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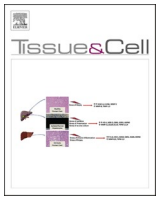

Umbilical cord mesenchymal stem cells and lung cancer: We should be hopeful or hopeless?

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ABSTRACT

Lung cancer (LC) is one of the leading causes of cancer-caused death that possesses a poor prognosis and low survival rate worldwide. In general, LC is classified into small-cell (SCLC) and non-small-cell carcinoma (NSCLC) (involving 80% of patients). Although chemotherapy, radiotherapy, surgery, and molecular-targeted therapy are considered standard approaches for LC treatment, these options have low success with detrimental effects on the life quality of patients. Ergo, recommending treatment with maximum effectiveness and minimum side effects for LC patients has been a substantial challenge for researchers and clinicians in the present era. Recently, mesenchymal stem cells (MSCs)-based strategies have sparked much interest in preventing or treating numerous illnesses. These multipotent stem cells can be isolated from diverse sources, such as umbilical cord, bone marrow, and adipose tissue. Among these sources, umbilical cord mesenchymal stem cells (UC-MSCs) have been in the spotlight of MSCs-based therapies thanks to their considerable advantages, such as high proliferation ability, low immune reactions and tumorigenesis, and easiness in collection and isolation. Some experimental studies have investigated the functionality of intact UC-MSCs and extracellular vesicles, exosomes, and conditioned medium derived from UC-MSCs, as well as genetically engineered UC-MSCs. In this review, we aimed to highlight the influences of these UMSCs-based methods in LC treatment with cellular and molecular insights.

1. Introduction

Lung cancer (LC) is named the most common malignancy worldwide and accounts for 18% of all death cases (1.8 million deaths) because of cancer in 2020 (Abatay-Sel et al., 2023). Most LC patients are recognized at an advanced stage owing to the asymptomatic nature of this cancer at the early stage, which results in poor prognosis (Altorki et al., 2019). In this stage of the disease, the 5-year survival rate of subjects is almost 4.2 percent (Lei, 2024). LC is also associated with poor survival in light of distant metastasis (e.g., adrenal glands, bone, liver, and brain), the main cause of mortality of LC individuals (Altorki et al., 2019). Generally, LC is categorized into small-cell (SCLC) (20% of cases) and non-small-cell

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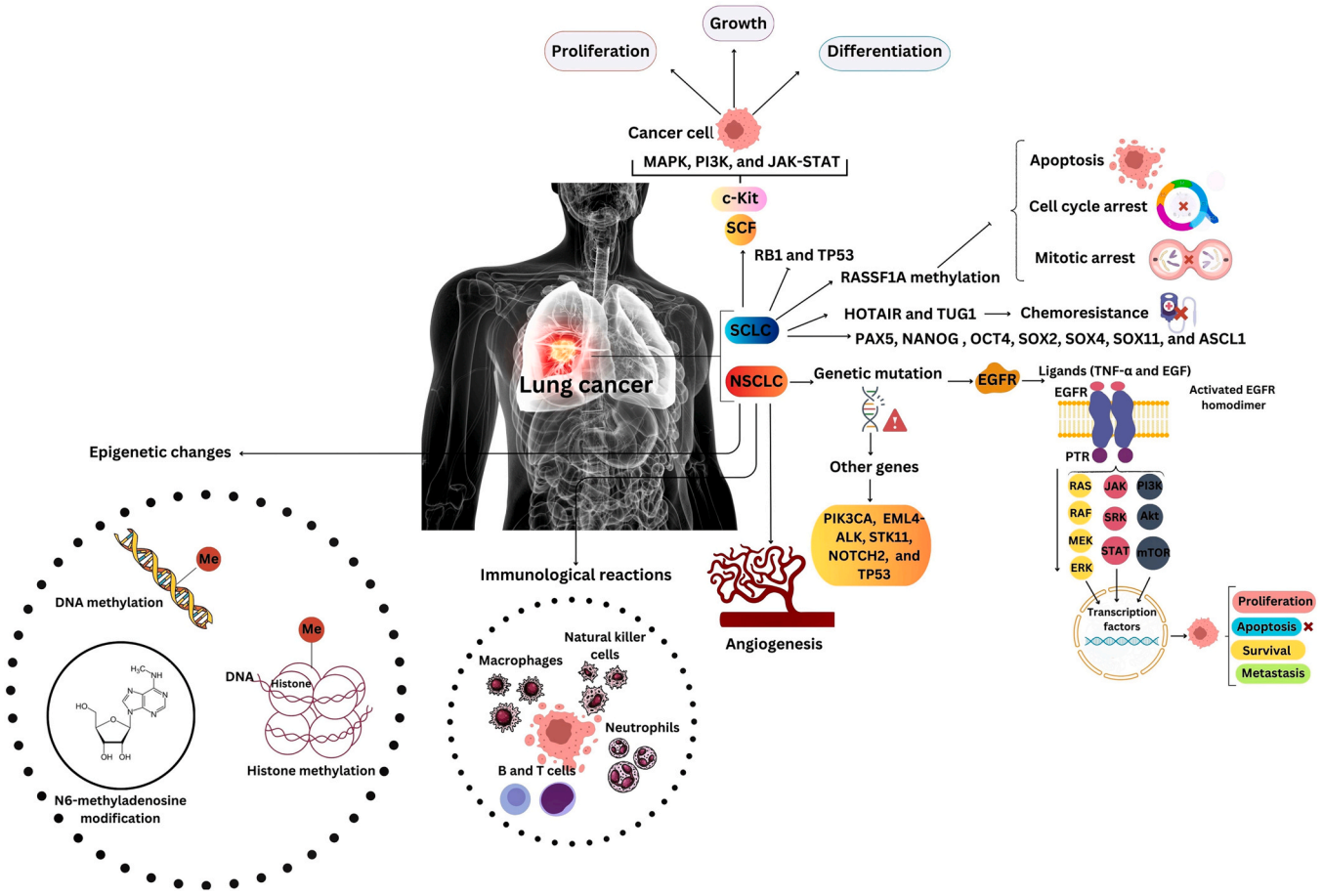

