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Epithelial–mesenchymal transition to Mitigate Age-Related Progression in Lung Cancer

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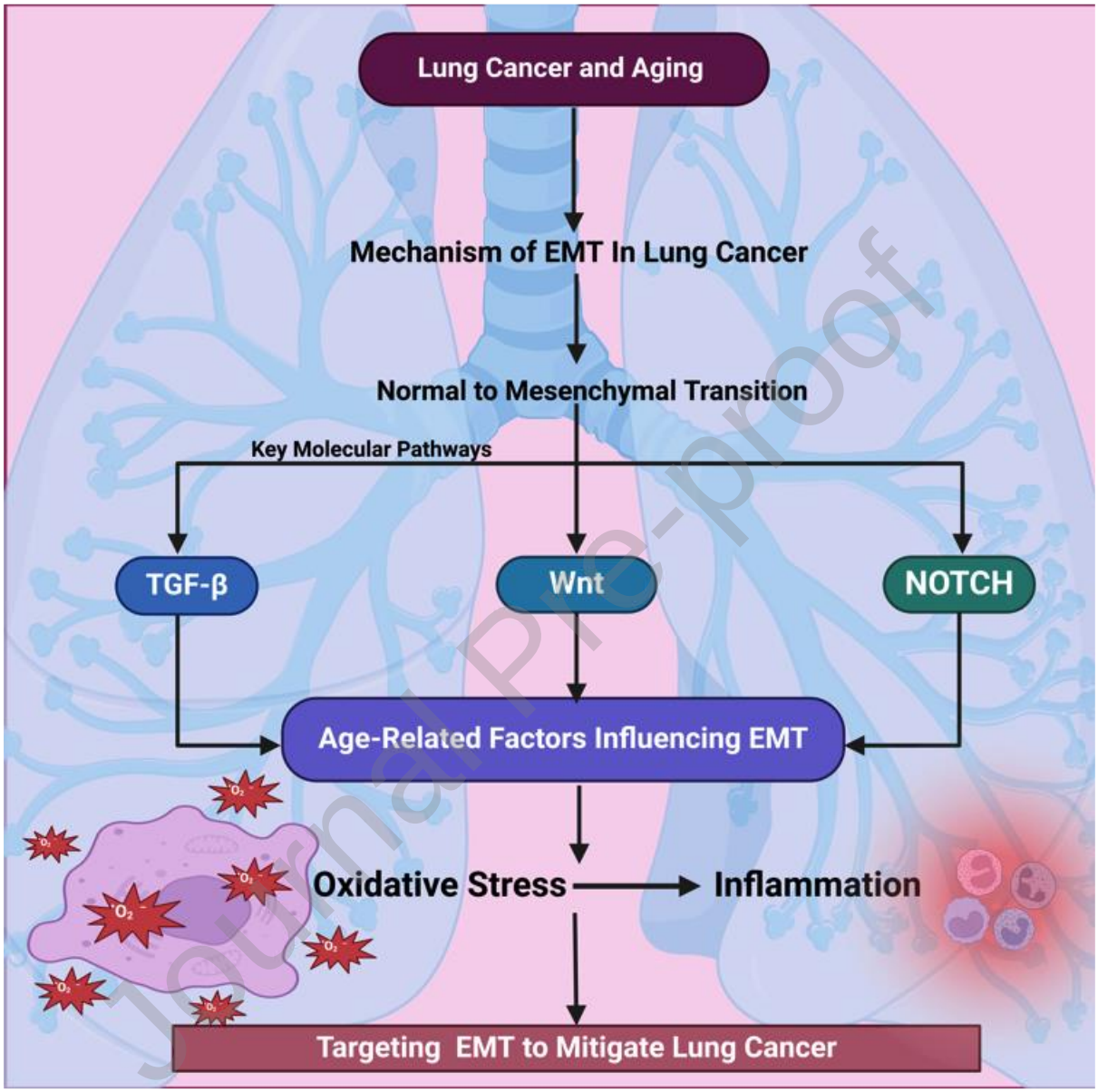
ABSTRACT

Epithelial–Mesenchymal Transition (EMT) is a fundamental biological process involved in embryonic development, wound healing, and cancer progression. In lung cancer, EMT is a key regulator of invasion and metastasis, significantly contributing to the fatal progression of the disease. Age-related factors such as cellular senescence, chronic inflammation, and epigenetic alterations exacerbate EMT, accelerating lung cancer development in the elderly. This review describes the complex mechanism among EMT and age-related pathways, highlighting key regulators such as TGF-β, WNT/β-catenin, NOTCH, and Hedgehog signalling. We also discuss the mechanisms by which oxidative stress, mediated through pathways involving NRF2 and ROS, telomere attrition, regulated by telomerase activity and shelterin complex, and immune system dysregulation, driven by alterations in cytokine profiles and immune cell senescence, upregulate or downregulate EMT induction. Additionally, we highlighted pathways of transcription such as SNAIL, TWIST, ZEB, SIRT1, TP53, NF-κB, and miRNAs regulating these processes. Understanding these mechanisms, we highlight potential therapeutic interventions targeting these critical molecules and pathways.

Keywords: EMT, cancer, lung cancer, oxidative stress, telomere attrition, cellular senescence, TGF-β, WNT, and NOTCH

GRAPHICAL ABSTRACT



1. INTRODUCTION

1.1. Lung Cancer and its Implications in the Elderly Population

Lung cancer is the leading cause of cancer-related deaths worldwide, affecting the elderly population at a significantly high rate [1]. With advancing age, people have ever-increasing cumulative exposure to tobacco smoke, environmental pollutants, and work-related carcinogens, all of which elevate the risk of lung cancer [2]. Old age is also related to inefficient DNA repair and immune surveillance mechanisms, which contribute to an elevated risk of cancer in older adults [3]. Importantly, comorbidities frequently detected in the elderly, such as chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, might exert profound and negative influences on lung cancer diagnosis and treatment, respectively [4]. This is partly explained by the lower use of screening strategies, such as low-dose computed tomography (LDCT), in elderly patients with the possibility that screening may be hesitant due to comorbid conditions as well as concerns about the side effects of potential treatments [5, 6]. Since late diagnosis significantly affects the prognosis of lung cancer, the survival rates are consequently low. This is because, at the time of diagnosis, lung cancer is often already in an advanced stage, making treatment and management more challenging [7]. Elderly patients might also be relatively intolerant to aggressive treatments, including chemotherapy, radiotherapy, and surgical interventions, making it essential to weigh treatment benefits with the quality of life [8, 9]. Treatment outcomes in the elderly lung cancer population can be improved by physicians considering the unique physiological and psychological needs of this patient age group [10, 11]. This comprises a multidisciplinary approach that includes the assessment of foundation benefits, individualized treatment plans, and procedural care for refined treatment of lung cancer in this particular population [12, 13]. To enhance the survival

rate and quality of life of older adults with lung cancer, there is a need for age-targeted therapeutic approaches and interventions [14].

1.2 Epithelial–Mesenchymal Transition (EMT) and its Role in Cancer Progression

Epithelial–Mesenchymal Transition (EMT) is a key biological event in tumor development where epithelial-cells converted into a mesenchymal-like state. This transition leads to cancer cells becoming more migratory, invasive, and metastatic [15]. Tumor EMT is regulated by a complex network involving various signaling pathways, including WNT, TGF-β, and NOTCH, which collectively downregulate epithelial-specific genes and upregulate mesenchymal genes [16, 17]. In cancer, EMT enables tumor cells to acquire stem cell-like properties, apoptosis resistance, and degradation of the extracellular matrix, which is useful for local dissemination and colony seeding at secondary sites during metastasis [18, 19]. In addition, EMT contributes to resistance to therapies, reducing the effectiveness of standard treatments such as chemotherapy and targeted therapies [20]. One of the reasons for this resistance is the fact that cancer cells are very plastic and can alter between epithelial and mesenchymal (E/M) states, depending on the microenvironmental stresses [21, 22]. Thus, a comprehensive understanding of EMT and its role in cancer progression is essential for developing new therapeutic strategies to inhibit or reverse this process. Therefore, novel therapeutics agents targeting EMT-associated pathways and factors may reduce proliferation, progression, metastasis and drug resistance, eventually could lead to improved outcome in the patients [23].

