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Understanding the molecular basis of radioresistance in lung cancer: A comprehensive review

Fatima Zohra Attouahri[1,2], Boutaina Addoum[1], Leila Benbacer[1], Samira Mimount[1], Bouchra El Mchichi[3], Abdelhamid Barakat[4], Hanane El Ouazzani[5], Ismail Rhorfi[5], Ahmed Abid[5], Mouna Ababou[2], Khalid Ennibi[3], Khaoula Errafii[6], Mohammed El Mzibri[1]*

[1]Department of Life Sciences, National Center for Nuclear Energy, Sciences and Techniques, Rabat, Morocco

[2]Laboratory of Biodiversity, Ecology and Genome, Department of Biology, Faculty of Sciences, Mohammed V University in Rabat, Rabat, Morocco

[3]Center of Virology, Infectious and Tropical Diseases, Mohammed V Military Teaching Hospital, Rabat, Morocco

[4]Laboratory of Genetics, Department of Research, Pasteur Institute of Morocco, Casablanca, Morocco

[5]Department of Pneumology, Faculty of Medicine and Pharmacy, Mohamed V Military Teaching Hospital, Rabat, Morocco

[6]African Genome Centre, Mohammed VI Polytechnic University, Benguerir, Rehamna, Morocco

***Corresponding author:**
Mohammed El Mzibri
(elmzibri@cnesten.org.ma)

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Abstract

Lung cancer (LC) remains the most common malignancy in both genders and is the leading cause of cancer-related death worldwide. Despite significant advances in therapeutic approaches, radiotherapy (RT) continues to be one of the main approaches to LC treatment. However, radioresistance represents a major challenge to effective disease management and contributes significantly to treatment failure and poor prognosis. Radioresistance can be intrinsic, existing before treatment, or acquired during RT. It is a highly complex and multifactorial mechanism involving various cellular and molecular processes that are not yet fully understood. Key mechanisms contributing to radioresistance include enhanced DNA damage repair, cell cycle redistribution, inhibition of apoptosis, disruption of intracellular signaling pathways, interaction with the tumor microenvironment, autophagy-mediated survival, cancer stem cell-related resistance, and deregulation of non-coding ribonucleic acids. Understanding these pathways is essential for identifying new therapeutic targets and developing strategies to overcome resistance and improve patient outcomes. This review provides a comprehensive overview of the molecular mechanisms underlying radioresistance in LC.

Keywords: Lung cancer; Radiotherapy; Radioresistance

1. Introduction

Globally, lung cancer (LC) is the leading cancer for both genders and remains the principal cause of cancer deaths worldwide.[1] Depending on the histology of the cancer cells, there

are two main types of LC: Non-small cell lung carcinoma (NSCLC), which accounts for around 80% of cases, and small cell lung carcinoma (SCLC), which accounts for the remaining 20%.[2] NSCLC can be divided primarily into lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LSCC), and large cell carcinoma. These subtypes can be classified into several groups depending on their genetic and molecular characteristics.[2] Lung metastases are common in many primary malignancies and are associated with a poor prognosis.[3]

Chemoradiotherapy (RT) is the most appropriate therapeutic approach for disease management in patients with locally advanced LC who are not eligible for surgery.[4] In combination with other approaches, such as surgery, immunotherapy, or chemotherapy, RT can improve local tumor control and thus long-term survival of LC patients, sometimes to the point of tumor cure.[5] However, despite remarkable technological advances that continue to refine its precision and power, RT often faces a critical challenge, such as resistance. In many cases, including LC, this resistance undermines treatment efficacy and ultimately leads to relapse.[6]

Radioresistance refers to the intrinsic or acquired ability of tumor cells to evade the cytotoxic effects of ionizing radiation (IR) and represents a critical barrier to effective cancer therapy. By diminishing treatment responsiveness, it significantly undermines therapeutic success and contributes to disease persistence, treatment failure, the occurrence of metastases and tumor recurrence, and a worse prognosis. Despite advances in RT techniques, radioresistance remains a fundamental obstacle to improving treatment outcomes.[7] The resistance of tumor cells to RT can be classified into intrinsic and acquired resistance. Intrinsic radiation resistance, or primary resistance, describes the presence of tumor cells initially able to resist irradiation. Acquired radioresistance, on the other hand, involves the ability of cancer cells to adapt to radiation-induced modifications, thus becoming resistant to treatment.[8]

Resistance to RT is linked to several factors, including genetic characteristics and tumor heterogeneity, altered signaling pathways, and interactions with the tumor microenvironment (TME).[9] The response to IR involves several molecular mechanisms, mainly associated with DNA damage pathways, apoptosis, cell cycle deregulation, hypoxia, stem cell population, metabolic reprogramming, and non-coding ribonucleic acids (RNAs).[10-12] A better understanding of the molecular pathways underlying radioresistance is required to improve therapeutic approaches, develop new therapeutic targets, and enhance the overall efficacy of RT in LC patients. By elucidating these mechanisms, it may be possible to overcome treatment resistance, reduce relapse rates, and ultimately increase patient survival. In this context, this review aims to synthesize and explore current knowledge on the cellular and molecular determinants of radioresistance in LC, with the main objective of shedding light on the potential therapeutic targets and informing the development of more effective, personalized RT strategies.

2. RT as an oncological treatment

By delivering sufficient doses of radiation, RT ensures the destruction of cancer cells. The rate of cell differentiation, mitotic activity, and histological type of tumor determine these radical dosages.[13] RT can be administered by brachytherapy (internal RT) or external RT. The latter comprises several techniques, including 3-D conformal RT, hypofractionated and intensity-modulated RT, stereotactic body RT, prophylactic cranial irradiation, and proton therapy.[14] RT can be used for radical therapy, elimination of residual disease as adjuvant therapy after surgery, and palliative care. It is an independent type of therapy that can be used in the early stages if surgery is not possible.[13]

RT acts directly by causing DNA damage through its physical effects on the DNA molecule, and indirectly through radiolysis of the water, which contributes to an oxidative attack followed by DNA damage, through the formation of reactive oxygen species (ROS).[14] ROS can damage cellular DNA by several mechanisms, including oxidation of protein and lipids, oxidative stress-induced destruction of pyrimidine and purine bases, and DNA fractures, which can occur on a single or both strands of the helix.[15]

After the induction of DNA damage, cancer cells are eradicated through numerous mechanisms, including apoptotic signaling, autophagy machinery, necrosis, and necroptosis. Irradiated cells can also die of senescence and mitotic catastrophe after several cycles of cell division due to non-repaired DNA lesions and abnormal chromosome segregation.[16] By introducing irreparable DNA damage, radiation can trigger the apoptotic machinery to prevent the accumulation of mutations in daughter cells.[17]

RT can also modify tumor behavior and the TME. Of particular interest, new arguments suggest that radiation can also stimulate the immune system. RT can induce immunogenic cell death, which triggers the secretion of cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukins (ILs) 6 and 8, as well as danger-associated molecular patterns.[18] These tumor cell immunogens also signal the immune system to trigger inflammation and stimulate an anti-tumor immunity to limit tumor cell growth.[19] RT overcomes the immune repression exerted

by the TME by blocking immune checkpoints and immunosuppressive molecules and increasing the cross-presentation of antigens to cytotoxic T cells.[20] In this field, RT ensures upregulation of intratumoral levels of FS7-associated cell surface antigen (Fas) ligand, granzyme B, and the ability to destroy tumor-infiltrating $CD8^+$ T lymphocytes directly.[21]

3. Molecular mechanisms of radioresistance

3.1. Reprogramming DNA damage repair

In tumor tissue exposed to RT, several forms of DNA disruption can be induced by IR, representing the curative potential of RT. Upon deposition of radiation energy in DNA molecules, several DNA lesions are generated within one or two helical turns, leading to a fraction of DNA damage sites.[22] This damage affects base and sugar, DNA-protein and DNA-DNA crosslinks, and single- and double-strand breaks (SSBs and DSBs).[23] Of note, scientific evidence has shown that DSBs are the major lethal lesions.[24] To treat these various types of lesions, repair mechanisms, including mismatch repair, nucleotide or base excision repair, and DSB repair, are implemented.[7] In cancer cells, the major cause of radioresistance is enhanced by the DNA repair capability. Therefore, overcoming radioresistance can be achieved by understanding the mechanism implicated in DNA damage response (DDR).

Poly ADP-ribose polymerase (PARP) and the ataxia telangiectasia and rad3-related protein (ATR)/checkpoint kinase 1 (CHK1) kinase axis ensure SSB repair (Figure 1).[25] When SSBs occur in radiation-damaged DNA, PARP rapidly detects the rupture site via its zinc finger structural domain[7] and recruits proteins involved in the repair process, such as X-ray repair cross-complementing protein 1, to the site of damage. Then, DNA polymerase δ/ε fills a small lesion sequence in the presence of proliferating cell nuclear antigen (PCNA).[26] The flap endonuclease resects the generated extension of DNA bases, and then the DNA ligase 1 bridges the gap at the restored DNA region.[27] A previous study showed that anti-PARP agents can sensitize SCLC cell lines to irradiation even at low doses, particularly inhibitors with greater PARP sequestration capacity.[28] In the ATR/CHK1 signaling pathway, the recruitment of ATR to the site of the lesion is mediated by ATR-interacting protein.[29] Then, after its binding to DNA topoisomerase II-binding protein 1 and then to the

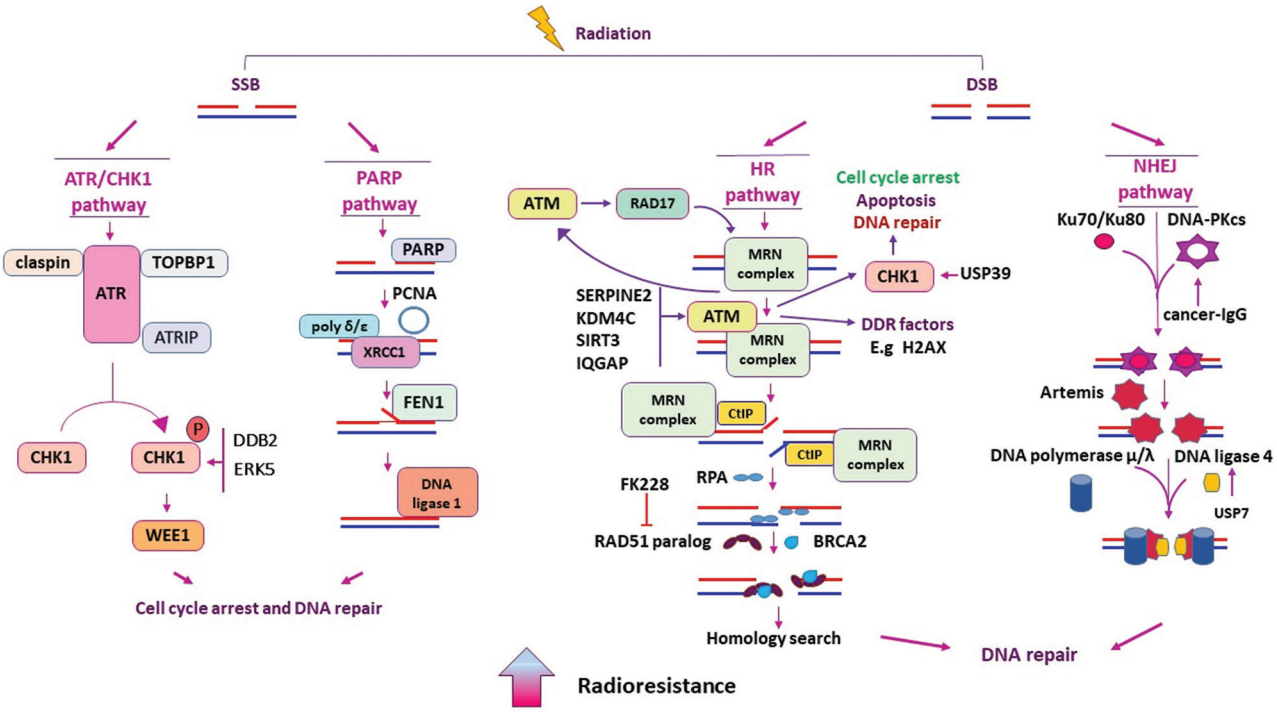

Figure 1. DNA damage repair mechanisms in lung cancer radioresistance. The cytotoxic action of radiation causes DNA damage, leading to the activation of the DNA damage response, which consists of the recognition of DNA lesions, followed by the activation of DNA repair processes. SSBs are repaired by the ATR-CHK1 pathway and the PARP pathway. In the case of DSBs, two signaling pathways are involved: The NHEJ and HR pathways. Figure created with Microsoft PowerPoint.