Fig. 1. A schematic presentation regarding pathogenic cellular and molecular events related to two types of lung cancer, including small-cell (SCLC) and non-small-cell carcinoma (NSCLC). SCF, Stem cell factor; RASSF1A, RAS-association domain family 1, isoform A; HOTAIR, Homeobox transcript antisense intergenic RNA; TUG1, Taurine up-regulated 1; ASCL1, Achaete-scute homolog 1; SOX, Sry-related HMG box; EGFR, Epidermal growth factor receptor; TNF-α, Tumor necrosis factor-α; PIK3CA, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit a; EML4-ALK, Echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase; PTR, Phosphorylated tyrosine residues; ERK, Extracellular-signal-regulated kinase; JAK, Janus kinase; STAT, Signal transducer and activator of transcription; mTOR, Mammalian target of rapamycin; PI3K, Phosphatidylinositol 3-kinase.

carcinoma (NSCLC) (80% of cases) (Eslami-S et al., 2024; Chang et al., 2024). Chest pain, chronic cough, and shortness of breath are the most common LC symptoms. Poor appetite, fatigue, fever, dyspnea, and weight loss are other signs and symptoms of the disease (Xing et al., 2019). The major risk factor for this neoplasia is long-term contact with tobacco smoke, leading to bronchial lesions. Other causative factors may include infection, chronic obstructive pneumonia, hereditary predispositions, and environmental pollution (e.g., much air pollution and radon exposure) (Taucher et al., 2022; Srivastava et al., 2024). Routinely, the detection of neoplasms is carried out via nuclear magnetic resonance imaging, molybdenum target imaging, ultrasound imaging technology, and tissue biopsy (Yi et al., 2023). Chemotherapy, radiotherapy, surgical techniques (e.g., robot-assisted thoracoscopic surgery, video-assisted thoracoscopic surgery lobectomy, and sleeve lobectomy), and molecular-targeted therapy, alone or in combination, are among the most common therapies at the present time (Liu et al., 2021; Cai et al., 2023a). In spite of considerable achievement in the outcomes of therapeutic methods for LC, there are still some obstacles, for example, insignificant survival rate and drug resistance (Ebrahimi et al., 2023). Furthermore, tissue engineering strategies, despite reflecting their clinical application in LC, may have the risk of graft rejection, immunogenicity, and tumorigenicity (Wang et al., 2022a; Tan et al., 2017; Seah, 2017; Yang et al., 2023). Therefore, offering an efficient strategy with minimum challenges is a key issue (Ebrahimi et al., 2023). These days, stem cell-based strategies, especially mesenchymal stem cell (MSC) therapy, have heralded a promising outlook for patients afflicted with malignancies in different body organs (Hoang et al., 2022; Mao et al., 2022). MSCs can be detected in different organs, such as bone marrow, muscle, adipose, pancreas, umbilical cord, thymus, lung, kidney, liver, spleen, dental tissues (e.g., periodontal ligament, gingiva, dental follicle, and dental pulp) and brain (Kusindarta and Wihadmadyatami, 2021; Rajan et al., 2017). Among different mesenchymal sources, umbilical cord mesenchymal stem cells (UC-MSCs) have attracted much attention in MSC-based therapies. UC is known as a postpartum waste specimen rich in MSCs with minimum problems ethically, and its collection and isolation processes are pain-free and minimally invasive (Chin et al., 2024). Several clinical trials pointed out that the administration of allogeneic UC-MSC is safe (Can et al., 2017). This mesenchymal source is a gelatinous tissue in a yellow-to-white color and creates a bridge between the placenta and the fetus. For isolating UC-MSCs, Wharton's jelly, perivascular tissue, and veins are generally used for therapeutic purposes (Bahmanpour et al., 2019 Feb 1). UC-MSCs have low immunogenicity, tumorigenicity, transplantation rejection rate, and higher proliferative action than other mesenchymal sources (ArefNezhad and Motedayyen, 2023; Tavakoli et al., 2022). Furthermore, in light of their migratory ability toward cancer cells, they may be useful to target cancer cells and transmit anti-cancer drugs locally (Rezaei-Tazangi et al., 2020). Interestingly, there are reports indicating that UC-MSCs can be a potential therapeutic candidate in the fight against LC (Li et al., 2020a). In this line, several scientific projects

have explored the efficiency of intact UC-MSCs and extracellular vehicles (EVs), exosomes, and conditioned medium (CM) derived from this mesenchymal source, as well as genetically engineered UC-MSCs on LC *in vitro* and *in vivo*. Hence, in this literature review, we intend to focus on the efficiency of these approaches for treating LC by noticing cellular and molecular mechanisms.

2. Lung cancer and pathogenic occurrences

The pathogenic processes participating in the onset or progress of LC have not been understood yet, but various factors have been considered. Basically, LC initiation and development stem from normal epithelium histologically or a sequence of progressive morphological alteration alongside molecular changes (Klebe and Henderson, 2013).