1.3 Age-Related Factors and their Impact on EMT

Aging is associated with numerous biological events that affect the EMT process in cancer [24]. Cellular senescence is a key age-related factor that influences epithelial-to-mesenchymal transition (EMT). It is linked to a senescent phenotype that produces a variety of pro-

inflammatory cytokines, chemokines, and growth factors, collectively referred as senescence-associated secretory phenotype (SASP) [25, 26]. By forming a senescent microenvironment characterized by a chronic inflammatory response that represents a key feature of SASP, these SASP factors may activate a feedforward loop to further drive EMT and consequently, tumor progression and metastasis [27, 28]. EMT is also dependent on immunosenescence, and reduced functioning of the immune system that occurs with age [29]. This reduction in immune surveillance impairs the immune system's ability to kill nascent cancer cells, allowing EMT-activated cancer cells to persist and spread [30, 31]. As individuals age, oxidative stress increases owing to the accumulation of reactive oxygen species (ROS). This increase can activate various signaling pathways, including NF-κB, TGF-β, and WNT, which are recognized for their roles in promoting EMT [32, 33]. The aged ECM is remodelled, acquiring stiffness and compositional changes that can further elevate EMT and promote cancer cell invasion [34]. Furthermore, age-related epigenetic modifications and telomere shortening increase genomic instability, further enhancing EMT and carcinogenesis [35]. A deep understanding of how TGF-beta affects the relationship between aging and EMT is essential to develop tailored therapies for the increasing number of cancer patients older than 65 years of age [36, 37]. Interventions that target the aging microenvironment boost the immune system, and interconnected mechanisms with oxidative stress may prevent EMT progression or minimize its consequences for cancer progression [38]. Similarly, strategies for the elimination of senescent cells or the downregulation of SASP might provide new opportunities for therapeutic intervention against some age-associated cancers with a parallel beneficial effect on metastasis, improving the outcome of treatment in the elderly [39, 40].

2. MOLECULAR MECHANISMS OF EMT IN LUNG CANCER

2.1. Transcriptional Regulators of EMT

The activity of transcriptional regulators is important for the EMT progression in lung cancer. SNAIL, TWIST, SLUG, and ZEB1/2 are key inducers of EMT, controlling gene expression that defines the epithelial and mesenchymal phenotypes [41, 42]. SNAIL and SLUG downregulate E-cadherin (CDH1), an essential epithelial marker, which results in the disruption of epithelial cohesion and cell-cell junctions [43, 44]. TWIST promotes mesenchymal markers like N-cadherin (CDH2), vimentin, and fibronectin, enabling motility and invasiveness [19, 45]. ZEB1 and ZEB2 similarly repress epithelial genes while inducing mesenchymal traits [46]. These transcription factors (TFs) are influenced by the TGF-β, Wnt, Notch, and Hedgehog pathways, which modulate their stability *via* post-translational modifications such as phosphorylation and ubiquitination [47]. Collectively, these pathways form a network that drives the dynamic process of EMT [48, 49]. Targeting these regulators and their respective signaling pathways could offer a promising therapeutic approach to suppress EMT and prevent metastasis in lung cancer [50-52].

2.1.1 Snail Family TFs

The Snail family, including SNAIL1 (SNAI1) and SNAIL2 (SLUG), plays a pivotal role in EMT regulation and is dysregulated in lung cancer [53]. These zinc finger proteins bind to E-box motifs in epithelial gene promoters, such as CDH1, and repress their transcription, leading to the loss of cell-cell adhesion and increased motility [54]. In addition to CDH1, Snail proteins suppress other epithelial markers such as claudins and occludins, while inducing mesenchymal markers, such as vimentin and fibronectin, promoting the mesenchymal state [55, 56]. Snail's activity is modulated by various signaling pathways, such as TGF-β and Wnt, and is regulated through post-translational modifications like GSK-3β-mediated phosphorylation, which can trigger its degradation through the ubiquitin-proteasome pathway [57, 58]. Elevated Snail expression is associated with reduced survival rates in lung cancer due to its contribution to

metastasis and resistance to apoptosis [59-61]. Thus, inhibition of Snail and its regulatory networks may offer a therapeutic approach to suppress EMT and enhance treatment outcomes. [62, 63].

2.1.2 TWIST Family TFs

The Twist family, particularly TWIST1 and TWIST2, is essential in promoting EMT in lung cancer [64]. These bHLH proteins promote mesenchymal characteristics by increasing the expression of CDH2, VIM, and FN1, while downregulating the epithelial marker CDH1, resulting in reduced cell-cell adhesion and increased motility [65-67]. TWIST proteins also promote stem cell-like characteristics in cancer cells, increasing tumorigenicity and resistance to therapy [68]. Pathways like TGF-β, WNT, and NF-κB influence TWIST, modulating its activity at both transcriptional and post-transcriptional levels [69]. Targeting TWIST and its regulatory networks may offer a strategy to suppress EMT and improve treatment outcomes for lung cancer patients [70, 71].

2.1.3 ZEB Family TFs

ZEB1 and ZEB2 are key regulators of EMT in lung cancer [72]. These TFs repress epithelial markers, such as CDH1, by binding to E-boxes in their promoters, disrupting cell-cell adhesion and promoting cell motility [73-75]. Simultaneously, they upregulate mesenchymal markers like vimentin and CDH2, driving the mesenchymal phenotype [44, 76]. ZEB proteins are controlled by signaling pathways such as TGF-β, WNT, and NOTCH, with miRNAs (miR-200) playing a key role in optimizing their expression. [77]. Due to their central role in EMT and metastasis, ZEB TFs are potential therapeutic targets for preventing cancer dissemination and improving lung cancer treatment outcomes [78].

2.2 Signaling Pathways Involved in EMT

2.2.1 TGF-β Signaling Pathway

The TGF-β signaling pathway is a key regulator of EMT in lung cancer, driving the transition from epithelial to mesenchymal phenotypes, which promotes cancer cell invasion and metastasis [44, 79]. TGF-β receptors (TβRI and TβRII) phosphorylate Smad2/3, which forms a complex with Smad4 and translocates to the nucleus, regulating EMT-related gene expression [80]. This cascade represses epithelial markers like CDH1 and induces mesenchymal markers such as CDH2, vimentin, and fibronectin [81]. Additionally, TGF-β activates non-Smad pathways (MAPK, PI3K/AKT, Rho GTPase), further enhancing EMT [82]. TGF-β-induced TFs like SNAIL, SLUG, TWIST, and ZEB reinforce the EMT process [83, 84]. Given its central role, targeting the TGF-β pathway with inhibitors offers a promising strategy to reduce invasiveness and metastasis in lung cancer, potentially improving patient outcomes [85, 86].

2.2.2 Wnt/β-catenin Signaling Pathway

The WNT/β-catenin signaling pathway is essential for regulating the EMT in lung cancer, and it significantly influences cancer progression by promoting proliferation, migration, and metastasis. [87, 88]. Wnt ligands turn on this pathway by attaching to Frizzled receptors and LRP5/6 co-receptors, which inhibit the destruction complex, leading to the stabilization of β-catenin (CTNNB1).[89]. Stabilized CTNNB1 builds up in the cytoplasm and moves into the nucleus, where it interacts with TCF/LEF TFs to control the expression of mesenchymal genes, such as CDH2, vimentin, and fibronectin, while simultaneously inhibiting epithelial markers, such as CDH1 [90-92]. Wnt/β-catenin signaling also promotes the upregulation of EMT TFs like SNAIL, TWIST, and ZEB [93, 94]. Constitutive activation of this pathway in lung cancer results in enhanced tumor aggressiveness and metastasis [95]. Focusing on WNT ligands, Frizzled receptors, or CTNNB1 presents a promising therapeutic approach to inhibit EMT and enhance clinical outcomes[96].

2.2.3 Notch Signaling Pathway

The Notch signaling pathway is a key mediator of EMT in lung cancer, promoting tumor progression and metastasis [97]. When a ligand binds to the Notch receptor, it undergoes cleavage that releases the Notch intracellular domain (NICD). This domain then moves into the nucleus, where it activates genes associated with EMT, including SNAIL, SLUG, and TWIST [98, 99]. This pathway represses epithelial markers while increasing mesenchymal markers such as CDH2 and VIM [100]. Notch signaling also affects cell survival, proliferation, and differentiation, increasing the invasiveness of cancer cells [101]. Its activation is linked to a worse prognosis in lung cancer, as it promotes EMT and contributes to resistance against therapies [102]. Targeting Notch with γ-secretase inhibitors, monoclonal antibodies, or small molecules may offer a promising therapeutic approach to block EMT and metastasis in lung cancer [103].

