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Review Article

Resistance to radiotherapy in lung cancer

Yufeng Liu[1*], Xiang Chen[1*], Qingqing Hu[2*], Jinhong Huang[3], Chunhua Ling[1]

Departments of [1]Respiratory Diseases, [2]Oncology, The First Affiliated Hospital of Soochow University, Suzhou, China; [3]Department of Respiratory Diseases, The Second People's Hospital of Changshu, Suzhou, China. [*]Equal contributors.

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Abstract: Radiation therapy (RT) is a highly effective treatment that kills cancer cells in human malignancies but resistance to radiation is a major obstacle contributing to treatment failure and tumor relapse. Although mechanisms of radiotherapy resistance have not been entirely uncovered, several biological factors of tumors have been shown to correlate with resistance to radiotherapy. These factors include presence of tumor stem cells, redistribution of the cell cycle, repair of DNA damage, dysregulation of miRNAs, hypoxia, angiogenesis, epithelia mesenchymal transition, autophagy, and apoptosis. Therefore, further exploration and a better understanding of the mechanisms will increase our ability to overcome radiotherapy resistance, as different resistance mechanisms of radiotherapy may require different molecular targeting radiosensitization strategies. This study gives an overview of the current literature regarding lung cancer resistance to radiation and explores potential therapeutic approaches for future radiation treatment.

Keywords: Lung cancer, radiotherapy resistance, cancer stem cells, cell cycle redistribution, dna damage repair, epithelia-mesenchymal transition

Introduction

Despite progress made in cancer therapy, lung cancer remains the leading cause of cancer-related deaths [1], causing more deaths than the three most common cancers combined: breast, prostate, and colon. Lung cancer is comprised of two distinct pathological classes: small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC), further classified into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [2]. SCLC makes up approximately 15% of cases and NSCLC accounts of about 85% of all lung cancers [1]. It has been reported that approximately 50% of all cancer patients received radiation treatment in some form, either alone or in combination with chemotherapy and/or surgery [3]. Although radiation therapy plays an important role in the treatment of lung cancer, resistance to radiation presents a significant clinical challenge and contributes largely to disease progression, recurrence, and increased cancer mortality [4]. Clinical factors have been shown to affect outcome after radiotherapy. One example is advanced tumor stage and/or large tumors. These require that more tumor cells need be killed in the same ionizing radiation dose, thereby reducing local control probability. In addition, there are numerous biological factors implicated in resistance to ionizing radiation, including presence of tumor stem cells, redistribution of the cell cycle, repair of DNA damage, dysregulation of miRNAs, tumor microenvironment, epithelia mesenchymal transition, autophagy, and apoptosis. The aim of this review was to report various mechanisms involved in radioresistance and highlight strategies for enhancing antitumor effectiveness.

Mechanism of radiation resistance

Radioresistance and cancer stem cells

Cancer stem cells (CSCs)

Since the stem cell concept of cancer was first described in leukemia, solid tumors (lung cancer, prostate, liver, glioblastoma) have demonstrated the existence of CSCs. CSCs have self-

renewal capacity and repopulation potential, enabling tumors to initiate and maintain tumor development. Therefore, to cure cancer, CSCs must be eradicated [5, 6]. The development of a variety of approaches has allowed isolation of cancer stem cells by expressing CSC-specific cell surface markers, or proteins, such as CD133 [7-10], CD44 [11-13], ALDH [14-17], side-population [18, 19], and Oct-4 [20]. It has been shown that CSCs subpopulations are more radioresistant, compared to non-CSCs subpopulations, which could lead to radiation treatment failure [21]. CSCs express high levels of DNA repair enzymes [22], drug-resistance transporter proteins (e.g. ABC) [23], and anti-apoptotic proteins [24], highly relating to resistance to traditional therapies such as chemotherapy and radiotherapy.