Abbreviations: DSB: Double-strand breaks; SSB: Single-strand breaks; PARP: Poly ADP-ribose polymerase; ATR: Ataxia telangiectasia and rad3-related protein; CHK1: Checkpoint kinase 1; NHEJ: Non-homologous end-joining; HR: Homologous recombination.

claspin protein, ATR ensures CHK1 phosphorylation, the latter permitting WEE1 phosphorylation, stopping the cell cycle, and ensuring repair of DNA damage.[25,30] In NSCLC, DNA damage binding protein 2 and extracellular signal-regulated kinase (ERK) 5 can protect cells from IR-induced apoptosis by phosphorylation of CHK1.[31,32]

Homologous recombination (HR) and non-homologous end-joining (NHEJ) are the two mechanisms used for DSB repair.[33] Repair based on HR (RHR) is a complex and error-free pathway.[34] It occurs when the cell is in the S/G2 branch of the cell cycle, because it needs a homologous sequence to be present as a donor template.[26] In HR, three units (meiotic recombination complex 11 homologous 1 [MRE11]; DNA repair protein [RAD]; Nijmegen breakage syndrome 1 protein [NBS1], make up the MRE11-RAD50-NBS1 (MRN) complex that is involved in sensing, recognizing, and initiating the repair of radiation-induced DSBs.[30] The protein kinase ataxia telangiectasia mutated (ATM) phosphorylates the cell-cycle checkpoint RAD17, enabling it to interact with NBS1 and recruit the MRN complex to DSBs.[35] The MRN complex serves to further activate ATM.[26] From there, ATM promotes the nucleolytic activity of MRE11 and C-terminal binding protein-interacting protein,[36] to trigger DNA end resection to form 3'-ssDNA overhangs,[37] which are subsequently coated with replication protein A.[38] Then, ATM signaling initiates a waterfall of phosphorylation events and recruits effectors such as the recombinase RAD51 and the breast cancer-associated protein 2 on chromatin flanking DSBs,[36] and forms discrete foci, including H2A histone family member X (H2AX).[39] Using the homologous chromosome, RAD51 will find a homology match, then connect this template DNA to the damaged DNA.[40] In radiation-resistant SCLC cells, it is found that romidepsin, a bicyclic tetra-peptide compound, augments radiation-induced DNA damage by impairing the positioning of RAD51 at DSB break sites.[41] Furthermore, IR-induced unrepaired DNA damage was significantly increased in RAD51c-depleted A549 LC cell lines, an RAD51 paralog member.[42] ATM also phosphorylates checkpoint kinase 2 (CHK2) at Thr68 site, which induces CHK2 dimerization and autophosphorylation, and triggers it to phosphorylate multiple downstream targets to induce different cellular responses, namely the prevention of cell cycle progression, programmed cell death, or the repair of DNA.[43,44]

Other molecules are known to regulate RHR and radioresistance in LC, such as the C-terminus of serine proteinase inhibitor clade E member 2, which promotes ATM phosphorylation by directly interacting with MRE11 and ATM to regulate DNA damage repair.[33] Moreover, lysine-specific demethylase 4C can activate the ATM/CHK2 pathway by stimulating the transforming growth factor-β (TGF-β) 2/suppressor of mothers against decapentaplegic pathway (SMAD) signal axis, resulting in reduced radiosensitivity of LC.[45] In addition, ubiquitin-specific peptidase (USP) 39 regulates the level and stability of the CHK2 in a proteasome-dependent way, influencing cell cycle and apoptosis. Consequently, reducing USP39 levels increases radiosensitivity in LC cells.[46] Similarly, sirtuin 3, an NAD-dependent deacetylase, promotes radioresistance in NSCLC by triggering the ATM/CHK2 pathway.[47] Besides, IQ motif containing GTPase-activating protein can promote radiosensitization in LC, through its interaction with RAD17, followed by recruitment of the MRN complex and activating downstream ATM/CHK2 and ATR/CHK1 signaling pathways.[48]

NHEJ is a rapid and error-prone pathway that involves the synapsis of broken DNA ends, which is activated at any stage in the cell cycle.[49] In NHEJ, Ku heterodimer (Ku70/Ku80) binds at the extremities of the DSB, recruiting the DNA-dependent protein kinase catalytic subunit (DNA-PKcs), which ensures phosphorylation of various substrates.[50] This includes Artemis, which facilitates end processing followed by ligation under the action of the DNA ligase 4 (LIG4) complex.[30] Inhibition of DNA-PKcs action directly reduces the ability to repair DNA errors and radiosensitizes LC cells with acquired radioresistance.[51] Plakophilin 2 (PKP2), which belongs to the ARM protein superfamily, promotes NHEJ and radioresistance in LC by stabilizing β-catenin through human USP7, enhancing the PKP2/β-catenin/LIG4 pathway.[52] In addition, cancer-derived immunoglobulin G activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/DNA-PKcs signaling pathway and induces activation of proteins required for the repair process, leading to increased radioresistance in LUADs.[53]

Radioresistance in LC is largely driven by the tumor cells' enhanced ability to repair DNA damage. Delving into the molecular machinery responsible for repairing SSBs and DSBs reveals critical targets for intervention. Inhibitors of key DNA repair regulators, such as PARP, DNA-PKcs, ATM, and ATR, have emerged as powerful tools to disrupt this defense and sensitize tumors to RT. The integration of these agents into future clinical trials alongside RT holds the promise of transforming LC management through personalized treatment strategies.

3.2. Cell cycle redistribution and apoptosis

The cell cycle is a highly organized process divided into four stages: G0/G1, S, G2, and M, whose progression leads to cell proliferation.[54] In the case of IR, cell cycle checkpoints can be activated to inhibit cycle entry or

progression, to ensure the cell has sufficient time to repair its DNA (Figure 2).[11] In general terms, the S phase is the most resistant phase to radiation. While the G2/M stage is characterized by the highest sensitivity, cells in G0/G1 are known to have the highest radioresistance.[55] Cyclins and cyclin-dependent kinases (CDKs) act to regulate the passage from one stage to another during the cell cycle. Checkpoints present at the G1/S and G2/M interphases ensure the inhibition of cyclins and CDKs in case of stress developed after radiation, to inhibit cell cycle progression and enable DNA repair.[56] Zhao *et al.*[57] reported that the phosphorylation of cell division cycle 25C by CHK1 and CHK2 acts as an early G2-phase checkpoint, which saves time to repair DNA damage caused by RT in human LUAD bronchioloalveolar carcinoma. G2/M checkpoint arrest is induced by CDK1 inhibition that causes G2 arrest, persistent DSB, inhibition of HR repair, and apoptosis in A549 and H1299 LC cell lines.[58] Importantly, the knockdown of G2 and S phase-expressed 1, a cell cycle-related protein that regulates G1/S cell cycle transition expression, could impair the DNA damage repair process and inhibit the radioresistance effect.[59] Cyclin K activates the wingless-related integration site (WNT)/β-catenin/Cyclin D1 pathway. Its depletion worsens DNA damage and restores radiosensitivity by disrupting the G2/M checkpoint.[60] Inhibition of SH2-containing tyrosine phosphatase delays the G1/S checkpoint by impairing the expression of CDK4, CyclinD1, and P16, ensuring the radiosensitivity of NSCLC cells.[61] Knockdown of single-strand DNA-binding protein 1, a protein linked to radioresistance, induced mitochondrial dysfunction and accumulation of ROS of mitochondrial origin, prolonging cell cycle arrest in the G2/M phase and increasing IR-induced cell death by apoptosis. This stimulates radiosensitivity in the LC cell line H1299.[62] Downregulation of AKT and ERK signaling cascades via inhibition of vascular endothelial growth factor receptor 2 may improve radiation sensitivity by inhibiting DSB repair through increased G2/M phase arrest in NSCLC cells.[63]

Tumor cells may develop strategies to escape cell death, such as enhanced expression of apoptosis-inhibiting factors, including B-cell lymphoma (BCL)-2 and BCL-XL, or survival signals, and loss of tumor protein (TP) p53 tumor suppressor function leading to radioresistance to RT, thus affecting patient outcome and prognosis.[64] Inhibition of BCL-2 and BCL-XL overcomes radioresistance in LC cells and enhances the sensitivity to radiation cytotoxicity.[65] In addition, the P53 and DNA damage-regulated gene 1 oncogene can inhibit ATM to block the ATM/P53 pathway, preventing apoptosis and promoting proliferation, particularly under the effect of irradiation.[66] Increased levels of gelsolin, a cytoskeletal remodeling protein, decrease apoptosis and reduce caspase-3 and PARP cleavage, leading to increased radioresistance in NSCLC cells.[67] Deletion of Fas ligand-induced caspase-8-like inhibitory protein (FLIP), which inhibits apoptosis by blocking procaspase-8 activation, enhances apoptosis. In contrast, cell death following radiation in LC is reduced by either downregulation of procaspase-8 or upregulation of FLIP expression.[68]

Disruption of cell cycle checkpoints and inhibition of apoptotic pathways are central mechanisms by which LC cells escape radiation-induced death. Therapeutically,

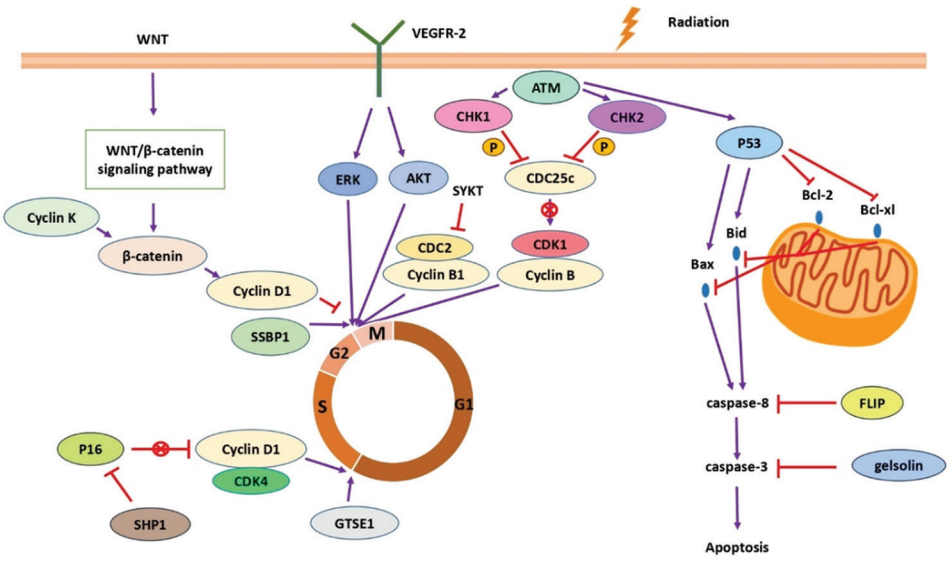

Figure 2. The effects of cell cycle redistribution and apoptosis on lung cancer radioresistance. Figure created with Microsoft PowerPoint.

this resistance can be challenged by combining RT with agents that target cell cycle checkpoints or pro-apoptotic modulators. Such combinations offer a compelling approach to re-sensitize tumors to RT and enhance clinical outcomes for patients with LC.