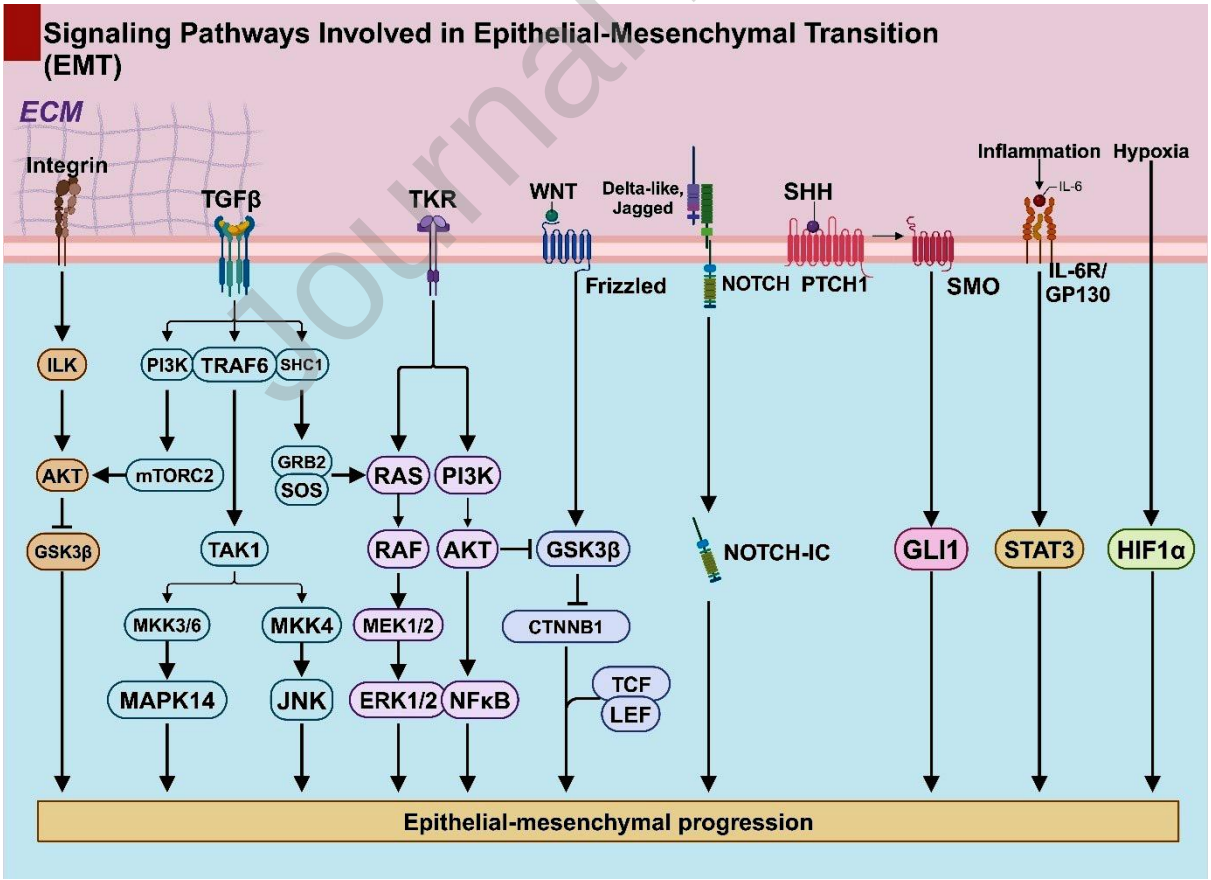


Figure-1: Different key signaling pathways involved in Epithelial-Mesenchymal Transition (EMT), including TGF-β, Wnt, Notch, SHH, and inflammation pathways, and their contribution to the progression of EMT through various molecular mechanisms

2.3 Epigenetic Regulation of EMT

Epigenetic modifications play a vital function in regulating EMT in lung cancer by modulating gene expression without altering gene sequence [104]. DNA methylation silences epithelial markers, like CDH1, while hypomethylation of mesenchymal genes, such as CDH2 and VIM, promotes EMT [105, 106]. Histone modifications play a role in EMT regulation, where HDACs suppress epithelial gene expression, and HATs promote mesenchymal gene activation by modifying chromatin accessibility [107]. Non-coding RNAs such as miR-200 inhibit EMT by targeting ZEB1 and ZEB2 [108]. These epigenetic mechanisms provide insights into potential therapeutic strategies, with agents like DNMT and HDAC inhibitors showing promise in managing lung cancer by targeting the epigenetic regulation of the EMT [109, 110][77, 111].

3. AGE-RELATED FACTORS AND THEIR INFLUENCE ON EMT

3.1 Cellular Senescence and EMT

Cellular senescence is irreversible cell cycle arrest of proliferating cells caused by strong mitogenic stimuli, mechanical stimulation, DNA damage, and oncogene activation [112]. This is especially important in aging and cancer, where the senescent cell burden increases and ads to the pro-inflammatory milieu [113]. Senescent cells display a SENP and are characterized by the secretion of a plethora of inflammatory cytokines, chemokines, growth factors and proteases [114, 115]. These SASP factors significantly promote the EMT in lung cancer. Senescent cells establish an EMT-supporting tumor microenvironment (TME), which encourages chronic inflammation and extracellular matrix remodeling by secreting SASP [116,

117]. Secretory cytokines, such as IL-6, and IL-8 secreted by senescent cells activate multiple signaling pathways that have been established to stimulate EMT [118]. Additional SASP elements, including growth factors, directly initiate EMT by engaging both Smad-dependent and Smad-independent pathways, which reduce epithelial markers and enhance mesenchymal markers [119, 120]. In addition, senescent cells trigger and accelerate the process of EMT by increasing ROS levels, leading to oxidative stress [121]. ROS have been shown to activate multiple EMT-associated signaling pathways, such as TGF-β, Wnt, and Notch, and to enhance the invasive and metastatic traits of cancer cells [122, 123]. Cellular senescence also brings about changes in systemic functioning of the immune system, termed immunosenescence, which characterizes the immunological changes that occur with aging [124]. Due to this decline, it becomes more difficult for the immune system to remove these senescent and pre-malignant cells, and this environment can support EMT and tumor progression [125]. Targeting senescent cells or modifying specific components of SASP may represent new therapeutic approaches to attenuate/modulate EMT to prevent cancer proliferation and progression [126]. Strategies such as senolytic compounds that actively expand the senescent burden or SASP inhibitors could potentially reverse senescence-induced pro-EMT effects and improve outcome in elderly lung cancer patients [127, 128].

3.2 Inflammation and EMT

Chronic inflammation drives EMT contributes to tumor progression and metastasis in human lung cancer. Several inflammatory cytokines, including IL-8, IL-6, TNF-α, and TGF-β, are critical coordinators for EMT progression in the TME [129]. These cytokines activate signaling pathways, including STAT3, NF-κB, and MAPK, which in turn induce prompt expression of EMT-associated genes [130, 131]. For instance, IL-6 and IL-8 activate the STAT3 pathway and promote the expression of the mesenchymal markers CDH2 and VIM, whereas they

suppress the expression of epithelial markers such as CDH1 [22]. TGF-β, a major inducer of EMT, functions through Smad-dependent or independent pathways, leading to the suppression of epithelial aspects as well as gain of mesenchymal properties [132, 133]. Moreover, inflammation-enhanced oxidative stress also induces the promotion of EMT to a great extent by producing ROS that activate the EMT-promoting Wnt and Notch pathways [134]. This pro-tumorigenic microenvironment involves chronic inflammation and oxidative stress and promotes the invasion of transformed cells and their resistance to apoptosis [135]. Therefore, targeting the inflammatory pathways and cytokines associated with EMT is an attractive means of preventing EMT and lung cancer metastasis, which may ultimately lead to improved treatment outcomes in lung cancer patients [136].

3.3 Oxidative Stress and EMT

Oxidative stress, an inducer of EMT in lung cancer, is induced by an increase in ROS production, which plays a central role in promoting EMT [137]. ROS are produced by a variety of cellular processes such as mitochondrial respiration and inflammation [138]. High levels of ROS damage cellular proteins, DNA, and lipids, stimulating the signal transduction pathways that drive EMT [139]. The most well-known pathways involved are TGF-β, Wnt, and NF-κB, all of which play a key roles in the regulation of EMT by oxidative stress [140]. ROS can promote TGF-β signaling to repress epithelial markers and enhance mesenchymal marker expression, which causes EMT [116]. Moreover, oxidative stress activates the Wnt/β-catenin pathway, which upregulates the transcription of many EMT-related genes [118]. Subsequently, they interact with EMT TFs including SNAIL, SLUG, and TWIST to accelerate the activation of EMT and enhance the migration, invasion, and apoptotic resistance in the cancer cells [141]. Targeting these proteins may suppress EMT and enhance the metastasis of lung cancer cells, thus providing effective therapies for patients with lung cancer [133].

3.4 Telomere Attrition and EMT

Telomere attrition is a primary marker of cellular aging and has recently shown a role in regulating EMT in lung cancer [142]. Telomeres protect chromosome ends from fraying; however, as cells divide, telomeres become shorter, and when they reach a crucial length, they result in either cellular senescence, apoptosis [143]. However, cancer cells can escape from growth arrest signals through the activation of ALT, reinitiating cell division, and progressing within the tumor [144]. Telomeres are one of several potential causes of genomic instability that fuel cancer progression and metastasis [145]. Telomere attrition can activate the DNA Damage Response (DDR) and TP53 signaling pathways, which are known to affect EMT. DDR signaling, which is continuously triggered in cells harboring almost unsafe short telomeres may drive the expression of proinflammatory cytokines and other SASP molecules that recruit EMT in the microenvironment [146, 147]. Aberrant functioning of telomerase is associated with the activation of EMT TFs, leading to EMT, promoting the mesenchymal phenotype, and upregulating the invasive capacity of cells [148]. Thus, knowledge of telomere attrition leading to EMT opens up a horizon for an understanding cancer biology [149]. EMT may be averted and reduce tumor metastasis either through suppression of EMT-associated DDR or telomere maintenance mechanisms, which may be a new opportunity for therapeutics, thus improving outcome in lung cancer patients [150].

