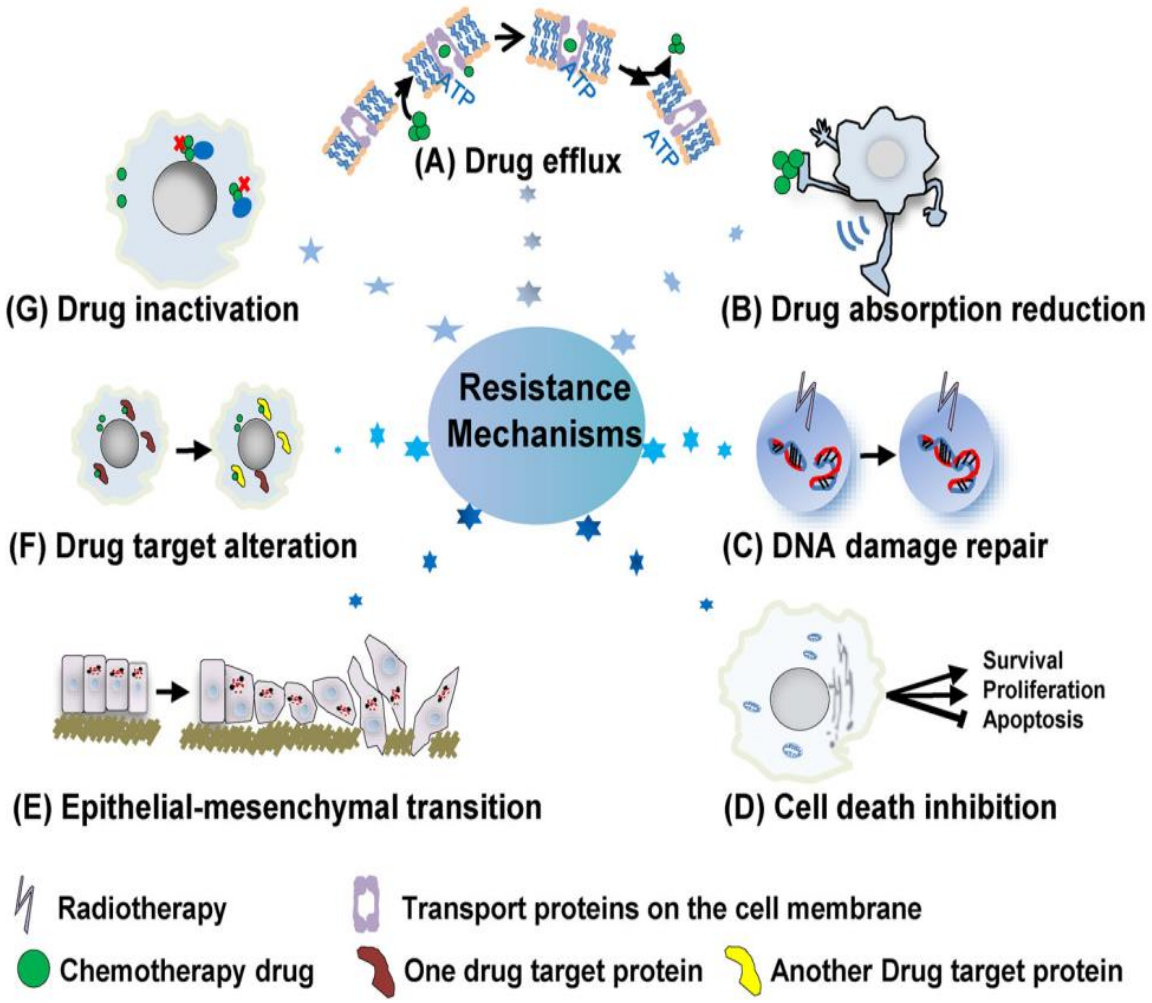

Figure Molecular mechanisms of tumor chemoresistance and radioresistance. (A) Abnormal expression of ABC family contribute to drugs being pumped out of the cell, which causes intracellular drug concentrations too low to sensitive to drugs. (B) Changes in the expression of transport proteins in drug absorption lead to a decreased drug absorption rate and chemoresistance. (C) DNA damaged by chemotherapy and radiotherapy is repaired quickly, which is closely related to the acquisition of chemoresistance and radioresistance. (D) Cell death is inhibited, indicating that the balance between apoptosis and cell growth is disrupted, affected by the major gene families such as p53 and Bcl. (E)