Cancer stem cells and radiation resistance

Main mechanisms of radioresistance of CSCs include sub-lethal DNA damage repair, cell redistribution in the cell cycle, and hypoxia [25]. Recent findings have suggested that human lung CSCs contribute to radioresistance by regulation of DNA repair molecules, such as Exo1 and Rad51, which improve double strand break repair proficiency [8]. In addition to activation of the DNA repair process, CSCs also activate the DNA damage checkpoint, in response to radiation, which arrests cell cycle progression to allow DNA repair, resulting in radiation resistance [26]. Radioresistant H460 cell lines were induced by irradiation that displayed a cancer stem-like cell (CSC) phenotype, with further study finding that these cells cycle were redistributed [27]. Moreover, inhibition of cell cycle check point protein Chk1 was found to improve radiosensitivity in $CD133^{+}CD44^{+}$ DU145 CaP cells [28]. Besides the intrinsic mechanisms underlying CSC radioresistance, hypoxia reduces formation of Reactive Oxygen Species (ROSs) and, thus, decreases irreparable DNA damage. Hypoxia also activates Hypoxia Inducible Factors (HIFs) signaling, which independently promotes radioresistance [29]. It has been shown that mammary gland CSCs ($CD44^{+}$ $CD24^{-/low}$ Lin^{-} cells) and epithelial stem cells ($CD24^{med}$ $CD49^{fhigh}$ Lin^{-} cells) contain lower ROS levels, compared to their non-tumorigenic progeny, contributing to tumor radioresistance [30]. Besides, different signaling pathways play a role in cancer metastasis, progression, and chemo/radioresistance. Rho/ROCK, Notch, Hedgehog, and Wnt signal pathways are associated with CSC radioresistance, targeting these signaling pathways for overcoming therapeutic resistance [31-33].

Radioresistance and cell cycle redistribution

Cell cycle

Cell cycle, consisting of four difference phases, gap 1 (G1), synthesis (S), gap 2 (G2), and mitosis (M), is a complex sequence of events enabling cells to grow and replicate without perturbing genomic integrity [34]. The G1/S checkpoint preventing replication of damaged DNA is the ATM (ATR)/CHK2 (CHK1)-p53/MDM2-p21 pathway. During the S-phase, damaged DNA inhibits replicative DNA synthesis, which is regulated by ATM-NBS1-SMC1 and ATM/ATR-Chk1/Chk2-CDC25A pathways, and the G2/M checkpoint prevents cells from entry into mitosis, initiated by ATM-mediated activation of CHK1 and CHK2 [35-37]. Cell cycle checkpoints are activated in the presence of DNA damage due to oxidative stress, such as ionizing radiation (IR) and ultraviolet (UV light) [38, 39]. Progression of cell cycle is then arrested at G1, S, or G2 phases, allowing cells to repair DNA damage [40].

Cell cycle and radiation resistance

Accumulating evidence has suggested that cell cycle may play a role in the regulatory process of radioresistance [41]. The radiosensitivity of cells differs among the phases, with cells being most sensitive to irradiation during G2-M phase, less sensitive in G1 phase, and least sensitive during S phase [42, 43]. It has been observed that SHP-1 decreased the radiosensitivity of NSCLC cells through modulating cell cycle distribution induced by cell cycle related proteins such as p16, cylinD1, and CDK4 [44]. It has been reported that G2-M cell cycle arrest plays a role in mediating radioresistance of A549R cells and increase of Cdc25c is responsible for G2-M phase arrest [45]. Similarly, 14-3-3σ contributed to radioresistance by arresting cells in G2/M phase and enhancing non-homologous end joining (NHEJ) repair via regulating expression of Chk2 and PARP1 [46]. Besides, 17-DMAG enhances radiosensitivity *in vitro* and *in vivo* by abrogating of radiation-induced G2- and S-phase arrest [47]. However, TSA improves

sensitivity of radiation in NSCLC cells by enhancing G2/M cell cycle arrest [48].

Radioresistance and DNA damage repair

DNA damage and repair

Ionizing radiation induces all kinds of DNA lesions including abasic sites, oxidized base damage, single-strand breaks (SSBs), and double-strand breaks (DSBs) [49]. DSBs are mainly responsible for the cellular lethality of radiation [50]. Once DSBs are induced by IR, activation of a series of kinases is triggered, including PI3K-related kinases (PIKKs) such as ATM, ATR, and DNA-PKcs [51]. The characterization of DNA DSB is phosphorylation of histone H2AX (γ-H2AX) by ATM or ATR, which detects levels of DNA damage [52]. Repair of DSBs is implemented by two major repair pathways, homologous recombination (HR) and non-homologous DNA end joining (NHEJ). NHEJ plays a role in the G1 phase, repairing the majority directly with two ended DSBs. HR only acts on S and G2 phases of cell cycles, when sister chromatids are present [53].