3.5 Immune System Dysregulation and EMT

Immune system dysregulation is a critical determinant of EMT in lung cancer, which in turn affects tumor progression and metastasis [151]. With age, immune surveillance decrease due to a pseudo-inflammatory state of arrested immunity termed immunosenescence, and the body loses the ability to identify and destroy incipient cancer cells [152]. This low level of immune function creates an EMT-permissive microenvironment [153]. EMT is largely driven by

chronic inflammation and the accompanying dysfunction of the immune system [154]. In this condition, pro-inflammatory cytokines such as TNF-α, IL-6, and TGF-β are increased, and NF-κB and STAT3 can be activated [155]. These pathways enhance the expression of epithelial-to-mesenchymal transition transcription factors (EMT TFs), such as SNAIL, SLUG, and TWIST, while simultaneously leading to a decrease in epithelial markers and an increase in mesenchymal markers [156]. In addition, immune cells of TME, such as TAMs and MDSCs, secrete factors that support EMT [157]. TAMs produce TGF-β and other pro-tumorigenic cytokines that can directly induce EMT or support EMT through the TME [158]. The identification of immune system dysregulation and its effects on EMT provides a basis for potential therapeutic interventions [159]. Activation of immune surveillance and modulation of inflammatory responses and immunosuppressive cells in the TME can attenuate EMT induction, decrease metastasis incidence, and increase survival in individuals with lung cancer [160].

4. THERAPEUTIC INTERVENTIONS TARGETING EMT AND AGE-RELATED MECHANISMS

4.1 Small Molecule Inhibitors

Recently, small molecule inhibitors have been recognized as promising therapeutic agents for exploring the processes of EMT and aging [161]. These inhibitors are capable of interrupting EMT signaling pathways such as TGF-β, Wnt, and Notch, while also impeding fibrosis and metastasis [162]. Furthermore, a number of small molecules known to target age-related pathways have been reported to reduce senescence and contribute to successful aging [163, 164]. Advancing the development of these inhibitors to enhance their specificity and minimize off-target effects would constitute a significant breakthrough in the development of therapies for age-related diseases and cancer [165]. β-elemene, a sesquiterpene extract from *Curcuma*

wenyujin, exerts strong anti-tumor activity through EMT processes [166]. It interferes with various cell signaling pathways, prevents activated tumor growth and metastasis, and promotes apoptosis in cancer cells [167, 168]. Zou et al. developed radioresistant NSCLC cell lines (H1299-RR and A549-RR) and observed increased invasion, spheroid formation, and enhanced CSC characteristics compared to their parental cells. When β-elemene was administered prior to radiation therapy, it significantly improved radiosensitivity in A549 cells by reducing EMT and CSC markers and inhibiting the Prx-1/NF-kB/iNOS signaling pathway. These findings suggest that NSCLC radioresistance is associated with EMT and CSC activation, and that pre-treatment with β-elemene can enhance the efficacy of radiation therapy [169].

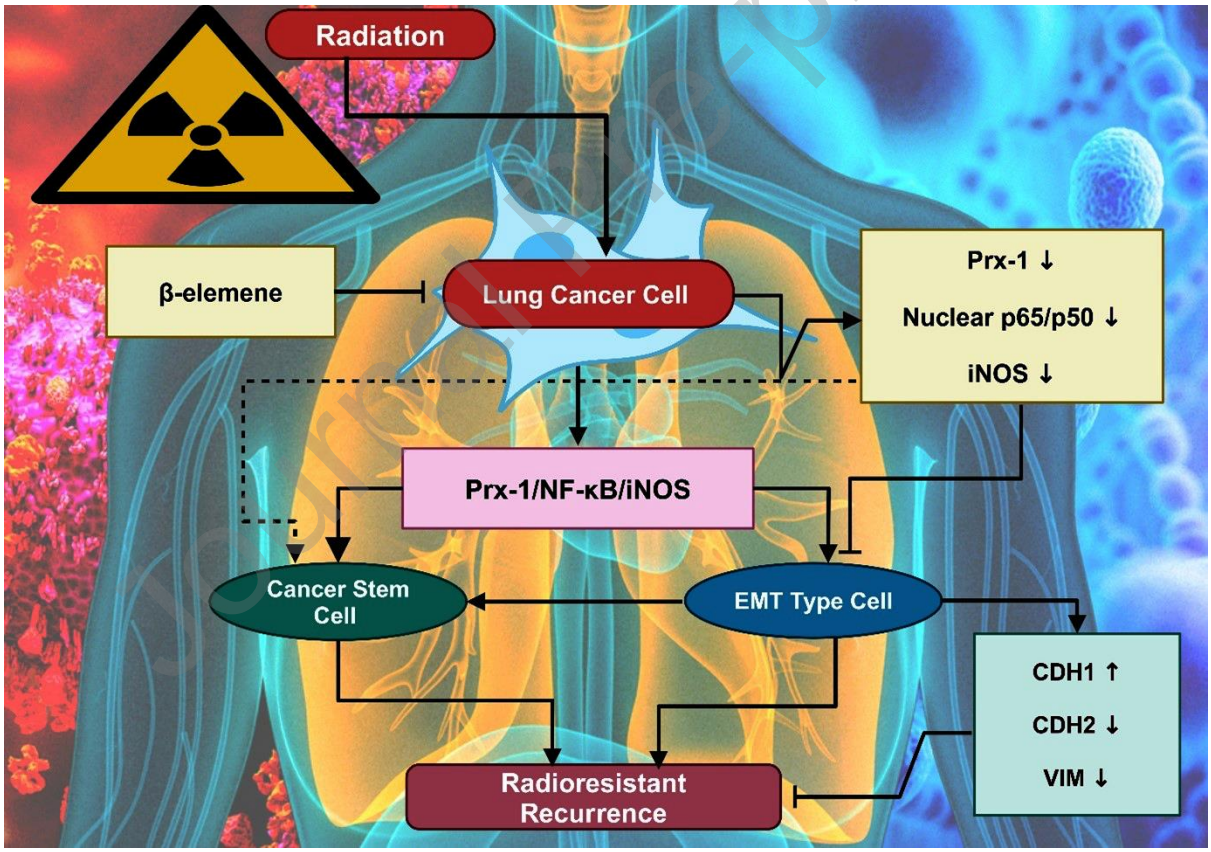


Figure-2: Role of β-elemene in sensitizing NSCLC cells to radiotherapy by inhibiting EMT and cancer stem cell-like properties *via* the Prx-1/NF-κB/iNOS signaling pathway

Phenolic acid resveratrol, a naturally occurring compound in grapes and red wine, has shown potential against both EMT and age-related deregulation [170]. It modulates SIRT1 activation

and key signaling pathways that reduce oxidative stress and inflammation, while blocking EMT and promoting longevity [171, 172]. Chen *et al* showed by overexpressing the tumor suppressor Rad9, the potential anti-cancer effect of RSV could induce cellular senescence as well as reverse EMT in breast and lung cancer cells, showing that Rad9 was overexpressed in the RSV-treated group, which downregulated the expression of EMT markers and SLUG, consequently leading to the deactivation of proliferation and EMT progression in cancer cells [173]. Previous studies have implicated mucin 1 (MUC1) plays a significant role in paclitaxel (PTX) resistance during cancer therapy [174]. In addition, MUC1 overexpression inhibits PTX-induced apoptotic responses, thereby reducing its efficacy [175]. Therefore, targeting MUC1 may increase the susceptibility of cancer cells to PTX and improve therapeutic efficacy [176, 177]. Ham *et al* examined the function of MUC1 in PTX resistance in NSCLC. They inferred that MUC1 increases stemness and EMT, resulting in PTX resistance. Similarly, MUC1 knockdown markedly attenuated these characteristics, implying that MUC1 inhibition may be a promising target to overcome drug resistance in lung cancer [178]. Similarly, Mano *et al* suggested that the Mullerian inhibiting substance (MIS) could be a potential therapeutic alternative. Lung cancer cells seeded on fluidic substrates resulted in IGFBP5 induced cellular senescence and cell cycle arrest through the TP53 signaling cascade. This method prevents EMT and may be valuable for the treatment of cancer [179]. Small-molecule inhibitors, natural agents such as β-elemene and resveratrol, and targeted strategies against MUC1 and MIS identification display a distinctive way to blunt EMT and aging-associated factors in cancer cells [180-182]. These developments have the potential to improve therapeutic performance and address the issue of drug resistance in different types of cancers [183, 184].