3.3. TME

Far more than a structural backdrop, TME is an environmental niche that contains different components such as extracellular matrix, signaling molecules, blood vessels, and non-cancer cells, including immune cells, stromal cells, and fibroblasts.[69] Changes in this microcosm evolve alongside the tumor, fueling its growth, invasion, and spread while serving as a major driver of therapeutic resistance.[70] RT can induce an immunosuppressive effect, inflammation, hypoxia, and vascular injury in TME (Figure 3).[71] The therapeutic efficacy of RT can be improved by decoding the complex crosstalk within the TME, thereby reprogramming it to overcome resistance. As a result, RT can be transformed from a blunt weapon into a precision-guided strategy that dismantles the tumor's protective shield and restores therapeutic sensitivity.

3.3.1. Hypoxia effect

Solid cell tumors are in chronic hypoxia when pO_2 is below 10 mmHg, which has been largely recognized as a source of radioresistance.[72] Several factors lead to a hypoxic environment and obstruct immune cell functions in tumors, including pathological vasculature, stroma composition, and tumor growth rate. This is because solid tumors, unlike normal tissue, contain dysfunctional vasculature.[69] Hypoxia affects RT through several processes, including apoptosis, and mediates cellular interaction through extracellular environmental factors after alteration of the expression of pro-survival genes.[73] The pro-apoptotic members (BID, BAD, and BAX) and the anti-apoptotic proteins (MCL-1, BFL-1, BCL-XL, BCL-2, BCL-W, and BCL-B) from the BCL-2 family of proteins control

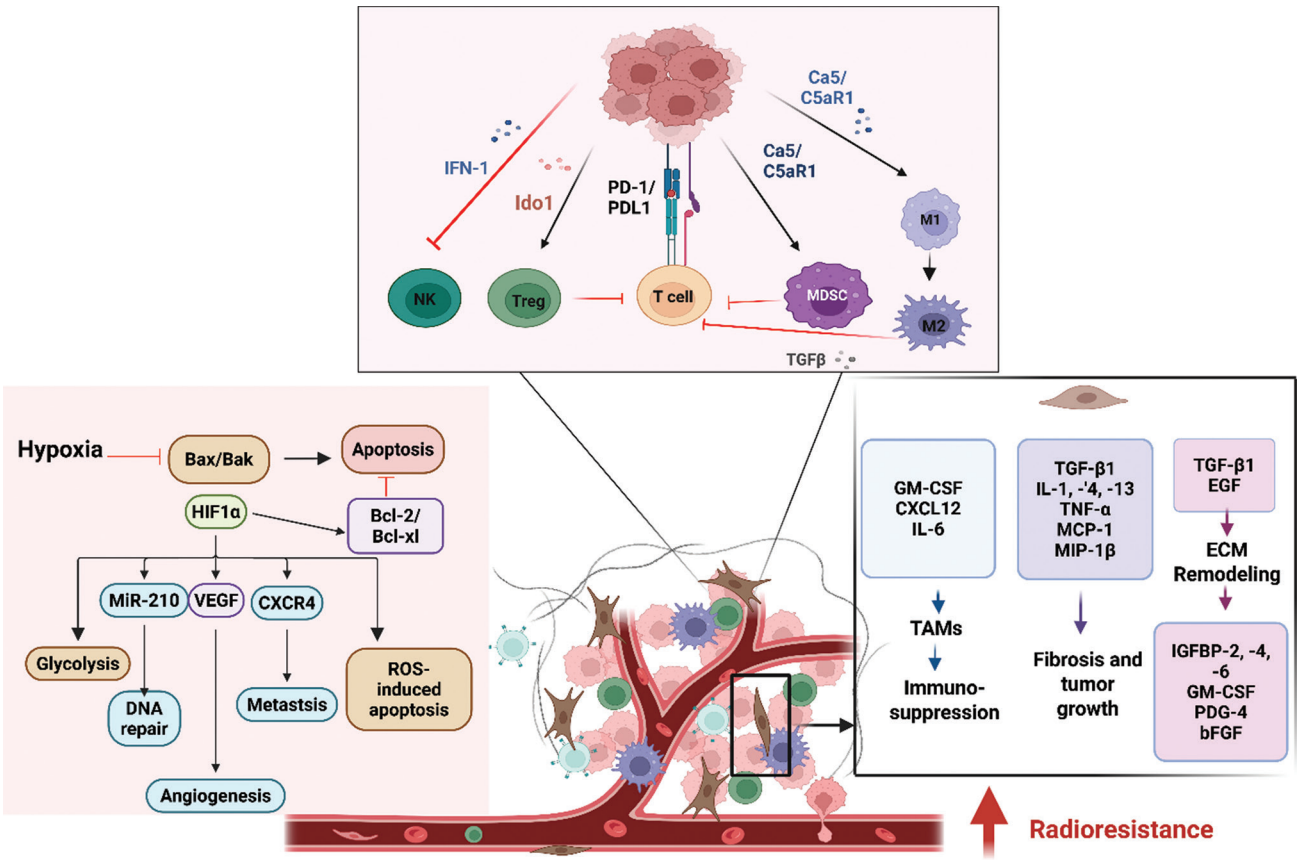

Figure 3. TME-related mechanisms in mediating lung cancer radioresistance. Alterations in the cell cycle, such as arrest in the radioresistant phases (notably the S phase), allow cancer cells more time to repair DNA damage, thereby reducing radiotherapy effectiveness. Additionally, defects in apoptotic pathways, including reduced expression of pro-apoptotic proteins or overactivation of survival signals, enable tumor cells to evade radiation-induced cell death. Figure created in BioRender. Attouahri, F. (2025) https://BioRender.com/18wtfdz.
Abbreviations: ECM: Extracellular matrix, ROS: Reactive oxygen species; TAMs: Tumor-associated macrophages; TME: Tumor microenvironment.

apoptosis processes.[74] Radiation therapy induces cell death by direct damage to the DNA and generation of ROS, and hypoxia can lead to a radioresistant phenotype through the downregulation of pro-apoptotic factors, which have a crucial role in irradiation-induced apoptosis.[75] In addition, during RT, oxygen represents a key factor that should be present at least during the lifetime of the ROS to produce apoptosis.[69] Compared with oxygenated cells, irradiated oxygen-deficient cells are 2 – 3 times more radioresistant.[76] The survival rate under hypoxia is significantly greater than that under normoxia of either A549 or H1299 cells after IR.[77] RT can stimulate the activation of hypoxia-inducible factor (HIF)-1α, which subsequently influences the response to radiation via numerous signaling pathways,[78] including the initiation of tumor angiogenesis and increased glucose metabolism, reducing the potency of RT.[79] For promoting revascularization, HIF-1α induced by radiation activates its downstream genes, mainly vascular endothelial growth factor (VEGF).[80] The inhibition of the HIF-1α/VEGF pathway blocks the resistance to RT by inhibiting the action of hypoxia on cell viability, angiogenesis, and migration in LC cell lines.[81] In hypoxic conditions, microRNA (miRNA)-210 expression induced by HIF-1 decreases apoptotic death and accelerates repair of the DSBs, promoting radioresistance in LC cell lines.[82] In addition, heat shock protein 90 (HSP90) facilitates stability, action, and the import of HIF-1α into the nucleus, which ensures the viability and adaptation of tumor cells to hypoxic stress.[83] Inhibition of HSP90 in normoxic and hypoxic lung A549 carcinoma removes the migration and invasion after irradiation.[84] In addition, after irradiation, HIF-1α and ROS play a role in irradiation-induced C-X-C chemokine receptor type 4 (CXCR4) expression. Subsequently, extracellular stromal cell-derived factor 1α activates radiation-induced CXCR4, leading to upregulation of matrix metalloproteinase-2/9 protein *via* activation of the pAKT and pERK1/2 pathways, promoting LC metastasis and invasiveness.[85]

3.3.2. Cancer-associated fibroblasts (CAFs)

CAFs represent one of the more important and abundant stromal constituents in the TME.[86] CAFs ensure remodeling of the extracellular matrix, secretion of growth factors, and modulation of epithelial-to-mesenchymal transition (EMT) to promote tumor invasion, migration, and metastasis.[87] From a radioresistance viewpoint, it has been shown that radioresistance has been increased by co-incubation of A549 and H1299 LC cells with human lung CAFs.[88] To resist cell death caused by radiation stress, CAFs secreted many growth factors, including insulin-like growth factor binding proteins-2, -4, and -6, epidermal growth factor, granulocyte-macrophage colony-stimulating factor, and platelet-derived growth factor-4, to promote survival signals.[89] Moreover, CAFs can promote tumor relapse by promoting the recovery of irradiated cancer cells and the induction of autophagy after IR application.[90] In this field, NSCLC cells' radioresistance is increased by radiation-induced senescence-like CAFs.[91] In addition, after receiving ablative IR, the secretome of CAFs from human NSCLC was changed, specifically angiogenic factors, including angiopoietin, were downregulated, whereas the expression of basic fibroblast growth factor-2, which has a radio-protective action, was upregulated.[92] After RT, several factors expressed by CAFs (TGF-β1, IL-1, -4, -13, TNF-α, monocyte chemoattractant protein-1, and macrophage inflammatory protein-1β) lead to the development of fibrosis, supporting tumor growth, radioresistance, and disease progression. Finally, CAFs can modify the extracellular matrix by recruiting macrophages and reinforcing their physiological activities. The interaction between CAFs and tumor-associated macrophages (TAMs) establishes immunosuppressive conditions within the EMT through the secretion of granulocyte macrophage colony-stimulating factor, C-X-C motif chemokine 12, and IL-6 by CAFs.[93]