2.1. SCLC

High-throughput genome-sequencing reports relying on whole genome, exome, and transcriptome and copy number assessments have mentioned the striking role of genetic and epigenetic mutations in SCLC (Wang et al., 2023a). A prominent genetic property of SCLC, unlike other types of LC, is blocking tumor suppressors, including RB1 and TP53 (Fig. 1) (Wu et al., 2023). A new case report study revealed that RB1 and TP53 deletion may promote the transformation from lung adenocarcinoma to SCLC through the expression of neuroendocrine markers (Li et al., 2022). Variable expression of markers related to neuroendocrine cell differentiation, such as chromogranin, neural cell adhesion molecule (NCAM/CD56), insulinoma-associated protein 1 (INSM1), and synaptophysin, has been addressed (Raso et al., 2021). The main gene expression regulators are transcription factors, which can affect different intracellular signal transduction pathways (Mitsis et al., 2020). SCLC atypically expresses multiple developmental transcription factors, for example, PAX5, NANOG, OCT4, SOX2, SOX4, SOX11, and ASCL1 (Teicher, 2014; Gazdar et al., 2017). The involvement of a large number of signaling pathways in SCLC has also been identified, especially phosphatase and tensin homolog (PTEN) and phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways. Concerning this issue, phosphorylated Akt has been recognized in about 70% of SCLCs. Furthermore, the increased protein expression of phosphorylated 4EBP1, S6K1, and mTOR has been reported in SCLC cells in comparison with normal epithelial cells (Krystal et al., 2002; Marinov et al., 2009). Transcriptomic analyses of SCLC cases also confirmed the decreased activity of the Notch signaling, which is crucial for neuroendocrine compartment regulation (George et al., 2015; Collins et al., 2004). SCLC incidence is also related to the dysfunction of tyrosine kinase receptors (TKRs), known as pivotal elements of signaling pathways involved in cell-to-cell communications (Cani et al., 2023). Indeed, TKRs are engaged in various signaling pathways, for instance, cell viability, proliferation, and migration (Cani et al., 2023). A piece of evidence manifested that following the binding of c-Kit, a subset of the platelet-derived growth factor (PDGF)/c-Kit tyrosine kinase receptor family, to its ligand (i.e., stem cell factor [SCF]), processes related to cell differentiation and growth are triggered by activating the mitogen-activated protein kinase (MAPK), PI3K, and Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling pathways, so participating in tumorigenesis (Fischer et al., 2007). Moreover, upregulation of c-MET, another key TKR, has been detected in SCLC (Titmarsh et al., 2020). In addition to the mentioned receptors, some cell surface receptors have been determined to be upregulated in cell cultures and clinical samples comprising G protein-coupled Receptors (GPCRs), for example, the vasopressin receptor (Teicher, 2014). Scientific evidence also unveiled high expression levels of C-X-C chemokine receptor type 4 (CXCR4), named a G-protein-coupled chemokine receptor, in SCLC cells. CXCR4 activation instigates cancer cell migration and binding to stromal cells that release C-X-C motif chemokine 12 (CXCL12). On the other hand, CXCL12, another name for stromal cell-derived factor 1 (SDF-1), provides signalings to tumor cell growth and drug resistance (Cho et al., 2011). Another genetic condition contributing to lung tumorigenesis is attributed to chromosomal aberrations, showing genome instability. Genomic analyses have implicated gains of 1p, 2p, 3q, 5p, 8q, and 19p in a large number of SCLCs. These sites have a central role in encoding oncogenes like KRAS and MYC (D'Angelo and Pietanza, 2010). SCLC cells with deletions of 18q and amplification of 1p, 2p, and 3q are also the characteristics of a malignant phenotype of the disease (Balsara and Testa, 2002). It is inferred that allele loss on chromosome 3p is one of the primer occurrences of LC that happens in SCLC with a frequency of 90%. Several regions of loss have been discovered, for instance, 3p12, 3p14.2, 3p21.3, and 3p24. Many genes placed in these areas possess tumor suppressor function, and generally, their expression is disrupted in light of epigenetic events (D'Angelo and Pietanza, 2010). Many investigations have documented the role of epigenetic alterations, like DNA methylation, histone modifications, and expression changes of non-coding RNAs (ncRNAs), in SCLC (Chen et al., 2022). In this direction, Kalari and co-workers, using genome-scale analysis of alterations of DNA methylation, detected hundreds of tumor-specific methylated genes, comprising SOX1 and NKX2–1, in SCLC (Kalari et al., 2013). Also, the methylation of a tumor suppressor gene, RAS-association domain family 1, isoform A (RASSF1A), often occurs in SCLC (Gazdar et al., 2017). An example of histone modifications is the histone acetyltransferase gene KAT6B and the histone methyltransferase genes KMT2D and KMT2C, which are abundantly mutated in this cancer (Simó-Riudalbas et al., 2015). NcRNAs are important regulators engaged in various key processes, for instance, cell proliferation, apoptosis, metabolism, differentiation, and post-transcriptional modifications (Arefnezhad et al., 2024). These RNAs can serve as oncogenes or tumor suppressors. In SCLC, the involvement of ncRNAs, especially long ncRNAs (HOTAIR, H19, and TUG1) and microRNAs (microRNA-134), have been demonstrated (Gazdar et al., 2017; Chen et al., 2015; Li et al., 2020b).

2.2. NSCLC

Several genetic changes, such as genetic mutations, inhibition of tumor suppressor genes (e.g., TP53 and p16), and genetic instability, have been known to be involved in NSCLC occurrence and progression (Raso and Wistuba, 2007). The majority of mutations occur in the epidermal growth factor receptor (EGFR) gene, influencing 10–30% of cases (Guo et al., 2022). EGFR is a subset of the ErbB family of RTKs that binds to its specific ligands, including EGF, amphiregulin, and transforming growth factor-α (TGF-α) (Chhouri et al., 2023). The existence of the variation of the EGFR T790M sequence has been detected in many NSCLC patients (Guo et al., 2022). Also, in 22%-25% of related cases, point mutations or cyclin-dependent kinase (CDK) 4/6 and cyclin D1–3 amplifications, leading to the strengthening of cell proliferation, have been shown (Tsironis et al., 2018). The cell cycle is monitored by multiple external signals by CDK4/6. In normal cells, signals associated with cell growth, for example, β-catenin, Akt, PI3K, Jun, RAF, and RAS, trigger cyclin D. Afterward, cyclin D binds to CDK4/6, resulting in the phosphorylation of retinoblastoma protein (Rb). As a result, cyclin E-CDK 2 is activated, and then, Rb phosphorylation is promoted (Zhang et al., 2021a). Next, Rb is separated from the early-region-2 transcription factor (E2F), authorizing uncontrolled cell proliferation (Xu et al., 2024). Other mutations have recently been reported in phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit a (PIK3CA), echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK), STK11, NOTCH2, and TP53 genes (Cai et al., 2023b). In addition to genetic-related agents, epigenetic factors, for instance, DNA methylation, histone methylation, and ncRNA modification, are among the key players in NSCLC pathogenesis (Yang et al., 2024). In this regard, Zhang and co-workers showed that DNA methylation inhibits DNA-methylation-repressed long ncRNA DIO3 opposite