4.1.1 Targeting Transcriptional Regulators

Transcription regulators currently represent an attractive therapeutic strategy for EMT and age-related mechanisms of cancer [185]. SNAIL, SLUG, and TWIST are TFs that maintain EMT

through the transcriptional repression of epithelial genes and induction of mesenchymal genes, subsequently promoting migration, invasion, and apoptosis resistance [186, 187]. Targeting these transcriptional regulators might be a potential therapeutic strategy for suppressing EMT-aggressiveness [188]. In addition, the comprehensive therapeutic strategy is further supplemented by the modulation of cellular senescence pathways, such as FOXO and TP53, which may potentially improve health span by targeting aging transcriptional regulators [189]. Brain metastasis from NSCLC is a major clinical problem and an important cause of poor survival [190]. Current therapeutic approaches are directed at targeted agents and novel agents to target the unique brain TME and resistance mechanisms in NSCLC brain metastases, given the necessity to prolong survival, relieve symptoms, and improve the quality of life of affected patients [191-193]. Wei *et al* studied the mechanism by which miR-330-3p mediates NSCLC brain metastasis. Increased miR-330-3p expression predicts brain metastasis. It enhanced EMT and metastasis *via* GRIA3 and GRIA3-TGF-β1 interaction. Silencing miR-330-3p reversed these effects, indicating that miR-330-3p may be a candidate biomarker and therapeutic target for NSCLC metastasis [194]. Radiation-induced radioresistance in cancer is frequently associated with EMT and metastasis [195]. EMT promotes resistance to radiotherapy and metastasis owing to its ability to improve the survival and mobility of tumor cells [196]. EMT pathways could be targeted to sensitize radioresistant cancer cells, inhibit metastatic spread, and accumulate cancer cell death to optimize cancer and prognosis [197, 198]. Yao *et al* explored the association between radioresistance, EMT, and metastasis in NSCLC. The mesenchymal characteristics and elevated migration include radiation-resistant cells. This promoted EMT by stabilizing ZEB1 *via* attenuation of LKB1-SIK1 signaling. LKB1 overexpression decreases EMT, reverses EMT, and attenuates radiation resistance. These results suggest that inhibition of EMT by targeting LKB1-SIK1-ZEB1 may enhance radiosensitivity in the treatment of NSCLC [199].

microRNAs act as cancer markers and play crucial roles in regulating genes involved in cellular proliferation, migration, and invasion [200, 201]. Specific targeting of miR-6884-5p could be a potential therapeutic strategy to suppress tumor growth and metastasis [202]. Zhang *et al* reported that miR-6884-5p inhibits EMT in NSCLC by targeting S100A16 and suggested that suppressing EMT and NSCLC progression by increasing miR-6884-5p expression may serve as a potential therapeutic strategy [203]. The airway fibrosis in patients with COPD is the result of chronic inflammation, repeated injury, fibrogenic signaling, and excessive deposition of extracellular matrix proteins [204, 205]. Fibrosis leads to airway obstruction and impaired lung function [206]. Targeted drugs prevent fibrosis by regulating some of the main signaling pathways in the fibrotic process [207]. Sohal *et al* revealed the role of EMT in mediating COPD-associated airway fibrosis and its positive relationship with lung cancer formation. They also highlighted the importance of elucidating EMT processes in COPD as novel biomarkers and drug targets for lung cancer prevention and COPD treatment [208]. 14-3-3ζ participates in cancer as an oncoprotein, promoting two important features of malignant transformation and resistance to therapy, *i.e.* tumor progression and therapy resistance, by activating the EMT and cell survival pathways [209-211]. Wei *et al* demonstrated that high 14-3-3ζ expression promoted EMT, tumor recurrence, metastasis, and chemoresistance in NSCLC High 14-3-3ζ expression promoted cell motility and invasion, indicating that it may serve as a predictive biomarker for lung cancer recurrence and treatment failure with anaplastic lymphoma kinase inhibitors [212]. Similarly, Li *et al* developed a prognosis-related prognostic model in LUSC using EMT-related genes; poor clinical outcome and distinctive tumor immune landscape were also observed in the high-risk group, suggesting that this signature might be an indicator for identifying patients with chemotherapy benefits and response to immunotherapy [213]. Zhang et al conducted a study in which they demonstrated that miR-224 exacerbates cancer-associated fibroblast (CAF)-induced NSCLC progression by activating a positive feedback loop

associated with the SIRT3/AMPK/mTOR/HIF-1α axis. Targeting miR-224 may provide an opportunity to alleviate CAF-induced malignancy in NSCLC, which could be considered a direction of therapy-triggered actions [214]. Additionally, Xu *et al* observed that hsa_circ_0018818 is significantly upregulated in NSCLC. Conversely, knockdown of hsa_circ_0018818 inhibited NSCLC cell proliferation, invasion, and EMT by mediating miR-767-3p and regulating the NID1/PI3K/Akt signaling pathway. Functional analysis indicated that hsa_circ_0018818 might be a useful therapeutic target for NSCLC [215].

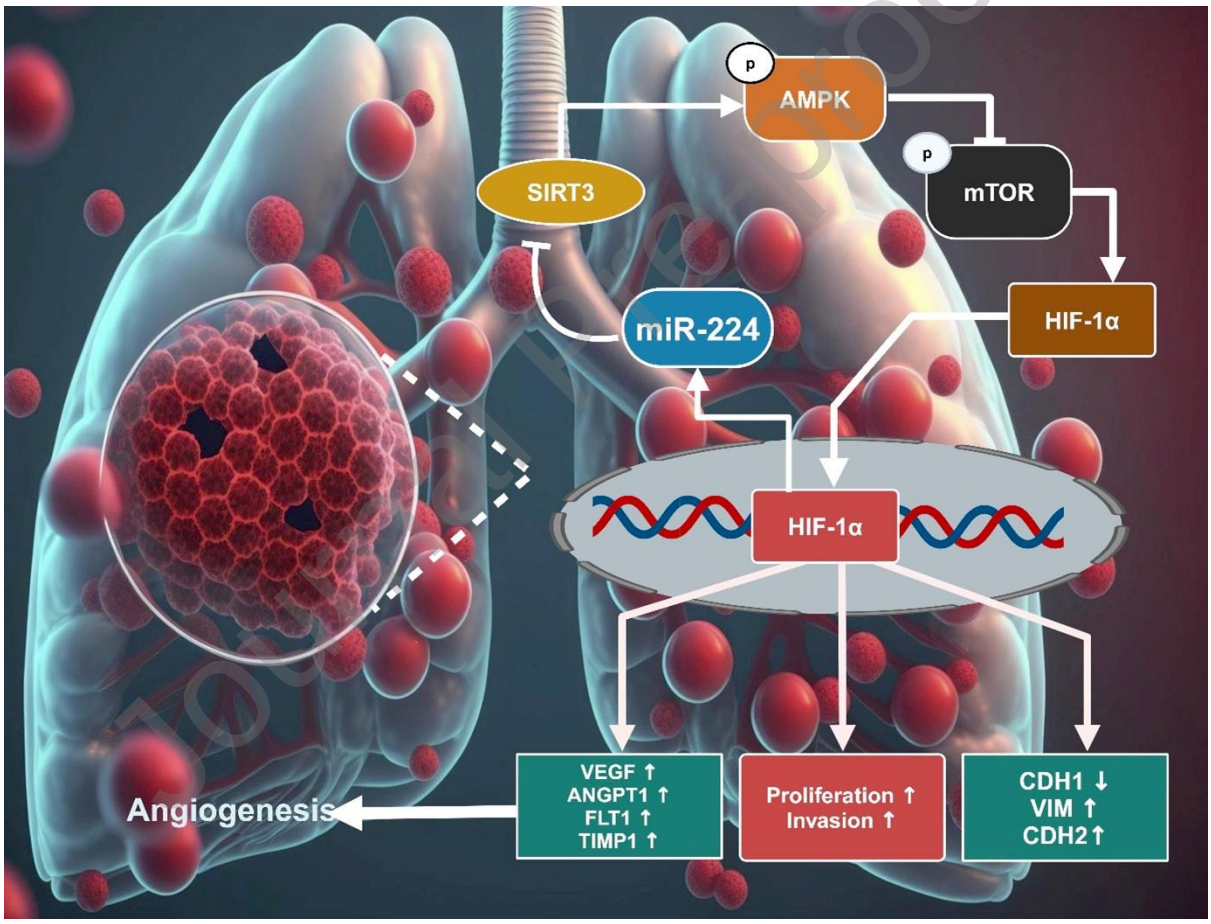


Figure-3: Mechanism of action of miR-224 in NSCLC progression. miR-224 exacerbates CAF-induced NSCLC progression by accelerating cellular proliferation and invasion through activation of a positive feedback loop involving the SIRT3/AMPK/mTOR/HIF-1α axis

4.1.2 Targeting Signaling Pathways

Targeting signaling pathways is essential for preventing EMT and age-related pathways in cancer [216]. EMT is regulated by key signaling pathways, including TGF-β, Wnt, and Notch, which control cell differentiation, migration, and invasion [217]. Compounds that inhibit EMT can be used to block these pathways and consequently prevent metastasis and potentiate existing therapies [218, 219]. Furthermore, manipulation of aging pathways, such as mTOR and MAPK, may reduce cell senescence and enhance therapeutic responses [220]. Therefore, they have significant potential for cancer and age-associated disease interventions using this precision medicine approach [30, 221]. One of the flavones in citrus, eriocitrin, has anticancer activity against lung cancer [222]. Its antitumor potential is mediated through the induction of apoptosis, inhibition of cell proliferation, and suppression of critical signaling cascades implicated in cancer development, including PI3K/Akt and MAPK, which decrease tumor growth and metastasis [223, 224]. Gao *et al* investigated the effects of eriocitrin in LUAD, which is a flavonoid glycoside found in lemon and other citrus. Eriocitrin suppressed cell viability, migration, and EMT by upregulating CDH1 and downregulating mesenchymal markers. It sensitizes cells to ferroptosis, as indicated by the increase in ROS and iron levels. Moreover, pretreatment of LUAD cells (A549 and H1299 cells) with the EMT and metastasis inhibitor eriocitrin, followed by the ferroptosis inhibitor ferrostatin-1, highlights the role of eriocitrin in inducing ferroptosis in these cells [225]. CUEDC1 also plays a regulatory role in the activity of ubiquitin ligases, and its deletion leads to destruction of the protein degradation process [226]. For instance, CUEDC1 function is linked to tumor suppression in cancer by restraining EMT, thereby diminishing cellular migratory properties and metastatic abilities [227]. Cui *et al* was to explore the function of CUEDC1 in NSCLC. This study identified CUEDC1 as a key regulator of EMT and metastasis in NSCLC. Low CUEDC1 expression correlates with increased lymph node metastasis, whereas CUEDC1 overexpression reduces metastasis and inhibits EMT by modulating the TβRI/Smad signaling pathway and interacting