3.3.3. Immune landscape of cancer

Tumors can develop radioresistance through upregulating programmed cell death protein 1 (PD-L1) expression in response to the local inflammatory environment induced by radiation. PD-L1 represents a component of the immune checkpoint that induces immune escape in the TME and dampens the immune response against the tumor, decreasing IR-induced antitumor immunity and generating the infiltration of tumor-specific T cells.[94] At the same time, in NSCLC cells and mice, it was established that the effect of RT could be stimulated by PD-L1 antibodies.[95] In NSCLC, RT induces PD-L1 overexpression via the PI3K/AKT and signal transducer and activator of transcription (STAT) 3 pathways, promoting EMT, tumor cell migration, and radioresistance.[96] TGF-β is a cytokine involved in immunosuppression and the establishment of local immune tolerance,[97] in part through the upregulation of PD-L1 and the downregulation of major histocompatibility complex expression and co-stimulatory molecules.[98] Following exposure of cells to IR, TGF-β is one of the most common cytokines that is released, and that has a direct relation with radiation dose.[99] Activation of the TGF-β/SMAD pathway in the A549 LC cell line has been demonstrated in IR-induced EMT-associated invasiveness and migratory activity. Moreover, 138 kDa C2 domain-containing phosphoprotein 138 protein positively modulates the TGF-β/SMAD signaling and promotes metastasis with radiation resistance in

LC.[100] Radiation-induced inflammation stimulates the recruitment of polymorphonuclear neutrophils and neutrophil extracellular traps to TME to promote tumor metastasis and induce radioresistance.[101] On the other hand, the complement component 5a (C5a) interacts with C5a receptor (C5aR) 1 and favors macrophage polarization to a pro-tumorigenic phenotype (M2 subtype) of TAMs.[102] C5a stimulates the exhaustion of $CD8^+$ T cells as it recruits myeloid-derived suppressor cells.[103] In this regard, RT induced local activation of the complement C5a/C5aR via the AKT/nuclear factor kappa-B (NF-κB) pathway, and led to suppression of acquired antitumor immunity, resulting in the development of radioresistance in NSCLC.[104] The development of radioresistance to the cytotoxic action of RT can be induced by the interferon (IFN)/STAT1 pathway. Accordingly, in the TME, it has been proposed that RT enhances IFN expression.[105] Tumor cells exposed to radiation enhance the transcription of IFN type I through sensing pattern recognition receptors by DSBs.[106] Unphosphorylated STAT2 combines with unphosphorylated STAT1 and interferon regulatory factor 9 to create the IFN-stimulated gene factor 3 complex, a powerful regulator that sparks the expression of genes fortifying resistance to radiation-induced DNA damage, helping cancer cells survive and driving resistance to RT.[107] Finally, STAT1-dependent activation of interferon-related DNA damage resistance signature is an intrinsic mechanism by which cancer cells enhance DNA repair and alter the function of natural killer and effector T cells, making them more resistant to the genotoxic stress induced by RT.[108] Inhibition of IFN/STAT1 signaling by SAR302503, a selected Janus kinase (JAK) 2 inhibitor, reduces PD-L1 levels and radioresistant NSCLC lineages.[109] In addition, RT treatment significantly promotes expression levels of indoleamine 2,3-dioxygenase 1 in NSCLC, which is involved in immune regulation, subsequently generating regulatory T cells that suppress immune response infiltration and T cell apoptosis.[110]

The action of the TME, such as hypoxia, CAFs, and immunosuppressive signals, plays a crucial role in the formation of radioresistance. Factors such as HIF-1α, VEGF, PD-L1, and CAFs-derived cytokines modulate immune evasion and tumor survival. By targeting these TME components with anti-angiogenic agents, checkpoint inhibitors, and stromal modulators, we have a powerful opportunity to boost RT effectiveness and prevent cancer recurrence.

3.4. Tumor stem cells

Cancer stem cells (CSCs) refer to a separate group of cells found in tumors, characterized by their self-renewal, differentiating abilities, and tumorigenic potential. CSCs have roles for initiation, metastatic distribution, and relapse of tumors; they are mainly located in areas with low pH, hypoxic, and less nutrient niches.[111] In many solid tumors, including LC, CSCs are linked to the activation of checkpoint pathways, which is necessary to delay transition between cell cycle phases and DNA repair following radiation therapy (Figure 4).[112] CD133 is a transmembrane glycoprotein and is one of the markers of CSCs. In $CD133^+$ CSCs in LC cells, an increased DNA repair capacity and a high expression of genes involved in the IR response were noted.[113] The protection from oxidative and toxic stresses implies the tumor suppressor kelch-like ECH-associated protein (KEAP) 1/nuclear factor E2-related factor (NRF2) pathway. Therefore, NRF2 in CSCs reduced ROS in LSCC and increased radioresistance.[114] After mild levels of irradiation, tumor

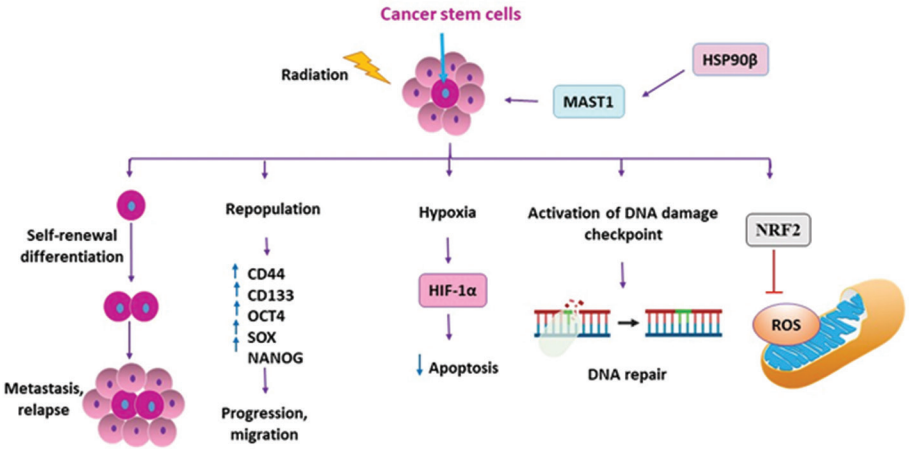

Figure 4. Mechanisms of cancer stem cells in lung cancer radioresistance. Figure created with Microsoft PowerPoint

persistence and regrowth in LC can be explained by the repopulation of tumors by radioresistant stem cells expressing several proteins, including CD44, CD133, OCT4, SOX, and NANOG, which are CSC markers.[115] SOX2 is involved in tumorigenesis and progression; it is a transcription factor particularly expressed in CSCs. The high expression level of SOX2 enhances RT-resistance by increasing levels of CSC hallmarks (CD133 and ALDH) and migration of NSCLC cells.[116] Furthermore, inhibiting the interaction between HSP90β and microtubule-associated serine/threonine kinase 1 (MAST1) promotes MAST1 degradation, reduces stem cell properties in NSCLC, and increases radiosensitivity.[117] Concerning hypoxia, it was shown that after irradiation, HIF-2 was upregulated in both stem and non-stem cell types. However, the apoptosis, death, and autophagy rates in A549 cells were much lower than in non-stem cells.[118] CSCs contribute to treatment failure and tumor regrowth after RT due to their enhanced DNA repair capacity and resistance to oxidative stress. Targeting CSCs with specific transcription factors or stress response modulators may improve therapeutic efficacy and minimize recurrence in LC patients.

3.5. Autophagy

Autophagy is a dynamic mechanism of cell metabolism that reuses damaged organelles and proteins using lysosomes.[119] Several processes can ensure autophagy-mediated radioresistance (Figure 5). Caveolin-1, a scaffolding protein of caveolae on the plasma membrane, can promote IR-resistant NSCLC cell proliferation through activating immunity-related GTPase family M protein-mediated autophagy.[120] Radioresistance in LC cells can be enhanced by autophagy through HIF-1α, which promotes the expression of BECLIN1, an important factor in initiating autophagy. Inhibition of hypoxia-induced autophagy decreased survival in LC after radiation therapy.[77] Furthermore, lactotransferrin has been shown to play a radioresistance role by activating AMPK/SP2/NEAT1/miRNA-214-5p feedback loop and activating autophagy in LSCC.[121] SHC-adaptor protein 1 gene can encode the Src homologous-collagen homolog adaptor protein, which induces ROS and autophagy to promote the survival of LC cells after irradiation. Elevated levels of AURKA kinase may facilitate autophagy and RT resistance. The cell cycle checkpoint pathways and autophagy cross-communicate for DNA repair and radioresistance.[122] Nuclear division cycle 80, a component of the kinetochore complex, enhances the expression of autophagy-related protein 7, promoting autophagy, cell proliferation, and radioresistance in LC cells.[123] Autophagy serves as a protective mechanism in irradiated LC cells, promoting survival and metabolic adaptation. Combining autophagy inhibitors with RT is a promising strategy and could help overcome the resistance of refractory tumors.

3.6. Metabolic reprogramming

Metabolic reprogramming is one of the most characteristic features of cancer, enabling tumor cells to adapt to metabolic stress and support uncontrolled proliferation.[124] In response to RT, tumor cells increase the metabolic flow

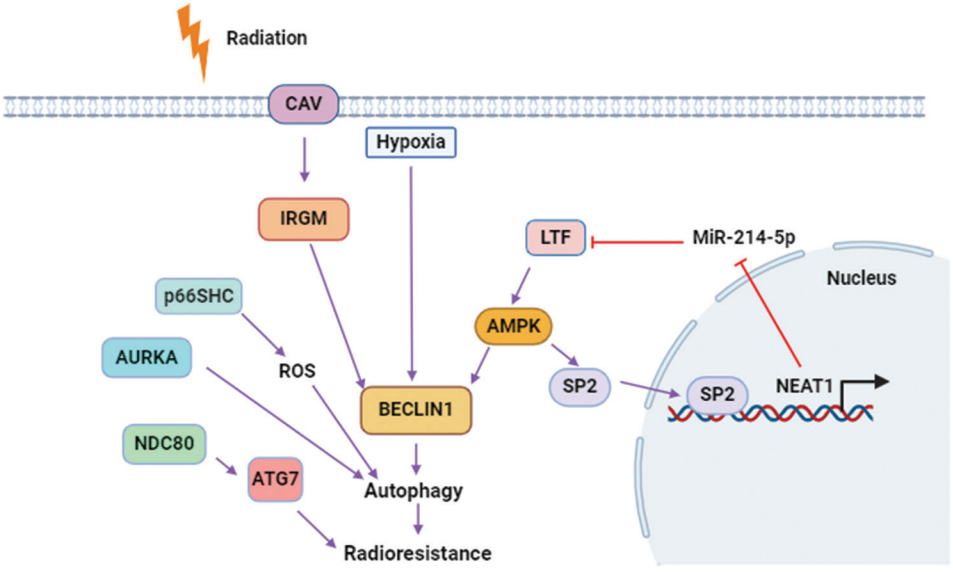

Figure 5. Autophagy in radioresistant lung cancer cells. Figure created in BioRender. Attouahri, F. (2025) https://BioRender.com/jvilb11.
Abbreviation: ROS: Reactive oxygen species.