DNA damage repair and radiation resistance

Radioresistant cells have more DNA repair pathway associated genes (DNA-PK, ATM, Rad52, MLH1, and BRCA1) and less γ-H2AX foci after irradiation, compared to parental cells. This is reflective of more efficient DSB repair in radioresistant cells [54]. Inhibitors of important molecules in DNA DSB repair, such as DNA-dependent protein kinase (DNA-PK) or Rad52, have been shown to sensitize cancer cells to radiotherapy [55, 56]. Overexpression of epidermal growth factor receptor vIII mutant (EGFRvIII) contributes to resistance to IR by accelerating DNA DSB repair through activation of DNA-PK. Treatment with DNA-PK inhibitors restores radiosensitivity in EGFRvIII overexpressing cells [57]. In addition to activation of DNA repair process, cell cycle checkpoints constitute other important components of the DNA damage response. DDB2 increases radioresistance of NSCLC cells by activating Chk1 and CRAF, driving tumor radioresistance via promoting CHK2 phosphorylation to enhance the tumor cell DNA damage response. Inhibitors of checkpoint kinases, CHK1 and CHK2, have been proposed to enhance the cytotoxicity of radiotherapy [58-60].

Radioresistance and microRNAs

Characteristics of miRNAs

Micro-RNAs (miRNAs) are a class of small non-coding endogenous molecules, about 22 nucleotides long, that play a role in gene expression by biding to the 3'-untranslated region (3'-UTR) of target mRNA, resulting in mRNA cleavage or translational repression [61, 62]. Dysregulation of miRNA expression may be involved in tumor development such as metastasis, invasion, angiogenesis, and resistance to various cancer treatments [63]. For example, overexpression of miR-17-92 cluster has been observed to act as oncogenes enhancing lung cancer cell growth [64]. Overexpression of miR-153 supports colorectal cancer progression through enhanced cellular invasion and reduced chemosensitivity [65]. Specific miRNA expression in tissues, serums, and sputum have been reported for early diagnosis or predicting the prognosis of cancer patients. For example, high miR-21 expression has been reported to be related to disease progression and survival in stage I lung adenocarcinoma [66].

miRNAs and radiation resistance

Many miRNAs, such as let-7g, miR-7, and miR-21, have been reported to be involved in radiotherapy resistance [67]. MiRNAs can regulate tumor radioresistance by affecting radiation-related signaling pathways including cell cycle regulation, DNA damage repair, and apoptosis [68]. For example, miR-21 contributes to radioresistance by promoting repair of DNA DSB, which is involved in targeting GSK3 and CDC25A and promoting radioresistance through inducing G2/M cell cycle arrest [69, 70]. Additionally, high expression of miR-21 and miR-95, in stem-like cells of $ALDH1^{+}CD133^{+}$ subpopulation, was thought to be responsible for radioresistance of NSCLC tumors [71]. Silencing miR-21 sensitizes radioresistant NSCLC A549 cells to ionizing radiation through inhibiting cell proliferation and improving cell apoptosis by inhibition of PI3K/Akt signaling pathways [72]. In addition, let-7g was downregulated in radioresistant H1299 cells compared to the radiosensitive counterpart. Inhibition of LIN-28B, an upstream regulator of let-7g, increased levels of let-7g in H1299 cells, possibly suppressing translation of KRAS and enhancing radiosensitivity [73]. Cells expressing miR-210

in normoxia exhibited radioresistance similar to control cells in hypoxia, showing that miR-210 stable expression mimics hypoxia-induced metabolic changes associated with HIF-1a [74]. Inhibition of miR-191 contributes to radiation resistance in lung cancer cells by increasing autophagy levels, with high levels of autophagy related proteins Beclin-1 and LC3-II having been observed [75]. In contrast, miR-205 promotes radiosensitivity by targeting zinc finger E-box binding homeobox 1 (ZEB1) and ubiquitin-conjugating enzyme Ubc13 [76].