with SMURF2. These findings highlight CUEDC1's potential as a therapeutic target for NSCLC [228]. Tian *et al* demonstrated that Sirt6 suppresses EMT in IPF by deactivating the TGF-β1/Smad3 pathway. Analysis of a model has also refined Sirt6 as a candidate for EMT-related TF impairment in IPF and has confirmed that overexpression of Sirt6 prevented fibrosis [229]. In another study Tang *et al* developed EMT-related signature genes such as HGF, CCR2, LGR4, ITGB1, FUT4, FSCN1, CTSL, CDH2, and ADM predict the prognosis of LUAD by analysing mRNA expression data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). A risk score model comprising nine EMT-related genes was established, and a nomogram integrating this signature with clinical features demonstrated a strong predictive accuracy for patient survival. These findings offer a reliable tool for the prognostic assessment of LUAD [230].

FAM83A is a protein that contributes to cancer progression and targeted therapy of resistant cells. It acts as an enhancer of EMT and a trigger for tumorigenesis due to upregulated oncogenic signaling pathways such as MAPK and PI3K/AKT; therefore, it has been proposed as a therapeutic target [231, 232]. Zhou *et al* showed that FAM83A act as an enhancer of EMT and metastasis *via* the PI3K/AKT/Snail signaling pathway in NSCLC. FAM83A downregulation represses NSCLC cell migration and invasion, whereas FAM83A overexpression facilitates these effects. FAM83A is considered a potential anti-LRRK2 target for NSCLC treatment because its overexpression activates downstream signalling pathways that contribute to tumor progression, and inhibiting FAM83A could potentially suppress these pathways, thereby reducing tumor growth and metastasis. [233]. PRMT5 is a type II protein arginine methyltransferase involved in numerous biological processes such as gene expression and RNA splicing [234]. PRMT5 is highly expressed in tumors and promotes tumor growth and survival through the regulation of key signaling pathways and cancer progression/metastasis, providing a theoretical basis for PRMT5-targeted cancer [235-237].

Zheng *et al* demonstrated that PRMT5 enhances HIF-1α/VEGFR/Akt signaling pathway to promote EMT and angiogenesis in lung cancer. Silencing and other inhibitor studies showed that this caused a decrease in EMT and tumor growth, and downregulated these pathways due to the inhibition of PRMT5. PRMT5 is a potential therapeutic target for this subtype of lung cancer with aberrant angiogenesis [238]. LUAD is a primary subtype of NSCLC in the clinic [239]. LUAD is aggressive, often metastatic, requires targeted therapy and comprehensive treatment plan to improve survival of patients [240]. Ni *et al* examined the impact of hepatic inflammatory microenvironment on the development of LUAD. Comprehensive mechanistic studies have shown that IL-6 enhances LUAD proliferation, migration, and EMT through YAP1, and METTL3 mediates N6-methylation of *YAP1* mRNA. This study provides evidence for the clinical diagnosis and treatment of liver metastasis of LUAD [241]. Similarly, Zhang *et al* used CAF-related genes to build a prognostic and immunotherapy response-predictive model for LUAD. CAFRS was developed based on seven genes, is closely related to immune function and treatment response, and is a potential prognostic marker for clinical practice in LUAD [242]. Ishizawa *et al* identified a subset of CD45/CD326 double-positive NSCLC cells in another study associated with a poor prognosis. This population of cells expressing both epithelial and non-epithelial markers is critical in the process of phenotypic transition, which is a cornerstone in disease progression and therapy resistance, and hence has priority for clinical care [243]. Furthermore, Sato *et al* showed that certain oncogenic alterations (CDK4, sh-p53, hTERT, KRAS, and MYC) are sufficient for malignant transformation of human bronchial epithelial cells (HBECs). This study provides information that can promote the understanding of molecular changes and potential targets that occur during lung cancer [244].

Klotho is an anti-aging protein and an emerging key modulator of a number of cellular processes such as oxidative stress and inflammation [245, 246]. It has age-related disease preventive effects and two studies on the inhibits of cancer progression through the suppression

of EMT [247]. Chen *et al* found that enhanced expression of Klotho restrained the production of IL-6 and IL-8 by SLF and attenuated STAT3 activity and EMT in NSCLC cells. Their findings suggest that Klotho could be a potential target for modulating the pro-tumoral effects of SLF in lung cancer [248]. KRASV12-induced senescence is an irreversible cell cycle arrest event that occurs in the G1 phase as a cellular response to oncogenic stress caused by KRASV12 mutation. This mechanism functions as a tumor-suppressive process by controlling the expansion of potentially cancerous cells [249]. However, in certain settings, such as in the presence of additional genetic mutations or in the TME, KRASV12-induced senescence may also contribute to tumor progression and resistance to therapy [250]. Muraki *et al* explored mutant KRASV12-induced senescence in hTERT/Cdk4-immortalized bronchial epithelial cells. The mutant KRASV12 induces partial EMT and senescence in a subset of cells, leading to higher levels of p21 and autophagic flux. Together, these results indicate that oncogene-induced senescence is inefficient in restraining KRASV12-induced transformation of these cells [251]. Similarly, Lee *et al* found that depletion of BCL-2 interacting suppressor (BIS) inhibits the migration and invasion of A549 cells by decreasing NF-κB activity and EMT markers ZEB1, SNAIL, and SLUG. BIS regulates cell invasion and EMT, indicating its potential as a novel therapeutic target for NSCLC [252]. Targeting signalling pathways, TFs, and proteins, including 14-3-3ζ, FAM83A, PRMT5, and CSNDC1, may also be a possible strategy to impair EMT and cancer progression [253, 254].

The TGF-β signaling pathway is essential for controlling EMT in lung cancer, via interaction of SMAD proteins [255]. Recent progress in the field has resulted in the creation of TGF-β receptor and TGF-β/Smad inhibitors designed to specifically target this pathway. As an example, A83-01, a selective inhibitor of TGF-β type I receptor, has the potential to block TGF-β-induced EMT, thus limiting cancer cell invasion and metastasis [256]. Additionally, TGF-β/Smad inhibitors, such as tranilast, have shown potential in suppressing Smad-mediated

signaling, which can prevent fibrosis and EMT-driven tumor progression [257]. CTI-82, another TGF-β/Smad inhibitor, interferes with the TGF-β/Smad cascade, effectively attenuating EMT as well as the tumor growth in preclinical models [258]. These compounds represent promising therapeutic avenues, particularly in combating EMT-driven resistance to standard therapies. Their ability to target specific nodes in the TGF-β signaling pathway offers an opportunity for more effective management of age-related lung cancer progression.

Table-1: Summarizes research on EMT and lung cancer, detailing various compounds/models, targeting pathways, mechanisms, and implications for lung cancer treatment, progression, and prognosis

Compound/ Model	Targeting Pathways	Mechanism/Findings	EMT and Lung Cancer Implications	References
β-elemene and NSCLC	Prx-1/NF-κB/iNOS	Increases radiosensitivity by inhibiting EMT and CSC traits	NSCLC treatment adjunct	[169]
Resveratrol (RSV) in cancer cells	Rad9 pathway	Induces senescence and inhibits EMT	Breast and lung cancer therapy	[173]
Mucin 1 (MUC1) in NSCLC	Not specified	Enhances stemness and EMT, leading to paclitaxel resistance	Overcoming drug resistance	[178]
Material-induced senescence (MIS) in cancer cells	IGFBP5/p53	Induces senescence, preventing EMT	Treatment-resistant cancers	[179]
miR-330-3p in NSCLC	GRIA3-TGF-β1	Promotes EMT and metastasis	NSCLC brain metastasis	[194]
Radioresistance and EMT in NSCLC	LKB1-SIK1-ZEB1	Attenuated LKB1-SIK1 signaling upregulates ZEB1, driving EMT	Radioresistant NSCLC	[199]
miR-6884-5p in NSCLC	S100A16	Inhibits EMT	Controlling NSCLC progression	[203]
EMT in COPD and lung cancer	Not specified	Highlights the role of EMT in COPD-related airway fibrosis	COPD and lung cancer link	[208]
14-3-3ζ in NSCLC	Not specified	Increases EMT, recurrence, metastasis, and chemotherapy resistance	NSCLC recurrence prediction	[212]
EMT-related genes in LUSC	Not specified	Prognostic model for chemotherapy sensitivity and immunotherapy response	LUSC prognosis	[213]
miR-224 in NSCLC	SIRT3/AMPK/mTOR/HIF-1α	Aggravates CAF-induced NSCLC progression	NSCLC therapeutic approach	[214]
hsa_circ_0018818 in NSCLC	miR-767-3p/NID1/PI3K/Akt	Inhibits NSCLC proliferation, invasion, and EMT	NSCLC treatment target	[215]