of energy sources such as glucose, fatty acids (FAs), and amino acids to generate enough substrates and energy necessary for DNA repair (Figure 6).[125] In addition, to counter the action of ROS, cancer cells upregulate the antioxidant mechanisms.[126] Active glycolysis in an aerobic environment represents an important mechanism in metabolic reprogramming, which participates in treatment resistance and tumor relapse in several cancers.[127] Glucose in cancer cells is upregulated by glucose transporters, which convert glucose through hexokinase 2 (HK2) to glucose-6-phosphate (G-6-P), which will then be converted to pyruvate under the activation of several enzymes, including the M2 isoform of pyruvate kinase (PKM2).[128] The lactate dehydrogenase (LDHA) acts as a last resort to form lactic acid.[12] The GLUT1 gene can bind to the DNA binding site on the HIF-1α protein in a hypoxic microenvironment, which increases GLUT-1 expression.[129] A previous study showed that downregulating HIF-1α decreased GLUT-1 expression and promoted radiosensitization in LUAD.[130] PKM2 is an isoform of pyruvate kinase mainly expressed in tumor cells and ensures the conversion of phosphoenolpyruvate into pyruvate.[131] Inhibition of PKM2 expression raises the sensitivity of NSCLC cell lines and xenografts to RT by inhibiting phosphorylation of AKT and 3-phosphoinositide-dependent kinase 1 and enhancing apoptosis and autophagy.[132] The inhibition of LDHA, a key enzyme involved in glycolysis, was linked to an increase in radiosensitivity due to a decrease in the number of cells present in the S phase, which is the most resistant phase, and inhibition of the cellular signaling pathways of G1/S genome integrity checkpoints in NSCLC.[133] Lactic acid is a by-product formed by glycolysis, which showed an association with radioresistance through improving immunosuppression of the TME.[134] The combination of RT and AZD3965—an inhibitor of monocarboxylate transporter-1 and a lactate transporter—showed an increased therapeutic effect compared with RT alone in SCLC xenografts.[135] After glycolysis, G-6-P enters the pentose phosphate pathway (PPP), where ribose 5-phosphate and nicotinamide adenine dinucleotide phosphate (NADPH) represent the principal metabolites generated. On the other hand, 6-phosphogluconate dehydrogenase (6PGD) is a key enzymatic protein of the PPP, which ensures the reduction of $NADP^+$ to NADPH.[136]

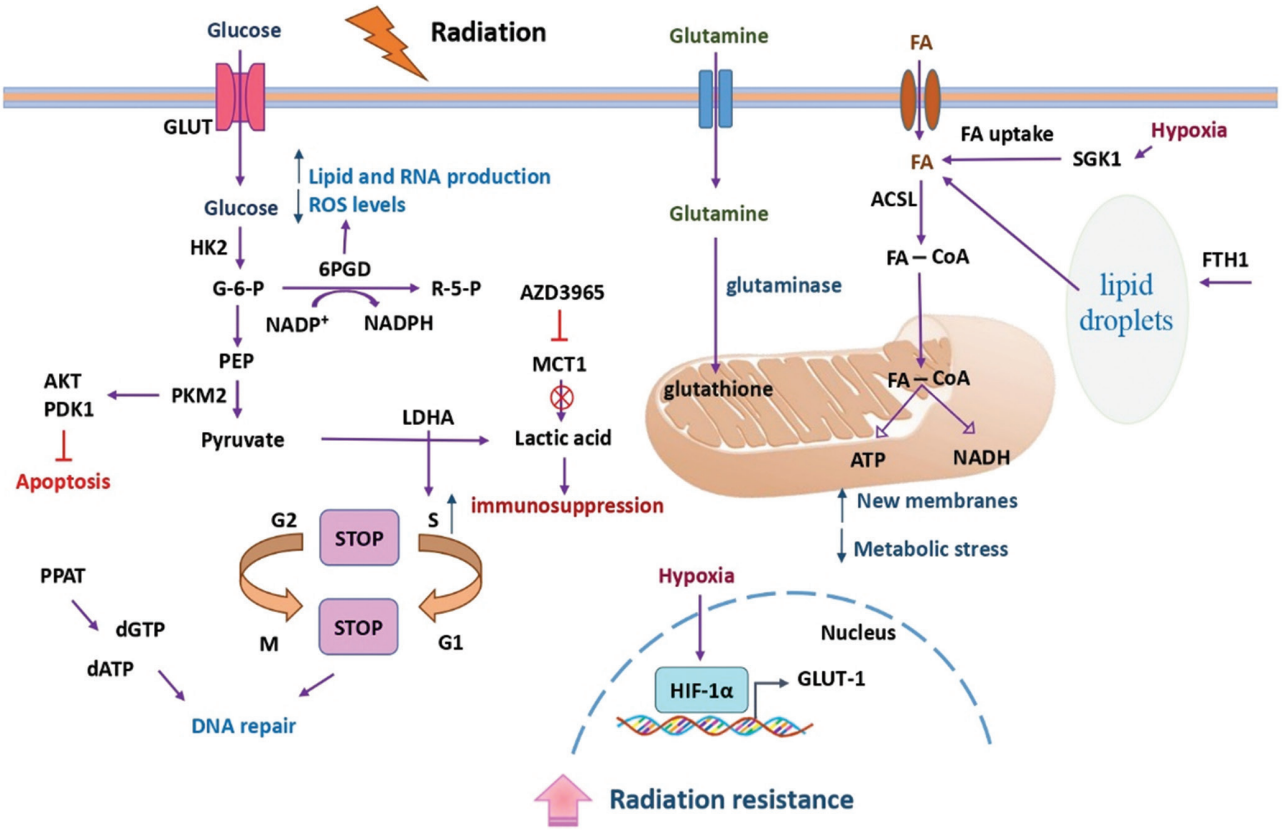

Figure 6. A schematic summary of metabolic pathways in response to radiotherapy in lung cancer. Figure created with Microsoft PowerPoint.
Abbreviation: FA: Fatty acid.

In LC cells, 6PGD activates lipid and RNA production and reduces ROS levels.[137]

Faced with stress, cells go beyond glycolysis, activating survival circuits like glutamine metabolism. This pathway is identified as a crucial ally in generating glutathione, an antioxidant that protects cells from radiation-induced oxidative stress.[138] Greater sensitivity to IR results from inhibition of glutaminase, which reduces glutathione synthesis in lung tumor cells.[139] FA metabolism supports cell survival, growth, and stress adaptation by generating ATP and nicotinamide adenine dinucleotide hydrogen (NADH) via acyl-CoA synthetase long-chain family members (ACSL). These metabolites are essential for countering oxidative stress. Moreover, FA metabolism is required for *de novo* lipid synthesis, which is essential for the formation of new membranes.[140] Glucocorticoid-inducible kinase (SGK1) is an important component for FA uptake in hypoxia and cell growth. SGK1 inhibition enhances the cytotoxicity of RT in LUAD cells.[141] To satisfy the demands of energy when glucose is insufficient, cells decompose lipids stored in lipid droplets (LDs) and then provide energy by oxidizing FAs in mitochondria.[142] Iron metabolism was largely connected to the level of LD and, particularly, with the expression of ferritin heavy chain (*FTH1*). Silencing *FTH1* increases radiosensitivity and reduces LD accumulation in LC cells.[143]

Because radioresistance implies an increased capacity for DNA repair, *de novo* nucleotide synthesis plays a crucial role and contributes to treatment resistance and tumor recurrence.[12] It has been shown that inhibition of phosphoribosyl pyrophosphate aminotransferase, which belongs to the purine/pyrimidine phosphoribosyltransferase family, allows *de novo* synthesis of purines and inhibits resistance to the effects of IR in LC cells.[144]

RT exerts its anticancer effects primarily through DNA damage and the generation of ROS. In response, tumor cells reprogram their metabolism to enhance survival, amplifying glycolysis, glutamine metabolism, and lipid oxidation to fuel DNA repair and mitigate oxidative stress. This adaptive metabolic flexibility contributes to radioresistance, presenting a major challenge in cancer therapy. However, targeting these metabolic pathways has shown promise: Inhibitors of glycolytic enzymes, glutaminase, and FA oxidation have demonstrated radiosensitizing effects, particularly in LC models. Integrating such metabolic modulators with RT represents a compelling strategy to overcome resistance, offering a new frontier for precision oncology and more effective, individualized treatment regimens.

3.7. Exosomes and non-coding RNA

Exosomes represent a class of 40 – 150 nm extracellular vesicles formed by the budding of the endosomal membrane and released upon fusion with the plasma membrane by multiple cells into the TME.[145] Exosomes have the particularity of reflecting a regulated sorting mechanism, making them representatives of their cells of origin.[146] It is marked that after RT, the number of releases of exosomes increases, mainly from cancer cells (Figure 7).[147] Exosomes are an essential environmental

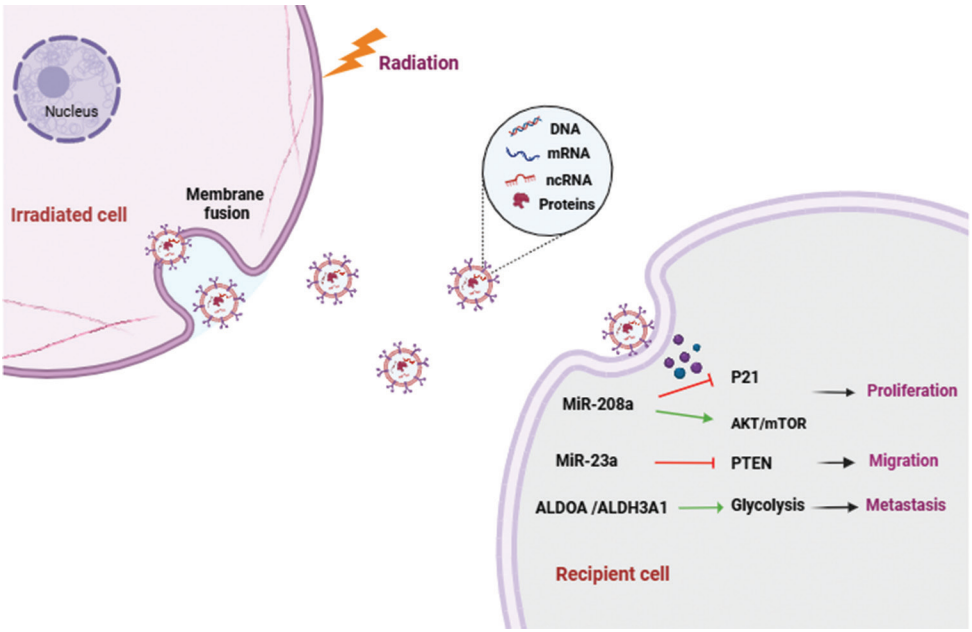

Figure 7. Roles of exosomes in regulating radioresistance in lung cancer. Figure created in BioRender. Attouahri, F. (2025) https://BioRender.com/lfc2nvk.