Tumor microenvironment

Tumor microenvironment (TME) is composed of different cell types such as cancer associated fibroblasts (CAFs) and endothelial and immune cells as well as factors such as extracellular matrix(ECM), oxygen levels, and pH [77, 78]. It has become increasingly evident that the tumor microenvironment is a critical regulator of tumor initiation, progression, and distant metastasis. More importantly, TME has been shown to be a critical factor inducing cancer therapeutic resistance [77-83]. For example, increasing stiffness of the subcellular matrix promotes proliferation and chemotherapeutic resistance in hepatocellular carcinoma [84].

Radioresistance and hypoxia

Tumor hypoxia: Overwhelming evidence has shown that hypoxia occurs in most tumors and it is a negative prognostic and predictive factor due to its association with resistance to different therapies, potentially contributing to poor patient survival [85]. In solid tumors, hypoxia (defined as pO_2<10 mm Hg, corresponding to <1.3% O_2 in vitro) results from an imbalance between oxygen supply and consumption, due to tumor microvasculature structural and functional abnormalities [86-88]. Tumor hypoxia includes four types: perfusion-related (acute) hypoxia, diffusion-related (chronic) hypoxia, anemic hypoxia, and toxic hypoxia [89]. The key feature of tumor hypoxia is Hypoxia Inducible Factor-1 (HIF-1), consisting of HIF1-α and HIF1-β. Under hypoxia, the HIF-1α protein is rapidly stabilized and translocates to nucleus and combines with HIF1-β, which mediates hypoxia-associated genes involved in survival, metabolism, invasion, and angiogenesis [90-92]. High expression levels of HIF-1 have been associated with increased patient mortality in cancers including cervical, breast, endometrial, stomach, and ovarian cancers [93].

Hypoxia and radiation resistance: Cells, at oxygen concentrations of less than around 1% (8 mm Hg), become more resistant to ionizing radiation and less than 0.02% (0.15 mm Hg) more resistant to killing by ionizing radiation by a factor of 2-3 [94]. Ionizing radiation can induce DNA damage by generating considerable cytotoxic reactive oxygen species (ROS), produced by the ionization of water [95]. However, under hypoxia, oxygen reduction interferes with ROS produced by ionizing radiation [96]. It has been reported that autophagy contributes to radiation resistance in hypoxia lung cancer cells by regulating ROS levels where mitochondria plays an important role [97]. Hypoxia/reoxygenation and TGF-β promote radioresistance of A549 lung cancer cells through ROS-mediated activation of Nrf2 and EGFR [98]. In addition, increased levels of HIFs can be associated with hypoxia within the tumor and has been shown to cause tumor radiation resistance [99]. HIF-1 also induces cancer cells to express VEGF, which confers radiation resistance to endothelial cells and increases the regrowth and proliferation of tumor blood vessels [100]. It has been found that hypoxia-induced autophagy contributes to radioresistance through HIF-1a promoted c-Jun phosphorylation, causing Beclin 1 expression [101]. Moreover, hypoxia induces Lysyl oxidase (LOX) expression *via* hypoxia-inducible factor-1a (HIF-1a), contributing to radioresistance in tumor cells. The mechanism may be through the promotion of DNA DSBs repair and G2/M cycle arrest, reducing apoptosis [102].

Radioresistance and angiogenesis

Overview of angiogenesis: Angiogenesis, the formation of new blood vessels from pre-existing vessels, is critical for many physiologic and pathophysiologic processes, such as chronic inflammation and cancer [103]. This process is regulated by pro-angiogenic molecules such as VEGF, bFGF, MMP-2/-9, uPA, EGF, and PDGF and anti-angiogenic molecules such as angiostatin, thrombospondin, and IFN-γ [104, 105]. It is widely accepted that the angiogenics switch when the balance between pro- and anti-angiogenic factors tends to a pro-angiogenic outcome. Mechanical stress, metabolic stress, immune/inflammatory response, and genetic

mutations can trigger this switch [106]. VEGF and its receptors play a pivotal role in angiogenesis and overexpression of VEGF has been related to tumor progression and poor prognosis in several tumor systems, including lung cancer, breast cancer, and colorectal carcinoma [107]. Hypoxia will increase HIF1 activity to upregulate VEGF to create a pro-angiogenic environment [108].