The production of cellular EMT properties causes resistance to chemotherapy and radiotherapy. (F) The molecular targets of drugs can be altered in tumor cells. (G) Drug inactivation, some detoxification-related proteins deactivate drugs in cells, which is followed by chemoresistance acquisition

Conclusion

This review focuses on the genetic basis of resistance to radiotherapy and chemotherapy in cancer, and the rationale of increasing cell sensitivity by targeting related key genes and signaling pathways has been discussed for use in the clinic. Radiation ionizes molecules and atoms to directly destroy DNA in cells in human tissue. Enhanced DNA repair, cell cycle redistribution, CSC resilience, EMT, and activation of prosurvival pathways are the main mechanisms by which radioresistance is induced in cancer. Many factors, such as ATM, p53, PARP, XRCC1, and Bim-1, greatly influence cancer radioresistance through these different mechanisms (Table 2). Furthermore, this review describes the role of some genes in the development of resistance to two commonly used chemotherapy drugs; cisplatin and 5-FU. Cancer cells can develop resistance to chemotherapy through a variety of mechanisms; for example, they can attenuate the accumulation of anticancer drugs, activate detoxification systems, enhance DNA damage repair, and evade drug-induced cell death. The phenomenon of MDR during chemotherapy is the main reason for the limited clinical efficiency of chemotherapy

References

Anuja K, Chowdhury AR, Saha A, et al. Radiation-induced DNA damage response and resistance in colorectal cancer stem-like cells. Int J Radiat Biol. 2019;95(6):667-679.

Aponte PM, Caicedo A. Stemness in cancer: stem cells, cancer stem cells, and their microenvironment. Stem Cells Int. 2017;2017:5619472.

Azzam EI, Jay-Gerin JP, Pain D. Ionizing radiation-induced metabolic oxidative stress and prolonged cell injury. Cancer Lett. 2012;327(1-2):48-60

Borrego-Soto G, Ortiz-Lopez R, Rojas-Martinez A. Ionizing radiation-induced DNA injury and damage detection in patients with breast cancer. Genet Mol Biol. 2015;38(4):420-432

Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: gLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424

Chen GZ, Zhu HC, Dai WS, Zeng XN, Luo JH, Sun XC. The mechanisms of radioresistance in esophageal squamous cell carcinoma and current strategies in radiosensitivity. J Thorac Dis. 2017;9(3):849-859.

Chen ZS, Tiwari AK. Multidrug resistance proteins (MRPs/ABCCs) in cancer chemotherapy and genetic diseases. FEBS J. 2011;278(18):3226-3245.

Chin KV, Ueda K, Pastan I, Gottesman MM. Modulation of activity of the promoter of the human MDR1 gene by Ras and p53. Science. 1992;255(5043):459-462.

Dmitriev OY. Mechanism of tumor resistance to cisplatin mediated by the copper transporter ATP7B. Biochem Cell Biol. 2011;89(2):138-147

Eid H, Geczi L, Magori A, Bodrogi I, Institoris E, Bak M. Drug resistance and sensitivity of germ cell testicular tumors: evaluation of clinical relevance of MDR1/Pgp, p53, and metallothionein (MT) proteins. Anticancer Res. 1998;18(4C):3059-3064.

Enzinger PC, Mayer RJ. Esophageal cancer. N Engl J Med. 2003;349(23):2241-2252.

Friboulet L, Olaussen KA, Pignon JP, et al. ERCC1 isoform expression and DNA repair in non-small-cell lung cancer. N Engl J Med. 2013;368(12):1101-1110

Gillet JP, Gottesman MM. Mechanisms of multidrug resistance in cancer. Methods Mol Biol. 2010;596:47-76

Gomez-Bougie P, Bataille R, Amiot M. Endogenous association of Bim BH3-only protein with Mcl-1, Bcl-xL and Bcl-2 on mitochondria in human B cells. Eur J Immunol. 2005;35(3):971-976

Gurpinar E, Vousden KH. Hitting cancers' weak spots: vulnerabilities imposed by p53 mutation. Trends Cell Biol. 2015;25(8):486-495

Huang RX, Zhou PK. DNA damage response signaling pathways and targets for radiotherapy sensitization in cancer. Signal Transduct Target Ther. 2020;5(1):60

Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461(7267):1071-1078.