component in cellular stress. Their composition, abundance, and possible effect on exosome receptor cells are strongly linked to the stress suffered by the cell. Radiation can induce exosome secretion and affect cell-to-cell exchanges through exosomes.[148] miRNAs represent a group of short non-coding RNAs ranging in size from 21 to 25 nucleotides that downregulate gene expression by targeting specific mRNAs. They can influence the response to radiation.[149] Indeed, it is becoming increasingly clear that this response involves altering exosomal miRNA profiles, whose expression can be altered under the stress conditions induced by RT.[150] Interactions with survival and apoptosis pathways mediated by exosomal non-coding RNAs represent the key mechanism of exosome-induced radioresistance. In a previous study, the proliferation and IR resistance in LC were linked to radiation-induced exosomal miRNA-208a, which targets P21 and AKT/mechanistic target of rapamycin pathway.[151] It has been demonstrated that the proangiogenic effect of exosomes was improved by exposure of A549 and H1299 culture lines to RT. This is explained by the release of miRNA-23a by these exosomes, which increases cell proliferation and migration through downregulation of phosphatase and tensin homolog.[152] Upon irradiation, A549 LC cells release exosomes enriched in metabolic enzymes, such as aldolase A and aldehyde dehydrogenase 3A1, which, when transferred to recipient cells, promote motility and metastasis by enhancing glycolysis.[153]

miRNAs interfere with DDR components and influence IR-induced DNA damage sensing or repair (Figure 8). In this context, miRNA-328-3p increases H2AX and DSBs and promotes radiosensitization.[154] Knockout of miRNA-1323 prevents DNA-PKcs recruitment and inhibits DDR in LC cells.[155] On the other hand, miRNA-30a acts by reducing activating transcription factor 1, thus decreasing phosphorylation of ATM kinase, which induces radiosensitivity in LC.[156] Reducing miRNA-16-5p expression promotes WEE1 expression, a key enzyme of DDR, and prevents radiation-induced apoptosis in LC cells.[157] The miRNA-16 family prevents cells from entering the S phase by repressing cyclin D1. MiRNA-16 can also silence several genes linked to the cell cycle, such as *CDK6, CCND3*, and *CCNE1*, to trigger G1 arrest.[158] MiRNA-25 overexpression alters B-cell translocation gene 2, which is an antiproliferative factor in the P53 apoptotic pathway, and protects H226 NSCLC cells from apoptosis induced by IR.[159] Reducing miRNA-95 expression promotes apoptosis and decreases tumor cell proliferation, thereby increasing the radiosensitivity of NSCLC.[160] In addition, miRNAs have been shown to modulate the radioresistance of LC by CSCs. Lung CSCs characterized by ALDH1$^+$ and CD133$^+$ markers exhibit elevated miRNA-21 and miRNA-

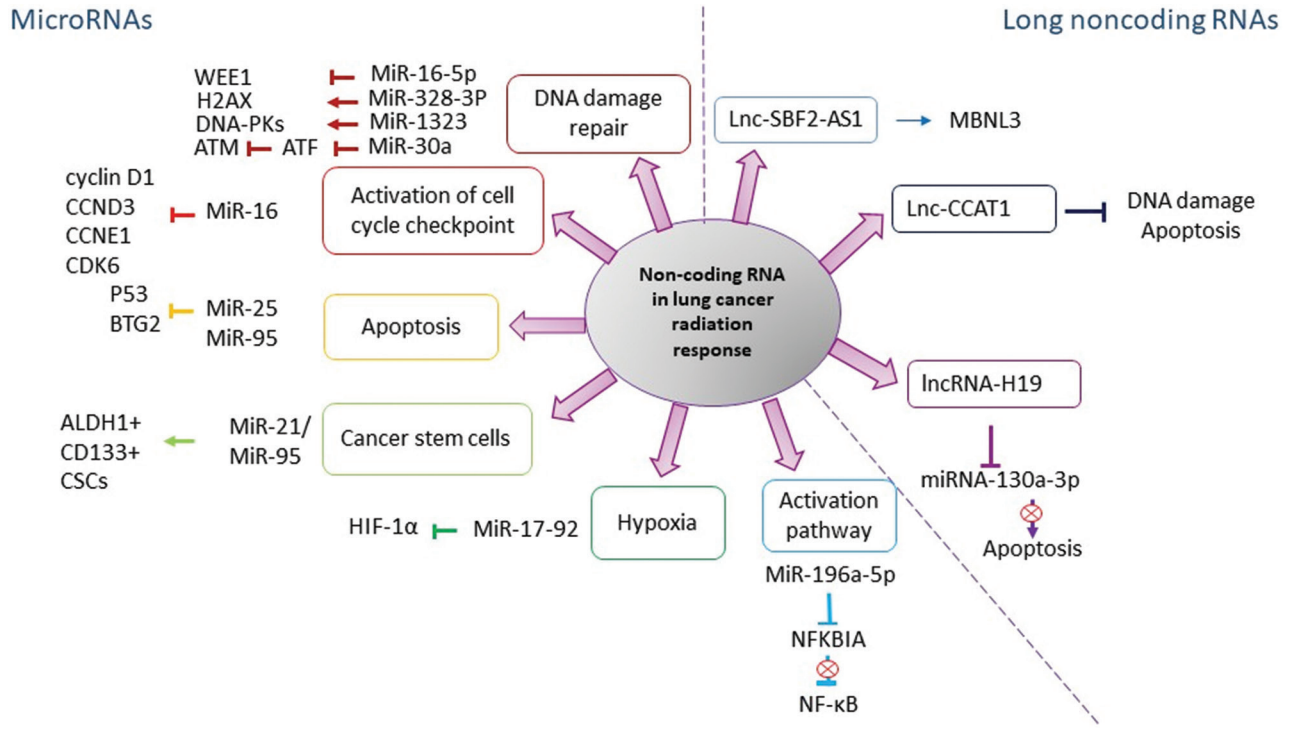

Figure 8. Radiation-induced changes in signaling pathways related to non-coding ribonucleic acid in lung cancer. Figure created with Microsoft PowerPoint.

95 expression, contributing to increased radioresistance.[161] Downregulation of miRNA-17-92 leads to overexpression of HIF-1α after exposure to irradiation.[162] MiRNA-196a-5p can activate the NF-κB pathway to increase the radioresistance of LC cells through inhibition of the expression of NF-κB inhibitor alpha.[163]

Long non-coding RNAs (lncRNAs) represent a group of non-coding RNAs with a length >200 nucleotides but without significant ability to encode proteins. They play important roles in controlling several biological functions, such as cell growth, carcinogenesis, immune response, and apoptosis.[164] LncRNAs affect the function of miRNAs and their targets, since they exert sponge-like effects on miRNAs.[165] LncRNAs have been reported as participants in radioresistance (Figure 8). Downregulation of lncRNA SBF2 antisense RNA 1 can enhance the sensitivity of RT of NSCLC by downregulating muscleblind-like 3.[166] Inhibition of lncRNA colon cancer-associated transcript 1 promotes radiation sensitivity in NSCLC by regulating the cell cycle, aggravating DNA damage, and inducing cell death, which may relate to the mitogen-activated protein kinases (MAPK) pathway.[167] LncRNA H19 can inhibit apoptosis by acting on miRNA-130a-3p, increasing radioresistance in NSCLC cells (A549-R11) compared with A549 cells.[168]

Exosomes and non-coding RNAs, including miRNAs and lncRNAs, are emerging as key mediators of radioresistance in LC due to their role in DNA repair, apoptosis regulation, metabolic reprogramming, and maintenance of stemness. Their potential to be secreted into the TME and to modulate surrounding cells makes them attractive targets for non-invasive biomarkers of therapy response. In clinical terms, targeting exosome biogenesis, specific miRNAs associated with radioresistance or lncRNAs, represents a promising avenue for overcoming resistance and improving the efficacy of RT. This expanding knowledge base opens the door to RNA-based therapeutics, such as inhibitors or mimics that can be integrated into precision RT protocols, ushering in a new era of personalized cancer treatment.

3.8. Ferroptosis

The iron-dependent cell death process, or ferroptosis, is an intracellular pathway with characteristics of loss of lipid peroxide repair due to blockage of glutathione peroxidase 4 (GPX4).[169] GPX4 inhibits ferroptosis by attenuating lipid peroxidation as it reduces glutathione and converts lipid hydroperoxides to lipid alcohols.[170] Tumor development and radiation response require a high amount of free iron and the oxidation capacity of polyunsaturated FA-containing phospholipids.[169] Ferroptosis is a cellular mechanism induced by radiation in apoptosis-resistant cells, either alone or in combination with apoptosis, offering great potential for killing tumor cells.[75] IR produces hydroxyl radicals (-OH), highly reactive oxidants responsible for phospholipid peroxidation. Therefore, IR can regulate iron metabolism.[171] Accumulation of labile iron leads to damaging reactions in the cell, resulting in oxidation and glycation of proteins and DNA breaks. If left unrepaired, accumulation of toxic lipid peroxides can damage cell membrane structure, leading to cell death by ferroptosis.[172] Hypoxia has been demonstrated to be a mechanism that protects against the ferroptosis pathway.[173] The exosomes derived from hypoxic NSCLC cells containing angiopoietin-like 4 could transmit radioresistance to surrounding normoxic NSCLC cells, inducing upregulation of GPX4 in the recipients and radioresistance.[174] Depletion of acyl-CoA synthetase long-chain family member 4, a lipid metabolism enzyme needed for ferroptosis, promotes radioresistance by eliminating ferroptosis induced by IR.[175] The radiosensitivity of NSCLC has been improved by erastin, a small molecule capable of triggering ferroptosis.[176] Radiation combined with GPX4 inhibition can block ferroptosis and reverse RT resistance in radioresistant NSCLC cells.[177] Hemin, a source of intracellular iron, can induce GPX4 degradation, thus stimulating ferroptosis and the radiosensitivity of LC cells.[178] Ferroptosis is a vital mechanism to bypass radioresistance in apoptosis-resistant LC cells. Clinically, combining RT with ferroptosis inducers offers a promising strategy to sensitize tumors that are otherwise refractory to treatment. By specifically targeting the ferroptotic pathways, this approach could revolutionize RT efficacy, particularly in NSCLC, and pave the way for innovative therapeutic protocols aimed at overcoming treatment resistance.