Angiogenesis and radiation resistance: IR stimulates tumor cells to increase pro-angiogenic molecules, such as basic fibroblast growth factor, VEGF, and MMP-9, which promote post-irradiation angiogenesis (PIA) and contribute to tumor radioresistance [109, 110]. Dying tumor cells, induced by irradiation, mediate PIA through a caspase 3 dependent mechanism and, importantly, it was found that VEGF-A, a downstream proangiogenic factor, is regulated by caspase 3 perhaps through Akt signaling [111]. Low-doses of ionizing radiation promotes angiogenesis, resulting in accelerated tumor growth and metastasis by activating VEGF receptor-2 [112]. It has been shown that upregulation of VEGF is responsible for formation of radioresistant lung cancer cells *via* regulation of Notch1 expression, which regulates distribution of the cell cycle to decrease apoptosis [113]. In addition, although radiosensitivity of VEGF-positive and VEGF-negative clones were equivalent *in vitro*, VEGF-positive xenografts were more resistant to cytotoxic effects of radiation than VEGF-negative xenografts in mice [114]. Moreover, activated HIF-1 enhanced radioresistance of tumor endothelial cells by upregulating expression of pro-angiogenic cytokine, VEGF [115].

Radioresistance and autophagy

Autophagy

Autophagy represents a dynamic lysosomal pathway in which cellular proteins and organelles are sequestered, delivered to lysosomes for degradation, and offered precursors such as nucleotides, fatty acids, and amino acids to be recycled and used for macromolecule synthesis [116, 117]. The autophagy process can be activated as an adaptive response to various conditions such as metabolic stress, deprivation of nutrients, hypoxia, and different types of anticancer treatment [118]. Autophagosome associated protein microtubule associated protein 1 light chain 3 (LC3) and Beclin-1 have been used as markers of autophagy [119]. There are various of types of autophagy, including macroautophagy and microautophagy, as well as chaperone-mediated autophagy (CMA), whose mechanisms and functions are different [120]. It has been reported that autophagy has dual roles in the regulation of tumorigenesis. In addition to playing an anti-tumor role in tumorigenesis, it also promotes the development of tumors [121].

Autophagy and radiation resistance

In response to radiotherapy, autophagy has two major and opposing functions in tumor cells. One is the cytoprotective function, which may confer resistance to therapy and increase sensitivity to therapy when blocked. The other is the cytotoxic function that can promote death of tumor cells and reduce sensitivity to therapy when blocked [122]. Irradiation induced accumulation of autophagosomes and increased expression of autophagy-related genes, such as atg3, atg4c, atg5, atg12, and beclin 1, and inhibited autophagy-related genes, has been beneficial in improving cytotoxicity of radiotherapy in resistant cancer cells [123]. Stathmin1 promotes radioresistance by activation of autophagy through PI3K/mTOR signaling pathways in non-small-cell lung cancer cells [124]. Under hypoxic conditions, autophagy mediates resistance of hypoxic tumor cells to ionizing radiation through the induction of autophagy independently of AMPK-signaling [125]. In contrast, it has been found that increased autophagy activity, *via* rapamycin application, sensitizes lung cancer cells to radiation, which has been associated with DNA damage repair inhibition [126]. Moreover, silencing of Pyruvate kinase M2 isoform (PKM2) expression increased sensitivity of NSCLC cell lines to radiotherapy by inducing autophagy and apoptosis, in vitro and in vivo, accompanied by inhibiting AKT signaling but increased ERK signaling [127].