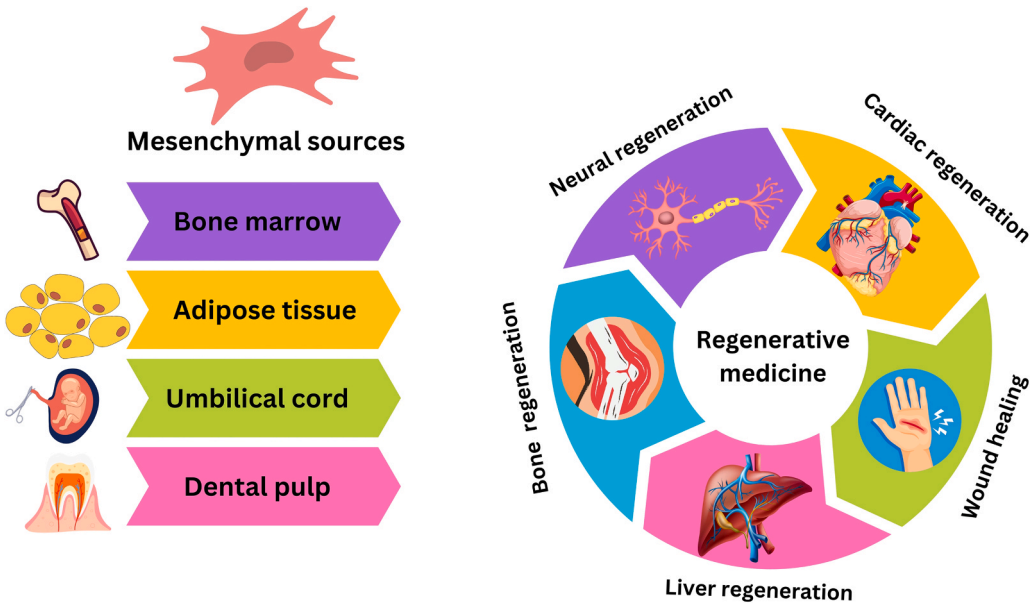

Fig. 2. Mesenchymal stem cells have a potential role in regenerative medicine (Margiana et al., 2022).

strand upstream RNA (DIO3OS), which is an important factor for protection against NSCLC, by regulating the hnRNPK-MYC-CDC25A axis (Zhang et al., 2021b). Changes in histone methylation regulators are also closely associated with LC (Schiffmann et al., 2016; Song et al., 2012). Kuo and colleagues demonstrated that JARID1B/KDM5B (jumonji AT-rich interactive domain 1B/lysine-specific demethylase 5B) is a potential prognostic index of NSCLC and potentiates cancer progression (Kuo et al., 2018). JARID1B/KDM5B is named a histone demethylase modulating differentiation and self-renewal in cancer and stem cells (Stewart et al., 2015). NcRNAs, which mainly comprise microRNA, long ncRNAs, and circular RNA, can also affect the development of NSCLC by regulating DNA methylation (Yan et al., 2024). It is stated that the expression of microRNA-221 and- 222 increases in cell lines and tissues of malignant NSCLC (Deng et al., 2015). Deng et al. pointed out that the overexpression of long ncRNA AFAP1-AS1 is linked with a weak prognosis in NSCLC subjects (Deng et al., 2015). Furthermore, some circular RNAs, such as circ_0016760, circSATB2, and circFGFR1, have reflected their roles in potentiating NSCLC by several mechanisms, including regulating the miR-1287/GAGE1 axis, modulating fascin homolog 1 (FSCN1) expression, and sponging miR-381–3p (Zhang et al., 2019, 2020; Li et al., 2018a). Alongside molecular agents, the involvement of cellular processes, like angiogenesis and inflammatory infiltration, in NSCLC has been approved (Rivas-Fuentes et al., 2015). Cancer cell growth basically depends on the supportive role of vasculature structures. Thereby, angiogenesis fosters the necessary microenvironment for tumor initiation and development (Coelho et al., 2017). It has to be said that angiogenesis not only solves the oxygen and nutrient requirements of the tumoral cells but also enhances the metastatic potential of tumor cells. This process is regulated by different key effectors, including PDGF, fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) (Xu et al., 2024). Inflammatory infiltration in NSCLC is mainly orchestrated by tumor-associated macrophages (TAM). In addition, the existence of tumor-infiltrating lymphocytes (TIL), such as tumor-associated neutrophils, natural killer cells, B cells, and T cells, has been determined in NSCLC (Rivas-Fuentes et al., 2015). Interestingly, the observed differences in inflammatory infiltration are associated with the formation of chemokines, which are crucial regulators of angiogenesis (Coussens and Werb, 2002).

2.3. *Mesenchymal stem cells and general features*

MSCs are a group of multipotent and heterogenous stromal cells identified by the following characteristics: their plastic adherence, abilities to express some surface markers (e.g., CD29, CD44, CD90, CD73, and CD105), and capacity to differentiate into many cell types of mesenchymal lineage, including chondrocytes, osteoblasts, adipocyte, skeletal myocytes, tenocytes, and visceral mesoderm cells. They are also differentiated into the cells of endodermal and ectodermal lineage, for instance, cardiomyocytes, neurons, and hepatocytes (Carluccio et al., 2020; Kuchemüller et al., 2024; Gu et al., 2024; Simeone et al., 2020). Moreover, MSCs can easily grow in the culture dish and release high levels of cytokine and growth factors useful in regenerative medicine (e.g., neural regeneration, cardiac regeneration, wound healing, liver regeneration, and bone regeneration) (Fig. 2), such as EGF, FGF, VEGF, and TGF-β (Pittenger et al., 2019; Liu et al., 2020; Noverina et al., 2019).