3.9. EMT

EMT is a hallmark of healthy tissue growth. Initiation of the EMT process involves several signaling pathways, including the WNT/β-catenin pathway.[179] The biological process during EMT involves changing cell morphology from epithelial morphology, with loss of E-cadherin, and the acquisition of mesenchymal morphology, such as N-cadherin, vimentin, and fibronectin.[180] The EMT process enables cells with epithelial morphology to lose apical-basal polarity and cell contacts and then acquire migratory properties.[181] It has been demonstrated that radiation resistance is closely related to EMT-mediated tumor metastasis.[182] RAS-related C3 botulinum toxin substrate 1, which belongs to the Rho GTPase family, can enhance radioresistance by promoting EMT in LC (Figure 9).[183] JAK2 belongs to the Janus family of kinases, which activate STAT signaling and are involved in the

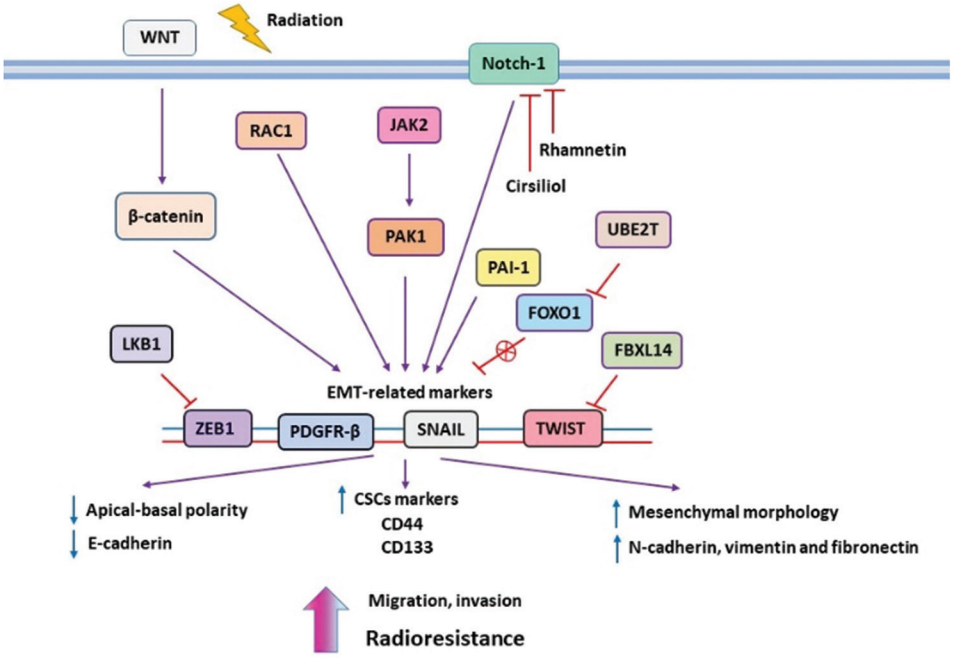

Figure 9. Epithelial-to-mesenchymal transition in lung cancer radioresistance. Figure created with Microsoft PowerPoint.
Abbreviations: CSCs: Cancer stem cells; EMT: Epithelial-to-mesenchymal transition.

modulation of gene expression that can promote pathways related to tumor progression, including angiogenesis, metastasis development, and immune evasion processes.[184] In LC cells, JAK2 promotes EMT and radioresistance by phosphorylation and stabilization of p21-activated Ser/Thr kinase 1 (PAK1).[185] Rhamnetin and cirsiliol block the Notch-1 pathway, reducing resistance to RT and reversing EMT aspects in NSCLC cells.[186] Temporary lowering of zinc-finger E-box-binding homeobox factor (ZEB) 2, an EMT-related marker, leads to reversal of EMT and radioresistance in SCLCs.[187] Plasminogen activator inhibitor-1 can increase the expression of EMT-related proteins *in vitro* and *in vivo*, as well as cell migration capability, reducing radiosensitivity in NSCLC cells.[188] Liver kinase B1 (LKB1), which has a tumor suppressor function, can suppress EMT and metastases by repressing ZEB1, ensuring sensitization of NSCLC cells to RT.[189] In addition, under EMT, epithelial tumor cells can develop CSC characteristics. A previous study showed that after the application of radiation, the cells presented a characteristic appearance with the presence of both CSC and EMT phenotypes, displaying markers linked to these processes, including CD44, Snail family zinc finger 1/2 (SNAIL), and platelet-derived growth factor receptor-β.[190] Ubiquitin-conjugating enzyme E2T (UBE2T) enhances radiation resistance in NSCLC by inducing EMT through ubiquitination-mediated forkhead transcription factor (FOXO) 1 degradation, which belongs to the FOXO family, and inhibits EMT.[191] In a previous study, irradiation of A549 cells improved migration and invasion capacity, with increased expression levels of phenotypic mesenchymal markers (N-cadherin, SNAIL, Vimentin, and twist-related protein [TWIST]) and CSCs markers (CD44 and CD133), and decreased expression of the epithelial marker.[192] TWIST1 expression enhanced radioresistance in NSCLC, but the addition of F-Box protein and leucine-rich repeat protein 14 (FBXL14) rendered treated cells radiosensitive, as it destabilized TWIST1.[193] The EMT process reinforces the invasive and radioresistant phenotype of LC cells, often along with cancer stemness. Targeting EMT-associated signaling pathways offers a dual advantage, hindering metastatic spread while simultaneously resensitizing tumors to IR. This dual therapeutic effect positions EMT inhibition as a promising strategy to enhance RT outcomes and improve patient prognosis.

3.10. Gene mutational status

Scientific evidence has clearly shown that some point mutations alter protein structure and/or function, ultimately disrupting corresponding signaling pathways. These disruptions can lead to cancer development, including LC progression and metastasis, making such mutations the best targets for personalized medicine (Figure 10).

Epidermal growth factor receptor (EGFR) is involved in the activation of the PI3K/AKT and MAPK pathways,

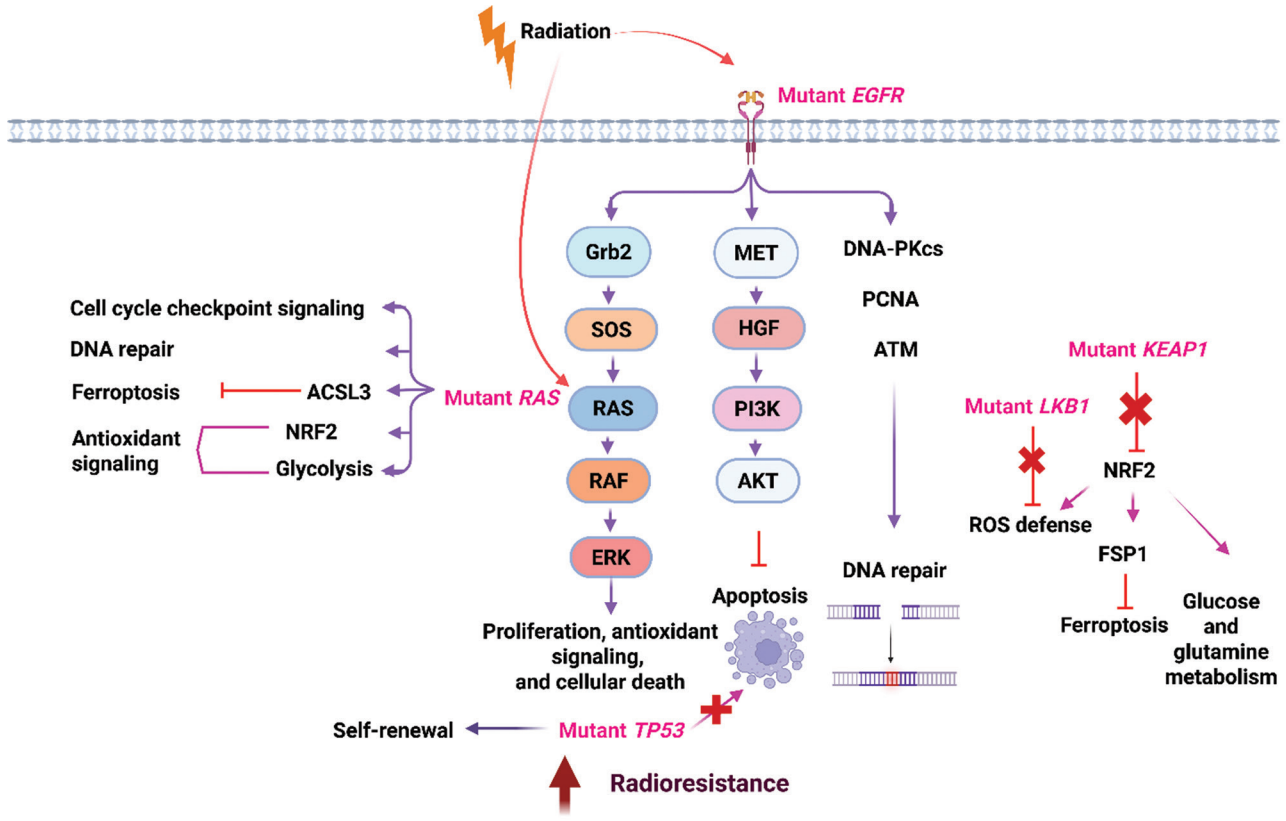

Figure 10. Roles of oncogene or tumor suppressor gene mutations in lung cancer radioresistance. Image created by the authors. Figure created in BioRender. Attouahri, F. (2025) https://BioRender.com/9fibjb1.
Abbreviation: ROS: Reactive oxygen species.

making it among the many commonly mutated motor genes implicated in the development of LC.[194] EGFR has been widely known as a contributor to NSCLC radioresistance.[195] EGFR-mediated radioresistance is linked to the activation of downstream pathways involved in proliferation and protection against radiation-induced death, notably the MAPK signal transduction pathway.[196] Besides, EGFR can stimulate DSB repair after irradiation through interaction with DNA-PKcs, PCNA, and ATM.[197] In addition, it can contribute to radioresistance by activating the mesenchymal–epithelial transition/hepatocyte growth factor axis, which is required to inhibit apoptosis by upregulation of the PI3K/AKT signaling pathway.[198]

The Kirsten rat sarcoma viral oncogene homolog (*KRAS)* gene codes for a GTPase required in the process of propagating cell signaling from the membrane to the nucleus.[199] Point mutations in this gene, especially in codons 12 and 13, provide oncogenic activity to the KRAS protein through constitutive activation, which explains why patients with LUAD who have *KRAS* mutations make up approximately 20 – 30% of all patients, who in most cases have a poor prognosis and lack of response to agents administered to target EGFR.[200] Cellular and clinical resistance to RT has been largely related to the presence of mutations in the *KRAS* gene.[201] Bioinformatics studies have shown that *KRAS* mutation can activate several pathways, including the ERK1/2 pathway, MAPK pathway, EGFR/PKC/AKT pathway, and cell cycle checkpoint signaling and repair pathways, to promote radioresistance in NSCLC.[202] *KRAS*-mutant LC routinely overexpresses ACSL3 to prevent ferroptosis in cells.[203] Furthermore, mutations in the *KRAS* gene lead to upregulation of the *NRF2* gene and increased glycolysis, enabling increased production of NADH and glutathione to regulate redox homeostasis in NSCLC.[204]

Tumor suppressor KEAP1 acts as a substrate adaptor to target NRF2 in the KEAP1-Cullin-3 ubiquitin ligase complex for proteasomal degradation.[205] *KEAP1* mutations in LC patients are known to correlate with an unfavorable prognosis, a short lifespan, and the presence of resistance to the majority of therapeutic procedures.[206] KEAP1 loss can enhance free radical scavenging to decrease DNA damage, leading to radioprotection.[207] Approximately 20%

Table 1. Key pathways and therapeutic targets involved in lung cancer radioresistance