Eriocitrin in LUAD	Ferroptosis	Induces ferroptosis, inhibiting EMT and metastasis	LUAD metastasis inhibition	[225]
CUEDC1 in NSCLC	TβRI/Smad	Inhibits EMT and tumor growth	NSCLC progression	[228]
Sirt6 in IPF	TGF-β1/Smad3	Inhibits EMT and prevents fibrosis	IPF and lung cancer	[229]
EMT-related gene signature in LUAD	Not specified	Predicts prognosis	LUAD clinical prognosis	[230]
FAM83A in NSCLC	PI3K/AKT/ Snail	Promotes EMT and metastasis	NSCLC therapeutic strategy	[233]
PRMT5 in lung cancer	HIF-1α/VEGFR/ Akt	Promotes EMT and angiogenesis	Lung cancer with angiogenesis	[238]
Hepatic microenvironment in LUAD	METTL3/YAP1	Promotes proliferation, migration, and EMT *via* N6-methyladenosine modification	LUAD liver metastasis	[241]
CAF-related genes in LUAD	Not specified	Predicts prognosis and immunotherapy response	LUAD clinical prognosis	[242]
CD45/CD326 cells in NSCLC	Not specified	Associated with poor prognosis	NSCLC clinical management	[243]
Oncogenic changes in HBECs	Not specified	Induces malignant transformation	Lung cancer progression	[244]
Klotho in senescent lung fibroblasts	STAT3/IL-6/IL-8	Inhibits pro-tumoral effects and EMT	NSCLC therapeutic factor	[248]
KRASV12-induced senescence in bronchial cells	p21/autophagic flux	Causes partial EMT and senescence	KRASV12-induced transformation	[251]
BIS in NSCLC	NF-κB/ZEB1/Snail/Slug	Regulates cell invasion and EMT	NSCLC therapeutic target	[252]

4.2 Epigenetic Modulators

The discovery of therapeutic approaches targeting epigenetic regulation offers potential treatments for cancer and age-associated disorders. One subset of these approaches involves the regulation of gene expression through specific enzymes controlling the epigenome, such as histone methyltransferases and demethylases [259, 260]. Another subset of epigenetic therapeutic options includes modulators of DNA methyltransferase and histone deacetylase (HDAC) inhibitors, such as 5-azacytidine (5-aza) and vorinostat, respectively. These agents are used to revert abnormal epigenetic changes linked to EMT and cellular senescence [261, 262].

By restoring the physiological expression patterns of genes, they can impede cancer progression, limit metastasis, and even mitigate aging-driven cellular dysfunctions, thus representing a novel therapeutic approach [263, 264]. hTERT is essential for telomerase activity that regenerates telomeric sequences and thus enables immortalization of cancer cells [265]. Overexpression of hTERT is frequently observed in cancer cells and promotes tumorigenesis, therefore, it is considered as a potential novel target for cancer therapy [266]. Prasad *et al* investigate the potential use of hTERT in EMT of lung cancer. Overexpression of hTERT promotes EMT by upregulating c-MET and mesenchymal markers while reducing epithelial markers, whereas hTERT downregulation lowers c-MET expression and reverses EMT. Their study revealed that hTERT modulates c-MET and EMT markers associated with lung cancer progression, which contributes to our understanding of the mechanism by which hTERT promotes lung cancer progression and suggests potential therapeutic strategies [267]. Lee *et al* analyzed the effects of histone lysine methylation/demethylation on EMT TFs in lung adenocarcinoma with brain metastasis. These data suggest that essential epigenetic regulators can that could be targeted for therapy to prevent metastasis [268]. *DIP2C* is involved in cellular development/lineage [269]. *DIP2C* also plays a role in EMT pathways that are integral to tumor progression and metastasis; therefore this protein may be a therapeutic target in cancers [270]. Larsson *et al* characterized the effects of DIP2C KO in cancer cells, which resulted in major changes in global DNA methylation and EMT characteristics. DIP2C loss caused changes in the expression of 780 genes, including EMT regulators, such as *ZEB1*. Further analysis showed that DIP2C knockdown promoted cellular senescence, facilitated wound healing, and may affect cancer progression [271].

4.3 Immunotherapeutic Strategies

Immunotherapeutic strategies have changed the approach for management of cancer by activating the immune system to recognize and attack tumor cells [272]. The most promising

of these includes various immune checkpoint inhibitors, CAR-T cell therapy, and cancer vaccines. Immune checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 blockers have shown significant success in the treatment of numerous malignancies *via* T-cell reactivation [273-275]. CAR-T cell therapy, involves modification of T-cells derived from a patient to recognize and fight cancer. In addition, cancer vaccines can help the immune system link with specific tumor antigens, these strategies provide hope for enhancing cancer outcomes and survival rates [276]. Lung cancer-derived MSCs are key regulators of the tumorigenic niches. Cytokines and growth factors secreted by CAFs can trigger EMT, modulate immune system, promote tumorigenesis, disseminate metastasis, and therapeutic evasion [277, 278]. Yan *et al* investigated the function of lung cancer-associated mesenchymal stem cells (LC-MSCs) in the development of cancer. Their results demonstrated that LC-MSCs induce partial EMT and stem-like traits in lung cancer cells, resulting in increased tumor metastatic potential and promotion of tumorigenesis. In co-culture systems with lung cancer cells and in animal models (mouse xenograft models), LC-MSCs increased SNAIL and SLUG expression to promote metastasis. Their results identified the important role of LC-MSCs in lung cancer growth, suggesting that LC-MSCs could be potential targets in lung cancer therapy [279].

4.4 Combinatorial Approaches

A hallmark of combinatorial cancer therapy is the simultaneous use of multiple treatment modalities to potentiate therapeutic efficacy and overcome resistance [280]. These strategies range from combining immune checkpoint inhibitors with targeted therapies, chemotherapy, or radiotherapy to allow them to act as a combined force against cancer cells [281], *e.g.*, immune checkpoint inhibitors combined with inhibitors of TGF-β, WNT, and NOTCH pathways have been shown to counteract EMT and metastasis with significant efficacy. Moreover, combining eriocitrin with current treatment may also serve as global strategy to enhance treatment modalities in cancer [275, 282, 283]. Cellular damage from ionizing radiation can result in

double-stranded DNA breaks, oxidative stress, and genomic instability, which can drive the development and progression of cancer [100, 284]. Furthermore, cancer cells can be drawn into EMT, which can enhance the invasiveness and metastatic potential of cancer cells and make cancer treatment difficult [45, 285]. Zhou *et al* characterised the effect of gemcitabine on ionizing radiation-induced EMT in lung cancer. Radiation enhances TGF-β/SMAD-mediated senescence and EMT. They estimated that gemcitabine promoted apoptosis in senescent cells, suppressed EMT, and diminished tumor growth and metastasis. These results indicate a need for gemcitabine to increase radiotherapy efficiency in lung cancer, which may lead to targeted senescence and EMT [286]. Using bioinformatics tools, Cheng et al. identified an EMT-related prognostic signature and developed a new nomogram using data from the GEO and TCGA databases. They developed an eight-gene signature for LUAD by analysing EMT-related genes, which demonstrated robust predictive ability for overall and progression-free survival. Key genes, including CCNB1, PLEK2, and DLGAP5, were identified, with PLEK2 highlighted for its role in reducing cell proliferation and migration through autophagy inhibition. These findings offer potential new therapeutic targets and support the use of this gene signature in precision medicine for LUAD [287]. This study has a few limitations, particularly regarding the need to improve the accuracy of the prognostic prediction model, as an AUC > 0.8 is typically regarded as ideal. Additionally, further *in vivo* and *in vitro* studies required to thoroughly explore the relevance of PLEK2 in lung cancer. In another study Hill *et al* demonstrated that autophagy blockade induces EMT in alveolar epithelial cells due to the accumulation of p62/SQSTM1 and induces pulmonary fibrosis. Moreover, the combined targeting of autophagy and EMT may be a therapeutic option for fibrosis-associated diseases [288]. Additionally, Pu *et al* demonstrated that liraglutide, a GLP-1 receptor agonist used to manage type 2 diabetes and obesity suffers from lung cancer cell proliferation and EMT, cell senescence and oxidative damage induced by high glucose in the lung. This study revealed that

liraglutide could inhibit lung cancer progression and ameliorate lung aging, showing a dual effect of liraglutide in patients with diabetes and lung cancer [289]. In another study, Zhu *et al* revealed that the MET inhibitor capmatinib reversed osimertinib resistance in NSCLC by inhibition of MET/Akt/Snail signaling and depleting CAFs. Capmatinib significantly enhanced otherwise incomplete inhibition of tumor growth by osimertinib, suggesting a possible combinatorial therapeutic approach [290]. Cisplatin is a commonly used chemotherapeutic agent effective against a number of cancers, including lung, ovarian, and bladder cancers [291]. It primarily interupt cancer cells during the S phase of the cell cycle by inducing DNA damage, which triggers the activation of DNA damage checkpoints and ultimately leads to apoptosis. However, the use of this agent is often restricted owing to serious side effects and resistance development [292, 293]. Tièche *et al* investigated the impact of prolonged pemetrexed pretreatment on NSCLC cells when followed by cisplatin treatment. Findings indicate that a 48-hour pemetrexed pretreatment significantly impairs long-term cell growth, reduces colony formation, and delays recovery from DNA damage. Additionally, this approach enhances apoptosis and senescence while sensitizing a resistant EMT subpopulation to cisplatin. The results suggest that modifying the standard pemetrexed-cisplatin regimen to include pretreatment could improve therapeutic efficacy [294]. The combined use of immune checkpoint inhibitors, targeted therapy, natural compounds, and chemotherapeutic agents such as cisplatin can overcome the limitations and resistance to single agents in cancer therapy [295]. The simultaneous blockade of EMT, induction of senescence, and attenuation of oncogenic pathways, such as those afforded through the combination of gemcitabine with radiation or osimertinib with capmatinib, may represent a strategy for blocking these negative responses and mechanisms in a synergistic modality [296-298]. Additional studies and clinical trials are warranted to optimize these combinations so that individualized therapeutic design could be implemented for the benefit of the cancer patients [299].