2.4. *Umbilical cord mesenchymal stem cells and biological features*

Numerous studies have highlighted different biological and therapeutic capacities of UC-MSCs, encompassing anti-cancer (Panahandeh et al., 2024), anti-oxidative (Yao et al., 2019), anti-inflammatory (Wang et al., 2023b), anti-viral (Hassen et al., 2023), and anti-bacterial (Kim et al., 2011) effects.

2.5. *Anti-cancer effects*

The ani-neoplasm action of UC-MSCs has been demonstrated in several cancer cell lines, such as breast cancer (Ma et al., 2012), colon cancer (Dong et al., 2019), ovarian cancer (Li and Li, 2019), and pancreatic cancer (Ding et al., 2019); however, there are some contradicting data yet (Ma et al., 2015). Therefore, there is a substantial need to understand the interaction between UC-MSCs and cancer cells thoroughly. A number of studies have revealed the anti-cancer capacity of UC-MSCs against malignancies, such as breast cancer, esophageal cancer, and ovarian cancer, through different mechanisms, like the stimulation of programmed cell death (apoptosis) of cancer cells, cell cycle arrest, and suppression/activation of influential signaling pathways, like Wnt and PI3K/Akt signaling pathways (Ma et al., 2012; Yuan et al., 2018; Aref Nezhad et al., 2023). However, some experimental investigations expressed the elevating role of this type of MSCs in the

cancer cell growth, migration, and invasion of breast and esophageal neoplasms by increasing the expression levels of metastasis-associated proteins (MMP [matrix metalloproteinase]-2 and MMP-9) and proliferation-pertained proteins (surviving and Bcl-2) and the secretion of epithelial-mesenchymal transformation (EMT)-related cytokines (IL [interleukin]-6 and IL-8) (Ma et al., 2015; Yang et al., 2014). Therefore, there is a substantial need to understand the interaction between UC-MSCs and cancer cells thoroughly.

2.6. Anti-oxidative effects

The protective role of UC-MSCs against oxidative stress conditions has also been mentioned. In this regard, it is stated that human UC-MSCs (hUC-MSCs) decrease renal oxidative stress in a rat model of type 2 diabetes mellitus via activating the nuclear erythroid 2-related factor 2 (Nrf2) signaling pathway, a marker for reduced reactive oxygen species (ROS) levels and activity of antioxidant enzymes (Nie et al., 2021). This mesenchymal source has unveiled its anti-oxidative function in animal models of Alzheimer's disease, renal ischemia/reperfusion injury, and cutaneous wound healing in type 2 diabetes by elevating the levels of nitric oxide (NO), neuronal nitric oxide synthase (nNOS), glutathione-S-transferase (GST), catalase, and reduced glutathione (GSH) and superoxide dismutase (SOD) activity, and dwindling the levels of malondialdehyde (Cui et al., 2017; Fahmy et al., 2017; Wang et al., 2023c). Of note, oxidative stress is an indicator of inflammatory occurrences (Li et al., 2012).

2.7. Anti-inflammatory effects

Researchers have pointed out that UC-MSCs can have a suppressive role in inflammatory-related conditions. In this line, the potential ability of UC-MSCs in repressing the lipopolysaccharide (LPS)-conferred elevation of serum levels of pro-inflammatory cytokines, including IL-1β, tumor necrosis factor-α (TNF-α), and IL-6, without influencing the level of anti-inflammatory mediator IL-10, in rats with acute lung injury has been documented (Li et al., 2012). In addition, Wang et al. illustrated that hUC-MSCs are capable of reducing the number of neutrophils recruiting to the intestines and polarizing them toward the N2 phenotype, expressing considerable levels of IL-8, C-C Motif Chemokine Ligand 2 (CCL2), VEGF, and CXCR4 and decreased levels of CCL3, intercellular adhesion molecule 1 (ICAM-1), and factor-associated suicide, in mice with inflammatory bowel disease that received hUC-MSCs (Wang et al., 2020).

2.8. Anti-viral effects

The viricidal action of UC-MSCs has been emphasized in some studies indirectly or directly. For example, it is approved the beneficial role of UC-MSCs in improving disrupted alveolar fluid clearance and protein penetrance of human alveolar epithelial cells infected by the influenza A virus (H5N1) and inhibiting the RNA replication of the hepatitis C virus (Loy et al., 2019; Qian et al., 2016). Interestingly, a phase 1 clinical study examined the safety of intravenous infusion of UC-MSCs (3×107 cells for each infusion) in coronavirus disease 2019 (COVID-19) cases. Finally, this study exhibited no remarked side effects related to UC-MSCs infusion. Also, all COVID-19 cases, whether underwent this therapy or not, were recuperated from this novel viral problem with the promotion of respiratory status, laboratory indices, and clinical symptoms (Meng et al., 2020).

3. Anti-bacterial effects

Regarding the effectuality of UC-MSCs on bacterial pathogens, there is also hopeful evidence. This source of MSCs suppresses the growth of imipenem-resistant *Pseudomonas aeruginosa* (PA) and *Escherichia coli* (EC) through the restoration of outer membrane protein expression in PA and release of beta-defensin- 2, a salt-sensitive peptide located in lung epithelium with antimicrobial action, in PA and EC, respectively (Ren et al., 2020; Sung et al., 2016; Inthasin et al., 2023). A new study (2023) provided a document indicating that MSCs extracted from animal umbilical cord tissue (canine) inherently express the messenger RNA of a number of peptides with antimicrobial features, such as secretory leukocyte protease inhibitor, lipocalin 2, hepcidin, elafin, and CXCL8 (Manna et al., 2023).