Radioresistance and epithelia-mesenchymal transition

Epithelial mesenchymal transition (EMT)

Epithelial to mesenchymal transition (EMT) is a fundamental biological process during which epithelial cells lose apico-basal polarity and cell-cell contacts and undergo biochemical

Table 1. Different signaling pathways in lung cancer radioresistance and inhibitors

Signaling pathways	Inhibitor	Target	Reference
PI3K/Akt/mTOR pathway	LY294002, CAL-101, GDC-0941	PI3K inhibition	[160-163]
	Everolimus, Ridaforolimus	mTOR inhibition	[164, 165]
	MK-2206, GSK690693, GDC-0941	AKT inhibition	[166, 167]
	GSK2126458, PKI-587	DualPI3K/mTOR inhibition	[168]
ERK pathway	U0126, Trametinib	MEK inhibition	[169-171]
	SCH772984, BVD-523, GDC-099	ERK inhibition	[172-174]
HER/EGFR pathway	CI-1033	HER pan-inhibition	[175]
	Gefitinib	HER1 inhibition	[176]
VEGF pathway	Tivozanib, Axitinib Lenvatinib, Sorafenib	VEGFR inhibition	[109, 177, 178]
Notch pathway	miR935	Notch1 inhibition	[179, 180]
	256A4, 256A8	Notch3 inhibition	[181]
Wnt/β-catenin pathway	RBM5, WNT974, WP232228	Wnt/β-catenin inhibition	[182-185]

Abbreviations: PI3K phosphatidylinositol 3-kinase AKT, Protein Kinase B; mTOR, mammalian target of rapamycin; ERK extracellular regulated protein kinases; VEGF: vascular endothelial growth factor; EGFR: epidermal growth factor receptor.

shifts to gain mesenchymal traits, such as fibroblast-like cell morphology [128]. This process involves decreased expression of epithelial markers, such as E-cadherin, and increased expression of mesenchymal markers, such as N-cadherin and vimentin, resulting in the acquisition of increased invasive and migratory properties [129, 130]. For example, overexpression of N-cadherin, TWIST1, SNAIL, and SLUG is a predictive marker of lymph node metastasis and has been associated with poor prognosis [131, 132]. EMT programs are regulated by transcription factors including Twist, Zeb, Snail, Slug, and others [133]. EMT can be classified by three different subtypes: Type-1 associated with embryo formation and normal tissue development, type-2 related to wound healing, and type-3 involved in tumor development and metastasis [134]. EMT plays a role in tumorigenesis and has also been linked with increased therapy resistance [135].

EMT and radiation resistance

Increasing evidence has supported the association of EMT with radioresistance [136]. It has been found that multiple EMT-associated proteins were significantly upregulated in radioresistant cells, compared to parental lung adenocarcinoma cells [4]. For instance, Zinc finger E-box binding homeobox 1 (ZEB1), a driver of EMT, regulates radioresistance through an ATM-ZEB1-CHK1 signaling axis. Overexpression of ZEB1, in radiosensitive mammary epithelial cell lines MCF7 and HMLE, led to increased radioresistance while knockdown of ZEB1 in cancer cell lines enhanced radiation induced cytotoxicity [137]. Accumulating evidence has implicated EMT as a process that associated with CSCs features [138]. EMT and CSCs are involved in CaP radiation resistance, *via* activation of PI3K/Akt/mTOR signaling pathways, and they use a dual PI3K/mTOR inhibitor BEZ235 to enhance the radiosensitivity of prostate cancer cells with reduced EMT/CSC phenotypes [139]. Hypoxia also helps to drive the linkage between EMT and radiotherapy resistance. Hypoxia contributes to tumor radioresistance *via* E-cadherin loss and EMT. Thus, molecular mechanisms associated with hypoxia-induced EMT like phenotypes are partly reversible upon reoxygenation [140]. Furthermore, activation of JAK2/PAK1/Snail pathways by IR promoted EMT and radioresistance in lung cancer cells and use of JAK2-inhibitor increased radiosensitization by inhibiting EMT in a xenograft mouse model [141].

Radioresistance and apoptosis

Apoptosis

Kerr et al. first used the terminology “apoptosis” to describe the characteristic morphology of cell death [142]. This process, also known as programmed cell death, is regulated by energy dependent and genetic control mechanisms [143]. Apoptosis can be activated by intrinsic or

mitochondrial pathways and extrinsic or death receptor pathways. Intracellular signals are triggered by multiple cellular stresses, such as hypoxia and DNA damage, and are regulated by Bcl-2 family proteins, comprised of anti-apoptotic members (such as Bcl-W, Bcl-2, and Bcl-Xl) and pro-apoptotic members (such as Bad, Bax, Bak, and Bcl-Xs). The extrinsic pathway comprises a variety of cell surface receptors including tumor necrosis factor receptors (TNFRs), TNF-related apoptosis-inducing ligand receptors (TRAILRs), and Fas (CD95/Apo1) [144]. Dysregulation of apoptotic pathways has been thought to play a central role in the development and progression of some cancers. Overexpression of antiapoptotic proteins Bcl-xL and Bcl-2 has been reported to associate with cisplatin resistance and tumor recurrence in breast, ovarian, and non-small cell lung cancer [145].