4.5 EMT and Resistance to EGFR-TKI in NSCLC

Developing resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) remains a significant challenge in the treatment of NSCLC. One of the key mechanisms driving this resistance is the EMT, which enhances the survival and migratory capabilities of cancer cells [300]. EMT leads to changes in cell shape and gene expression, including a decrease in epithelial markers, such as CDH1, and an increase in mesenchymal markers, such as vimentin, which decreases cancer cell sensitivity to EGFR-TKIs [301]. Studies in NSCLC patients with resistance to EGFR-TKIs (gefitinib and erlotinib) often display EMT characteristics. This phenotypic shift allows cancer cells to bypass EGFR-dependent growth signals and adopt alternative survival pathways [302]. For example, TGF-β signaling has been implicated in promoting EMT-mediated drug resistance, with evidence suggesting that the inhibition of TGF-β could potentially reverse EMT and restore sensitivity to EGFR-TKIs [303, 304]. In addition, the development of mesenchymal characteristics is frequently associated with the activation of alternative pathways, including MET amplification and increased AXL expression, which further strengthens the resistance to EGFR-TKIs [305]. Inhibiting these alternative pathways, in combination with targeting EMT-related mechanisms, may offer a novel therapeutic strategy to overcome EGFR-TKI resistance in NSCLC [306].

5.0 CHALLENGES AND FUTURE PERSPECTIVES

FGF7 inhibition in the precise phase of EMT in CAFs has the potential to overcome the unresponsiveness to current treatments, which is a major problem in treating age-associated lung cancer, especially EMT [307, 308]. However, cancer cells tend to acquire adaptive resistance, which is one of the reasons why treatments lose their efficacy [309]. Consequently, there is a dire necessity for not only the clarification of the molecular pathways that are initiated during EMT and leading to drug resistance, but also the improvement of new anti-EMT/pro-

EMT inhibitors that would specifically target these pathways, but not to the same extent that result in compensatory pro-survival mechanisms in the cancer cells [310, 311]. This strategy could be potentially beneficial to prevent resistance or to have a higher chance of overcoming resistance: a combination of drugs that simultaneously act on different pathways [312, 313].

The exploration of EMT in age-related lung cancer is an evolving area that requires further investigation. Future studies should focus on identifying the molecular drivers that link aging processes, such as cellular senescence and immune dysregulation, with EMT in lung cancer [314]. Specifically, multi-omics methods such as transcriptomics, proteomics, and epigenomics should be used to discover new biomarkers and therapeutic targets tailored to age-related EMT pathways [315, 316]. Additionally, incorporating artificial intelligence (AI) and machine learning *i.e.* ML algorithms into these studies could accelerate the discovery of predictive biomarkers for treatment response and resistance [317].

Another promising area is the development of combinatorial therapies targeting both the EMT and the aging microenvironment. Investigating the synergistic effects of small molecule inhibitors, epigenetic modulators, and immunotherapies could open new therapeutic avenues [318, 319]. Preclinical models that better mimic the aged TME, including patient-derived xenografts and organoid models, are also essential for translating these findings into the clinic [320, 321]. Future research should explore the potential of reversing EMT and restoring epithelial characteristics through novel therapeutic strategies. Understanding reversion of EMT may impacts drug sensitivity and cancer progression in older patients could lead to improved treatment outcomes. These directions not only provide a roadmap for addressing current gaps in knowledge, but also hold promise for enhancing patient survival and quality of life.

6.0 CONCLUSION

This work underscore the crucial role of EMT in the age-related progression of lung cancer, particularly through pathways such as TGF-β, Wnt, and Notch, which drive cancer invasion, metastasis, and therapeutic resistance. Our analysis reveals that age-related factors like cellular senescence, oxidative stress, and immune system dysregulation significantly exacerbate EMT, accelerating lung cancer development in older patients. Key transcriptional regulators, such as Snail, Twist, and Zeb, along with epigenetic modulators, such as DNA methylation and non-coding RNAs, have also been identified as critical influences on EMT, contributing to the progression of lung cancer.

From a critical perspective, although therapeutic interventions targeting these pathways have shown promise, many challenges remain in translating these findings into clinical practice. Current therapies still struggle with issues, such as treatment resistance and the requirement for specificity in targeting age-related EMT mechanisms. Moreover, existing preclinical models often fail to accurately replicate the complexities of the aging TME, which may hinder the applicability of these findings in real-world clinical settings. Future research should aim to develop novel biomarkers and combinatorial therapies that target both EMT and age-related changes in the TME. With advancements in multi-omics approaches and the integration of AI tools, the precision of therapeutic strategies can be enhanced.

Statements & Declarations

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Competing interests

MKK received consultant honoraria from the CBRS, Noida. Rest of the author declares no financial interests.

CRediT authorship contribution statement

R. Thapa: Conceptualization, Writing – original draft, **S. Gupta**: Conceptualization, Writing – original draft, **G. Gupta**: Conceptualization, Writing – original draft, **A. A. Bhat**: Writing – original draft, **Smriti**: Writing – original draft, **M. Singla**: Writing –review & editing, **H. Ali**: Writing – review and editing, **S. K. Singh**: Conceptualization, Writing – original draft, **K. Dua**: Conceptualization, Writing – original draft, Supervision, **M. K. Kashyap**: Conceptualization, Writing – original draft, Supervision.

Data Availability

All the data pertaining to this study has been provided in the manuscript.

ETHICS DECLARATIONS

This study involves review of literature and analysis and does not involve directly or indirectly any patient sample, cell line or even patients or normal subjects for participation in the study.

Ethics approval and consent to participate

The study does not involve any human subjects, so ethical approval and consent to participate is not applicable.

Consent to publish

All the authors agree to the content of the manuscript and have no conflict of interest for authorship.

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Declaration of Competing Interest

MKK has received consultant honoraria from the CBRS, Noida. Rest of the author declares that they have no financial interests.

Data Availability

All the data pertaining to this study has been provided in the manuscript.

ETHICS DECLARATIONS

This study involves review of literature and analysis and does not involve directly or indirectly any patient sample, cell line or even patients or normal subjects for participation in the study.

Ethics approval and consent to participate

The study does not involve any human subjects, so ethical approval and consent to participate is not applicable.

Consent to publish

All the authors agree to the content of the manuscript and have no conflict of interest for authorship.

CRediT authorship contribution statement

R. Thapa: Conceptualization, Writing – original draft, **S. Gupta**: Conceptualization, Writing – original draft, **G. Gupta**: Conceptualization, Writing – original draft, **A. A. Bhat**: Writing –original draft, **Smriti**: Writing – original draft, **M. Singla**: Writing –review & editing, **H. Ali**: Writing – review and editing, **S. K. Singh**: Conceptualization, Writing – original draft, **K. Dua**: Conceptualization, Writing – original draft, Supervision, **M. K. Kashyap**: Conceptualization, Writing – original draft, Supervision.

Highlights

1. **EMT's Role in Lung Cancer**: EMT is a critical biological process regulating invasion and metastasis, significantly contributing to the progression of lung cancer.
2. **Age-Related Factors**: Cellular senescence, chronic inflammation, and epigenetic changes in older individuals exacerbate EMT, hastening lung cancer development.
3. **Key Signaling Pathways**: The review underscores key signaling regulators like **TGF-β**, **Wnt/β-catenin**, **Notch**, and **Hedgehog**, which are crucial in EMT induction and progression.
4. **Oxidative Stress & Telomere Dynamics**: The roles of **Nrf2** and **ROS** in oxidative stress and telomere shortening, regulated by **telomerase** and the **shelterin complex**, are described as mechanisms driving EMT.

5. **Immune System Dysregulation**: Changes in cytokine profiles and immune cell aging contribute to EMT through immune system dysregulation.
6. **Transcriptional Regulators**: The review highlights transcription factors and molecules like **Snail**, **Twist**, **Zeb**, **SIRT1**, **p53**, **NF-κB**, and **miRNAs** that regulate EMT and its pathways.
7. **Therapeutic Interventions**: Potential therapies targeting these pathways and molecules are explored as ways to mitigate EMT-driven cancer progression.