3.1. The dark side of umbilical cord mesenchymal stem cells in medicine

Despite the mentioned potential ability of UC-MSCs in the medical arena, some challenges hinder their clinical utilization. In order to reach a successful stem cell transplantation, the restoration of both platelet and neutrophil production must happen. The observation of these clinical indices needs more time compared with MSCs derived from other sources, like bone marrow MSCs (Waller-Wise, 2011). One of the determining factors of engraftment time is cell dose, which is associated with the volume of the obtained UC blood. This factor is related to the content of profitable stem cells in the blood sample. Having considered the low volume of collected cells from UC blood, it can be expected that the content of MSCs originating from UC blood is not considerable. It has been expressed that this content is almost 10 percent lower than the content collected from the bone marrow (Moise Jr, 2005). UC-MSCs, like other mesenchymal sources, afford low capacity to proliferate in culture media. The activation of cellular senescence has been detected in various mesenchymal sources, such as UC, endometrium, dental pulp, and bone marrow. Interestingly, the restricted replicative potential of MSCs has some positive and negative aspects in the clinical setting (Kim and Park, 2017). On the one hand, the restricted replicative capacity of MSCs is a protective factor against malignant transformation following transplantation. On the other hand, cellular senescence can alter the differentiation ability and immunoregulatory action of hMSCs (Banfi et al., 2000; Carlos Sepúlveda et al., 2014). In addition to these problems, some probably detrimental effects regarding UC-MSCs have been highlighted, such as their tumorigenic capacity, procoagulant features participating in pulmonary embolism, and role in increasing the risk of viral transmission after prescription (ArefNezhad and Motedayyen, 2023).

3.2. Exogenous umbilical cord mesenchymal stem cells: their migration and fate

The migration of UC-MSCs probably relies on chemotactic signals originating from damaged tissue or the way of administration (Shen et al., 2015). For example, an experimental study revealed that the migration of MSCs to the damaged kidney in a mouse model of acute renal failure depends on CD44 expression on these stem cells (Eggenhofer et al., 2014). Concerning the administration route, it has been declared that the intravenous administration of MSCs, a popular method in most studies, gives rise to trapping a great number of MSCs in the lung organ after the first pass (Eggenhofer et al., 2014). Twenty-four hours later, MSCs are placed in other organs, especially spleen and liver (Eggenhofer et al., 2012; Kraitchman et al., 2005). They also arrive at the damaged tissue regions (Kraitchman et al., 2005). However, the viability of MSCs leaving the lung is a puzzle. According to the present evidence, MSCs are not viable after 24 hours following intravenous administration, but their radioactive marker can be identified in the liver (Eggenhofer et al., 2012). The removal of MSCs may be attributed to immunological occurrences. The capacity of infused MSCs to disappear does not conflict with the therapeutic influences of these cells. It has been addressed that the production of macrophages with a regulatory phenotype can stem from dead MSCs that underwent phagocytosis (Lu et al., 2013). Also, there is a theory expressing that a small number of MSCs evade death and have a causative role in exerting the therapeutic function of these cells (Eggenhofer et al., 2014).

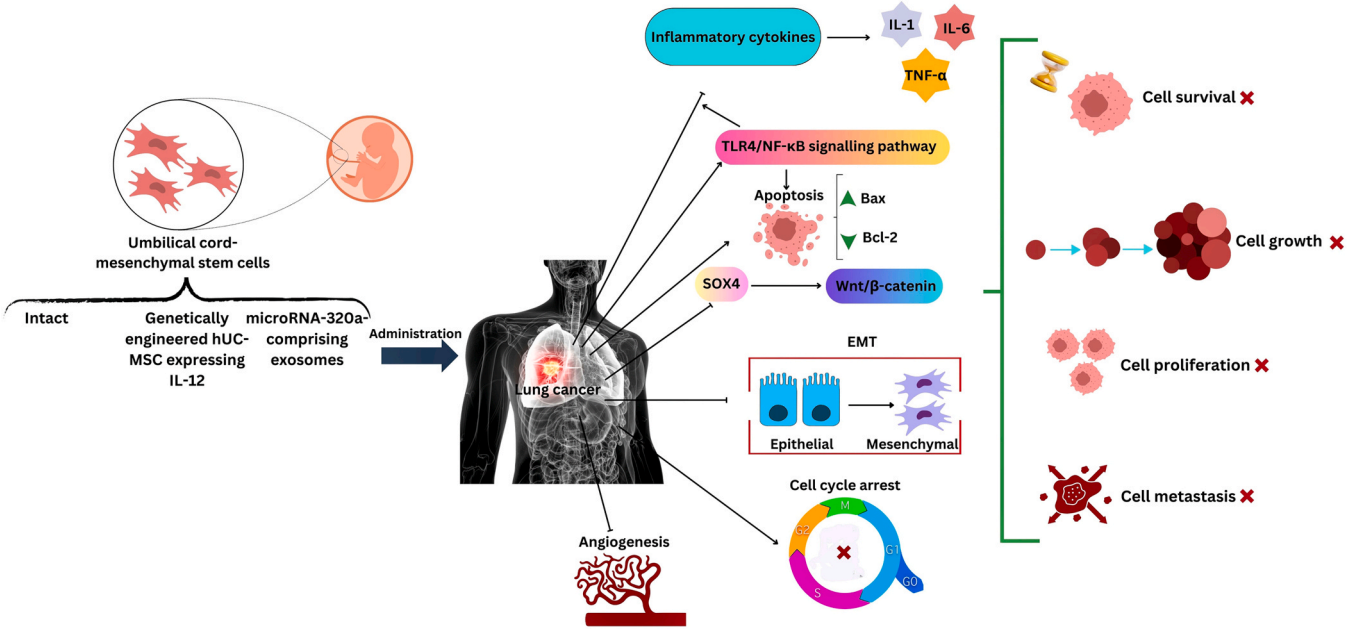

Fig. 3. The possible therapeutic effects and mechanism of mesenchymal stem cell therapy in lung cancer using umbilical cord mesenchymal stem cells. SOX4, Sex-determining region Y-related high-mobility-group box transcription factor 4; EMT, Epithelial-mesenchymal transformation; IL, Interleukin; TNF-α, Tumor necrosis factor-α.