Apoptosis and radiation resistance

Lack of appropriate apoptosis plays a crucial role in resistance of cancer cells to a variety of anticancer therapies [146]. For example, COL-1A1 is crucial for radioresistance in cervical cancer cells and plays a crucial role in anti-apoptosis by Caspase-3/PI3K/AKT pathways [147]. Livin, a novel inhibitor of apoptosis protein (IAP) family member, may cause radiation resistance by inhibiting apoptosis [148]. Moreover, it has been shown that acute low dose irradiation results in the translational upregulation of the intrinsic cellular anti-apoptotic protein X-linked inhibitor of apoptosis protein (XIAP) *via* a unique IRES (Internal Ribosome Entry Site)-mediated mechanism that associates with an elevated resistance to radiation in non-small cell lung carcinoma. Furthermore, antisense downregulation of XIAP has resulted in reduced radiation resistance [149]. Elevated miR-451 has sensitized radioresistant lung cancer cells to irradiation through the enhancement of apoptosis [150]. Astaxanthin has enhanced radiosensitivity and induced G2/M arrest and apoptosis by inhibiting CyclinB1, Bcl2, and Cdc2 and increasing Bax expression [151].

Conclusion

Radiotherapy mainly kills sensitive cells, leaving radiotherapy-resistant cells that can cause tumor recurrence and metastasis, becoming a major obstacle in radiotherapy treatment for cancers. Understanding these mechanisms is very important in exploration for future therapies and overcoming radiation resistance. For example, BBI608, a cancer stemness inhibitor, can decrease gene transcription driven by Stat3 and kill stemness high cancer cells, thus, effectively suppressing cancer relapse and metastasis [152]. Proteasome inhibitors increase radiosensitivity in non-small cell lung cancer through suppressing radiation-induced DNA double strand break repair by reducing homologous recombination [153]. MiRNAs can also enhance radiation sensitivity. For example, miR-15a/16 enhances radiation sensitivity by targeting TLR1/NF-kB signaling pathways in lung cancer cells [154]. BAY-84-7296, a novel inhibitor of mitochondrial complex I and HIF-1 stabilization, resolved tumor hypoxia and enhanced radiation response [155]. Vascular Endothelial Growth Factor Tyrosine Kinase Inhibitor AZD2171 sensitized tumor vasculature to radiation and inhibited angiogenesis, both *in vitro* and *in vivo* [156]. In addition, different signaling pathways play a role in cancer chemo/radioresistance. PI3K/Akt/mTOR, ERK, glycolysis, VEGF, Notch, and WNT/β-catenin pathways are highly correlated with cancer radiation resistance [157, 158] (**Table 1**). For example, radioresistance of K-Ras-mutated NSCLC cells was mediated through the EGFR-PI3K-AKT pathway and radioresistance of K-Ras mutated tumor cells can be abrogated through inhibition of EGFR-PI3K-AKT-survival pathways by EGFR- or PI3K-specific TK-inhibitors (BIBX1382BS or LY294002) [159]. In conclusion, understanding the various intracellular pathways involved in radioresistance will assist in the development of new molecularly-targeted therapies to overcome mechanisms of radiation resistance.

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Disclosure of conflict of interest

None.

Address correspondence to: Jinhong Huang, Department of Respiratory Diseases, The Second People's Hospital of Changshu, Suzhou 215000, China. Tel: +86 133 8212 5009; E-mail: john126272@sohu.com; Chunhua Ling, Department of Respiratory Diseases, The First Affiliated Hospital of Soochow University, Suzhou 215006, China. Tel: +86 1396 2146 558; E-mail: linchunhua88@hotmail.com

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