Joshi MB, Shirota Y, Danenberg KD, et al. High gene expression of TS1, GSTP1, and ERCC1 are risk factors for survival in patients treated with trimodality therapy for esophageal cancer. Clin Cancer Res. 2005;11(6):2215-2221

Kelland L. The resurgence of platinum-based cancer chemotherapy. Nat Rev Cancer. 2007;7(8):573-584.

Kimura M, Kuwabara Y, Mitsui A, et al. Thymidylate synthetase and dihydropyrimidine dehydrogenase mRNA levels in esophageal cancer. Oncol Lett. 2011;2(2):297-301.

Koberle B, Tomicic MT, Usanova S, Kaina B. Cisplatin resistance: preclinical findings and clinical implications. Biochim Biophys Acta. 2010;1806(2):172-182

Kunjachan S, Rychlik B, Storm G, Kiessling F, Lammers T. Multidrug resistance: physiological principles and nanomedical solutions. Adv Drug Deliv Rev. 2013;65(13-14):1852-1865.

Liedert B, Materna V, Schadendorf D, Thomale J, Lage H. Overexpression of cMOAT (MRP2/ABCC2) is associated with decreased formation of platinum-DNA adducts and decreased G2-arrest in melanoma cells resistant to cisplatin. J Invest Dermatol. 2003;121(1):172-176.

Liu JQ, Xue NN, Guo YX, et al. CircRNA_100367 regulated the radiation sensitivity of esophageal squamous cell carcinomas through miR-217/Wnt3 pathway. Aging-Us. 2019;11(24):12412-12427.

Lu SH. Alterations of oncogenes and tumor suppressor genes in esophageal cancer in China. Mutat Res. 2000;462(2-3):343-353

Mader RM, Müller M, Steger GG. Resistance to 5-fluorouracil. Gen Pharmacol. 1998;31(5):661-666.

Marechal A, Zou L. DNA damage sensing by the ATM and ATR kinases. Cold Spring Harb Perspect Biol. 2013;5(9).

McKenna WG, Muschel RJ. Targeting tumor cells by enhancing radiation sensitivity. Genes Chromosomes Cancer. 2003;38(4):330-338.

Nakajima M, Kato H. Treatment options for esophageal squamous cell carcinoma. Expert Opin Pharmacother. 2013;14(10):1345-1354

Nam HY, Han MW, Chang HW, Kim SY, Kim SW. Prolonged autophagy by MTOR inhibitor leads radioresistant cancer cells into senescence. Autophagy. 2013;9(10):1631-1632

Raleigh DR, Haas-Kogan DA. Molecular targets and mechanisms of radiosensitization using DNA damage response pathways. Future Oncol. 2013;9(2):219-233.

Safaei R, Maktabi MH, Blair BG, Larson CA, Howell SB. Effects of the loss of atox1 on the cellular pharmacology of cisplatin. J Inorg Biochem. 2009;103(3):333-341.

Santos Ramos F, Wons L, Cavalli IJ, Epithelial-mesenchymal transition in cancer: An overview. Ribeiro EMSF. 2017;4(3):10073.1–5

Su H, Jin X, Zhang X, et al. FH535 increases the radiosensitivity and reverses epithelial-to-mesenchymal transition of radioresistant esophageal cancer cell line KYSE-150R. J Transl Med. 2015;13:104

Tang Y, Xuan XY, Li M, Dong ZM. Roles of GST-pi and polbeta genes in chemoresistance of esophageal carcinoma cells. Asian Pac J Cancer Prev. 2013;14(12):7375-7379

Tembe V, Henderson BR. Protein trafficking in response to DNA damage. Cell Signal. 2007;19(6):1113-1120.

Wei N, Sun H, Liu GT. Advances in the targeting ATP-binding cassette transporters to overcome tumor multi-drug resistance. Yao Xue Xue Bao. 2010;45(10):1205-1211

Wu TS, Lin BR, Chang HH, Chang CC. Radio resistance mechanisms of cancers: an overview and future perspectives. Biol Med S. 2015;2:2

Xi Z, Guo W, Tian C, Wang F, Liu Y. Copper binding promotes the interaction of cisplatin with human copper chaperone Atox1. Chem Commun (Camb). 2013;49(95):11197-11199