3.3. Umbilical cord mesenchymal stem cells and lung cancer

Numerous investigations have assessed the potential effects of hUC-MSCs on LC by applying different methods preclinically. The majority of scientistic projects imply the anti-LC function of UC-MSCs (Li et al., 2020a; Chai et al., 2018; Maurya et al., 2010); however, some conflicting evidence challenges these findings (Wang et al., 2022b; Dong et al., 2018), which may be associated with the kind of studied cell lines and utilized manners and time for therapeutic strategies.

3.4. Regulation of cell survival, proliferation, and growth

One of the popular techniques for MSC therapy is using genetically engineered MSCs by viral or non-viral procedures (Wang et al., 2014). In the recent scientific effort of Goh and co-workers (2023), the anti-growth activity of genetically engineered hUC-MSC expressing IL-12 in human lung adenocarcinoma cells was monitored (Jiunn-Jye et al., 2023). IL-12 is an important immunoregulatory cytokine with anti-neoplasm function by exerting immunostimulatory and anti-angiogenic processes (Nguyen et al., 2020). At first, Goh et al. compared electroporation and adenoviral methods applied to produce hUC-MSCs expressing IL-12 (Jiunn-Jye et al., 2023). In this work, the adenoviral method, a non-integrating viral vector with the minimum genotoxicity risk, was selected as a superior choice in terms of hIL-12 protein expression, transfection efficiency, and cell survival at post-transfection. Consequently, hUC-MSCs expressing IL-12 were co-cultured with MRC-5 or H1975 cells. After three days of the co-culture of hUC-MSCs with H1975 cells, lung cancer cell survival was reduced by about 18% in comparison with untreated H1975 cells. Following five days of the co-culture, the reduction of cell survival reached 66.8%. On the contrary, hUC-MSCs did not affect the cell survival of MRC-5 human lung fibroblast cells. These outcomes indicate directly suppressing lung adenocarcinoma cell growth by hUC-MSCs. Surprisingly, the cell survival of MRC-5 cells was dramatically elevated by 150.4% following five days of co-culture with untransduced hUC-MSCs (Jiunn-Jye et al., 2023). In a different approach, Chen et al. evaluated the feasibility of utilization of UC-MSCs as a cellular vector for interferon-β (IFN-β), an extracellular cytokine serving as a tumor suppressor agent by lentiviral gene transduction, in nude mice receiving A549 cell subcutaneously. The results of this investigation indicated that UC-MSCs transfected with an IFN-β-overexpression plasmid have a remarked role in postponing tumor growth, as demonstrated by diminished tumor weight and volume without damaging internal organs of animals (i.e., lung, liver, and kidney) (Chen et al., 2019). Recently, the interplay between MSCs-originated exosomes and cancer cells has been one of the main topics of researchers in tumor-related projects (Wang et al., 2014). Exosomes are described as EVs in the size of 40–160 nm that convey critical signals for intercellular communications (Yu et al., 2023). Wang et al. inspected the impacts of hUC-MSCs and their exosomes on polyploid NSCLC cells. Subsequent to the characterization of MSCs by flow cytometry analyses, related cell culture protocols to obtain CM were performed (Wang et al., 2022b). For this goal, the supernatant of the last culture medium was collected, filtered, and considered CM, which contains various growth factors and cytokines. After that, the isolation and quantification processes of hUC-MSCs-derived exosomes were carried out by serial centrifugation and BCA protein quantification, respectively. They declared that hUC-MSCs and their extracted CM and exosomes did not influence the proliferation of H1299 and A549 cells (Wang et al., 2022b).

3.5. Regulation of EMT and cell migration and metastasis

In the scientific project of Xie et al., it was observed that microRNA-320a-comprising exosomes suppress EMT by regulating E-cadherin and N-cadherin expressions (Xie and Wang, 2022). Also, the molecular analyses of this study demonstrated that the malignant phenotype of LC is reverted through the attenuation of the Wnt/β-catenin pathway by affecting the gene expression of SOX4, an element belonging to the SOX (Sry-related high-mobility group box) family involved in metastasis and cellular transformation (Xie and Wang, 2022; Zong et al., 2023). On the contrary, Wang and colleagues, using Transwell assay and RT-qPCR analysis, revealed that these MSCs and their exosomes enhanced LC cell migration and EMT by reducing the expression of epithelial landmark E-cadherin and increasing the expression of mesenchymal landmark vimentin and N-cadherin in H1299 and A549 cells (Wang et al., 2022b).

Table 1
Reports regarding mesenchymal stem cell therapy using umbilical cord mesenchymal stem cells in the treatment of lung cancer *in vitro* and *in vivo*.