Pathways/ mechanisms	Biological role in radioresistance	Key molecules	Therapeutic target/strategy	References
DNA repair	DNA repair mechanisms improve detection and repair of radiation-induced DNA damage (SSB and DSB), enabling cancer cells to survive after RT through activation of the HR and NHEJ pathways, contributing to resistance	SSB Repair: PARP, XRCC1, PCNA, FEN1, LIG1, ATR, CHK1, WEE1, DDB2, and ERK5 HR: ATM, CHK2, RAD51, BRCA2, MRE11-RAD50-NBS1 complex, CtIP, H2AX, SIRT3, KDM4C, USP39, and IQGAP1 NHEJ: Ku70/Ku80, DNA-PKcs, Artemis, LIG4, PKP2, USP7, β-catenin, and cancer-IgG	PARP inhibitors, ATM/ATR/ CHK1/CHK2 inhibitors, RAD51 inhibitors, DNA-PKcs inhibitors, WEE1 inhibitors, and β-catenin modulators	25-53
Apoptosis regulation	Tumor cells escape radiation-induced cell death by overexpressing anti-apoptotic proteins (e.g., BCL-2, BCL-XL), losing pro-apoptotic signals (e.g., TP53), or disrupting caspase activation. This promotes survival after RT and contributes to resistance	BCL-2, BCL-XL, TP53, PDRG1, FLIP, procaspase-8, Gelsolin, Caspase-3, and PARP	BCL-2 inhibitors, p53 activators, FLIP modulators, and Caspase activators	57-68
Tumor microenvironment	TME contributes to radioresistance through chronic hypoxia, stromal remodeling, and immune evasion. Hypoxia reduces ROS-induced DNA damage and enhances HIF-1α/VEGF signaling, promoting angiogenesis and survival. CAFs secrete growth factors, promoting EMT, autophagy, and irradiated cell survival. Immune cells, including TAMs and MDSCs, promote immune suppression through signaling pathways such as IFN/STAT1 and TGF-β. Irradiation induces these responses, facilitating immune escape, angiogenesis, and resistance	HIF-1α, VEGF, HSP90, SDF-1α, CXCR4, MMP-2/9, CAFs, IGFBPs, bFGF, TGF-β, ILs, PD-L1, STAT1/2/3, IFNs, IRDS, CDP138, C5a/C5aR1, MDSCs, IDO1, IRF9, and U-ISGF3	HIF-1α/VEGF inhibitors, HSP90 inhibitors, anti-PD-L1/ PD-1 therapy, TGF-β blockers, STAT1/IFN/JAK inhibitors, CAF-modulating agents, and IDO1 inhibitors	77-110
Cancer stem cells	CSCs possess enhanced DNA repair capacity and resistance to oxidative stress. CSCs survive IR thanks to checkpoint activation and antioxidant defenses (e.g., KEAP1/ NRF2). They promote tumor repopulation after IR	CD133, CD44, ALDH, SOX2, OCT4, NANOG, KEAP1, NRF2, HIF-2α, HSP90β, and MAST1	CSC-targeting agents, SOX2/ NRF2 inhibitors, and HSP90β blockers	112-118
Autophagy	Autophagy promotes the survival of irradiated LC cells by degrading damaged components and supporting DNA repair	CAV1, IRGM, BECLIN1, ATG7, LTF, AMPK, SHC1/p66SHC, AURKA, and NDC80	Autophagy inhibitors, AMPK pathway modulators, and ATG7 blockers	120-123
Metabolism	Tumor cells adapt their metabolism after irradiation to promote DNA repair and counteract oxidative stress. Adaptations in glycolysis, PPP, glutamine, fatty acids, and iron metabolism, as well as *de novo* nucleotide synthesis, resulting in enhanced survival and reduced ROS-induced damage	GLUT-1, HK2, PKM2, LDHA, MCT1, 6PGD, NADPH, G6P, R-5-P, Glutaminase, SGK1, ACSL1 – 5, FTH1, and PPAT	Inhibitors of PKM2, LDHA, SGK1, 6PGD, glutaminase, and HIF-1α inhibition	128-144
Epithelial-to-mesenchymal transition	EMT confers invasive and migratory properties to epithelial cells, promoting metastasis and resistance to RT. Loss of E-cadherin and upregulation of mesenchymal markers (N-cadherin, vimentin) correlate with poor response. EMT may also induce CSC-like traits that reinforce radioresistance	E-cadherin, N-cadherin, Vimentin, Fibronectin, ZEB1/2, TWIST1, SNAIL, RAC1, JAK2, PAK1, FOXO1, UBE2T, Notch-1, CD44, CD133, PDGFR-β, PAI-1, FBXL14, and LKB1	EMT inhibitors (e.g., Notch blockers, JAK2 inhibitors), FOXO1 stabilizers, TWIST1 destabilizers, and LKB1 activation	183-193

(Cont'd...)

Table 1. ***(Continued)***

Pathways/ mechanisms	Biological role in radioresistance	Key molecules	Therapeutic target/strategy	References
Gene mutations	Mutations in key oncogenes and tumor suppressor genes (e.g., EGFR, KRAS, KEAP1, andTP53) alter DNA repair, redox balance, and survival pathways. EGFR promotes DSB repair and activates PI3K/AKT and MAPK pathways. KRAS activates multiple survival and repair mechanisms. KEAP1/NRF2 mutations enhance antioxidant responses, decrease ROS-induced damage, and impair ferroptosis. TP53 loss promotes stemness and impairs apoptosis. These mutations collectively drive RT resistance in lung cancer	EGFR, KRAS, KEAP1, NRF2, TP53, and LKB1	EGFR/KRAS inhibitors, NRF2 pathway blockers, ferroptosis inducers (e.g., FSP1-CoQ inhibitors), and TP53 reactivators	197-211

Abbreviations: Cafs: Cancer-Associated Fibroblasts; Cscs: Cancer Stem Cells; DSB: Double-Strand Break; EMT: Epithelial-To-Mesenchymal Transition; IR: Ionizing Radiation; LC: Lung Cancer; Mdscs: Myeloid-Derived Suppressor Cells; ROS: Reactive Oxygen Species; RT: Radiotherapy; SSB: Single-Strand Break; Tams: Tumor-Associated Macrophages; TME: Tumor Microenvironment; PARP: Poly ADP-Ribose Polymerase; ATR: Ataxia Telangiectasia And Rad3-Related Protein; CHK1: Checkpoint Kinase 1; HR: Homologous Recombination; NHEJ: Non-Homologous End-Joining; PCNA: Proliferating Cell Nuclear Antigen; ERK: Extracellular Signal-Regulated Kinase; MRE11: Meiotic Recombination Complex 11; RAD: DNA Repair Protein; NBS1: Nijmegen Breakage Syndrome 1 Protein, ATM: Ataxia Telangiectasia Mutated; Ctip: C-Terminal Binding Protein-Interacting; BRCA2: Breast Cancer-Associated Protein 2; H2AX: H2A Histone Family Member X; CHK2: Checkpoint Kinase 2; TGF-B: Transforming Growth Factor-B; USP: Ubiquitin-Specific Peptidase; DNA-Pkcs: DNA-Dependent Protein Kinase Catalytic Subunit; PKP2: Plakophilin 2; Cancer-Igg: Cancer-Derived Immunoglobulin G; PI3K: Phosphoinositide 3-Kinase; AKT: Protein Kinase B; VEGF: Vascular Endothelial Growth Factor; HIF: Hypoxia-Inducible Factor; HSP90: Heat Shock Protein 90; CXCR4: C-X-C Chemokine Receptor Type 4; MMP: Matrix Metalloproteinase; PD-L1: Programmed Cell Death Protein 1; STAT: Signal Transducer And Activator Of Transcription; CDP138: C2 Domain-Containing Phosphoprotein; IFN: Interferon; JAK: Janus Kinase; KEAP: Kelch-Like ECH-Associated Protein; NRF2: Nuclear Factor E2-Related Factor; MAST1: Microtubule-Associated Serine/Threonine Kinase 1; HK2: Hexokinase 2; LDHA: Lactate Dehydrogenase; PPP: Pentose Phosphate Pathway; G6P: Glucose-6-phosphate; NADPH: Nicotinamide adenine dinucleotide phosphate; 6PGD: 6-phosphogluconate dehydrogenase; ACSL: Acyl-CoA synthetase long-chain family members; FTH: Ferritin heavy chain; MAPK: Mitogen-activated protein kinases; ZEB: Zinc-finger E-box-binding homeobox factor; PAI-1: Plasminogen activator inhibitor-1; LKB1: Liver kinase B1; EGFR: Epidermal growth factor receptor; FSP1: Ferroptosis suppressor protein 1.

of NSCLCs have mutations in *KEAP1* or *NRF2*. KEAP1 can trigger and destroy the NRF2 transcription factor, which drives the expression of the ROS defense genes to induce an antioxidant effect and radioresistance.[208] Moreover, LKB1 loss is linked to the KEAP1/NRF2 pathway and can promote resistance to radiation-induced intracellular ROS generation.[209] Ferroptosis suppressor protein 1 (FSP1) is an NRF2 transcription factor target; pharmacological inhibition of the ubiquinone (CoQ)-FSP1 pathway ensures induction of ferroptosis, and subsequently enables RT sensitization of KEAP1-deficient LC cells or patient-derived xenograft tumors.[210] NRF2 is also associated with the redirection of glucose and glutamine toward the synthesis of glutathione, serine, and nucleotides of the purine type.[211] Inactivating mutations in *TP53* increase self-renewal, proliferation, and radioresistance in LSCC-mutated stem cells.[114]

Somatic mutations in key genes such as *EGFR*, *KRAS*, *KEAP1*, and *TP53* alter essential DNA repair and signaling pathways, thereby promoting radioresistance. By stratifying patients based on their mutational landscape, clinicians can tailor targeted therapies combined with RT for more effective treatment. Integrating tyrosine kinase inhibitors, ferroptosis inducers, or redox modulators with RT holds significant potential to overcome resistance and enhance therapeutic responses in mutation-defined patient subgroups, advancing precision oncology in LC care.

In summary, Table 1 outlines the key molecular pathways contributing to radioresistance in LC, including DNA repair, apoptosis evasion, metabolic reprogramming, EMT, cancer stem cells, autophagy, gene mutations, and TME. These pathways involve key molecules that boost tumor survival and reduce the efficacy of RT. Targeting these mechanisms may offer promising strategies for overcoming resistance and improving therapeutic outcomes.

4. Conclusion

Resistance to RT remains a major issue in the treatment of LC, with a significant impact on therapeutic outcomes. Although many molecular mechanisms contributing to radioresistance have been identified, including DNA repair, altered cell survival and death mechanisms, cancer stem cell-mediated resistance, alterations in intracellular signaling pathways, and the influence of the TME, overall

understanding remains incomplete due to the complexity and heterogeneity of lung tumors. To break through this therapeutic barrier, it is imperative to unravel the complex signaling networks that enable resistant cancer cells to survive, adapt, and proliferate. Only through such insight can we pave the way for next-generation interventions capable of overcoming radioresistance and improving survival for LC patients. Future research efforts should focus on elucidating the key processes involved in radioresistance and identifying new targets for intervention. Combining RT with radiosensitizing agents offers a promising strategy. However, a deeper understanding of their synergistic interactions is essential to maximize efficacy.

Also, integrating high-throughput OMICS technologies, including genomics, proteomics, transcriptomics, and metabolomics, opens a transformative window to identify predictive biomarkers, map tumor heterogeneity, and craft precision radiosensitization strategies tailored to each patient. Ultimately, by advancing our knowledge through these multidimensional approaches, we can move toward precision oncology and effective treatments that transcend current limitations and significantly improve outcomes for patients battling LC.

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Conflict of interest

The authors declare they have no competing interests.

Author contributions

Conceptualization: Mouna Ababou, Khaoula Errafii, Mohammed El Mzibri

Visualization: Boutaina Addoum, Leila Benbacer, Samira Mimount, Bouchra El Mchichi, Abdelhamid Barakat, Hanane El Ouazzani, Ismail Rhorfi, Ahmed Abid

Writing – original draft: Fatima Zohra Attouahri

Writing – review & editing: Khalid Ennibi, Khaoula Errafii, Mohammed El Mzibri

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