Used UC-MSCs	Target (s)	Effect/ Mechanism (s)	Model	Ref.
UC-MSCs	Akt, PI3K, and STAT3	Inducing apoptosis and repressing cell invasion	*In vitro*	(Chai et al., 2018)
Rat UC-MSCs	Cyclin A and CDK2	Repressing cell proliferation, decreasing colony size, arresting cell cycle, reducing tumor weight, and inducing apoptosis	*In vitro* and *in vivo*	(Maurya et al., 2010)
hUC-MSCs	Bax, Bcl-2, NF-κB, TLR4, TNF-α, IL-1, and IL-6	Repressing cell growth, decreasing tumor weight, promoting thymus index, suppressing inflammatory responses, and inducing apoptosis	*In vivo*	(Li et al., 2020a)
hUC-MSCs treated with nicotine	PCNA	Promoting cell proliferation, growth, and migration and tumor formation	*In vitro* and *in vivo*	(Li et al., 2018b)
hUC-MSCs delivering IL24	JNK, Akt, ERK-1/2, Bax, Bcl-2, p21, PARP, and caspases-3/8/9	Inducing apoptosis, arresting cell cycle, and repressing tumor growth and angiogenesis	*In vitro* and *in vivo*	(Zhang et al., 2013)
Genetically engineered hUC-MSCs expressing IL-12	-	Repressing cell growth	*In vitro*	(Jiunn-Jye et al., 2023)
hUC-MSCs delivering sTRAIL and genetically modified hUC-MSCs delivering ISZ-sTRAIL	MCP-1 and CCR2	Inducing apoptosis	*In vitro* and *in vivo*	(Zhao et al., 2018)
EVs delivering miR-410 derived from hUC-MSCs	PTEN	Potentiating cell growth	*In vitro* and *in vivo*	(Dong et al., 2018)
CM derived from hUC-MSCs	Caspase-7, Bcl-2, c-Myc, and β-catenin	Repressing cell proliferation and migration, arresting cell cycle, and inducing cell fusion	*In vitro*	(Yuan et al., 2018)
CM and exosomes derived form hUC-MSCs	NF-κB, MAPK, GSK-3β, Akt, and Smad2/3	Enhancing EMT and cell migration and invasion but inhibiting cell proliferation and inducing apoptosis	*In vitro*	(Zhao et al., 2018)
Exosomes delivering miR-320a derived from hUC-MSCs	E-cadherin, N-cadherin, and SOX4	Repressing cell growth and EMT	*In vitro* and *in vivo*	(Xie and Wang, 2022)
Exosomes derived form hUC-MSCs	p-AMPK, LC3A/B, p62, MMP-9, Bcl-xl, and Bak	Potentiating cell migration and EMT, attenuation apoptosis, and inducing autophagy	*In vitro*	(Wang et al., 2022b)

3.6. Regulation of apoptosis and autophagy

Li et al. explored the suppressive effects of hUC-MSCs on an animal model of Lewis lung cancer established by inoculating mice with suspension of Lewis lung cancer cells. In this experiment, 1×10^6 hUC-MSCs (weekly for two sequential weeks) were injected into mice of Lewis LC through a caudal vein (Li et al., 2020a). In the end, the authors inferred that apoptotic pathways can be targeted by hUC-MSCs in Lewis LC, as evidenced by enhanced expression of the Bax gene and suppressed expression of the Bcl-2 gene, which are apoptogenic and anti-apoptotic mediators, respectively (Li et al., 2020a). Appealingly, the apoptotic capacities of this mesenchymal therapy were attributed to the activation of the toll-like receptor 4 (TLR4)/nuclear factor kappa B (NF-κB) signaling pathway, which is pivotal signaling in suppressing tumorigenesis (Li et al., 2020a). Another experimental work assessed the impacts of microRNA-320a-comprising exosomes obtained from hUC-MSCs on LC cells (Xie and Wang, 2022). *In vitro* outcomes underscored that these exosomes induce apoptosis in LC cells (H460 and H1299) through caspase-3 activity potentiation (Xie and Wang, 2022). In contrast, the analyzed data of Wang et al. implicated autophagy induction (elevation of the LC3 puncta distribution) and apoptosis attenuation (reduction in the number of apoptotic cells) after exposing hUC-MSCs and their originated exosomes to H1299 and A549 cells. Eventually, Wang and colleagues introduced AMP-activated protein kinase (AMPK) signaling pathway activation as a possible molecular mechanism justifying the aforementioned results (Wang et al., 2022b).

3.7. Regulation of inflammatory and immune responses

The research of Li and co-workers showed the suppression of inflammatory reactions by repressing the activity of inflammatory cytokines, e.g., IL-1, TNF-α, and IL-6, and potentiation of thymus index (Fig. 3) following the administration of hUC-MSCs in the studied tumoral mice (Li et al., 2020a). The thymus index is a key indicator for clarifying the status of cellular immunity; also, it is related to hematopoietic function following chemotherapy (Gu et al., 2021).

4. Conclusion

LC, as a life-threatening disorder, affects a great number of people in the world, and the common treatments for this condition, like chemotherapy, radiotherapy, and surgery, have not provided a promising landscape for patients with this malignancy. Newly, MSCs-based therapy using UC-MSCs has acquired much interest in the treatments of cancers, especially LC. Overall, this mesenchymal source possesses different biological and pharmacological abilities, such as anti-cancer, antioxidative, anti-inflammatory, anti-viral, and anti-bacterial effects. In addition, from a technical vision, its collection and isolation are carried out easily, and its transplantation is accomplished with a low rate of immunogenicity and tumorgenicity. In order to reach the maximum efficiency of UC-MSCs on LC, different strategies have been applied and assessed, such as harnessing intact UC-MSCs and extracellular vesicles, exosomes, and CM originating from UC-MSCs, as well as genetically engineered UC-MSCs (Table 1). The studies evaluating the effectiveness of intact and genetically engineered UC-MSCs heralded promising outlook for LC patients, However, there are contradictory results regarding the functionality of methods based on EVs, exosomes, and CM in LC treatment. The majority of experimental studies highlighting the positive effects of this treatment on LC rely on different cellular and molecular mechanisms, like apoptosis stimulation (elevation of capsase-3 activity and Bax gene expression and attenuation of Bcl-2 gene expression) and inhibition of EMT (increment of E-cadherin expression and decrement of N-cadherin expression), inflammatory mediators (IL-1, TNF-α, and IL-6), cell migration, proliferation, and invasion, and tumor growth (reduction of tumor weight and volume). On the contrary, few studies revealed the adverse effects of hUC-MSCs-based therapy on

LC via autophagy stimulation (promotion of LC3A/B expression protein), apoptosis suppression (reduction of Bak expression and elevation of Bcl-xl expression), and EMT and metastasis promotion (increase of MMP-9, vimentin, and N-cadherin expression and decrease of E-cadherin expression). This discrepancy may be related to the type of investigated cell lines and used methods. Thus, it is expected that more *in vitro* and *in vivo* investigations, particularly concerning therapies based on EVs, exosomes, and CM, be conducted to better examine the efficiency of UC-MSCs and select the best strategies to benefit from this mesenchymal source to fight against LC.

Data availability

Data will be made available on request.

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