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Review Paper

Therapeutic Challenges in Sulfur Mustard Induced Pulmonary Complications and Mesenchymal Stem Cells

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ABSTRACT

Sulfur mustard (SM), an alkylating chemical agent, targets several organs, particularly the respiratory system, and results in early and late toxic effects. Currently, there is a considerable lack of adequate medical countermeasures for SM-associated lung injury. Mesenchymal stem cells (MSCs) are characterized by their self-renewal properties and differentiation capacity into multiple cell lineages. These features provide MSCs with the unique ability to engraft into injured tissues and exert immunomodulatory and tissue-repairing effects. Recent congruent findings on the usefulness of MSCs in the context of SM-induced pulmonary injury have raised the promise of their therapeutic use; however, their potential protective mechanisms are still unknown. A better understanding of the therapeutic mechanism of MSCs involved in SM-pulmonary injury would help figure out new target options. Accordingly, this study discusses the opportunities and therapeutic mechanisms of MSCs in SM poisoning. Recent advances in the treatment of SM-induced lung injury and the therapeutic mechanisms of MSCs as possible new treatments are highlighted. The PubMed and Scopus databases for published studies on the therapeutic approach of SM-induced lung manifestations were searched with a focus on the therapeutic mechanisms of MSCs.

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Introduction

Sulfur mustard

Sulfur Mustard (SM; bis-[2-chloroethyl] sulfide), with the formula CH_2CH_2CL, is a potent chemical warfare that was first used in Ypres (Belgium) during World War I [1, 2]. SM is an oily liquid with high solubility in organic solvents with an odor similar to garlic or onion [3]. Due to easy storage, delivery, and low-cost production, its usage threatens humanity [4, 5]. SM could be absorbed through inhalation, eye and skin contact, or the gastrointestinal tract. The eye, skin, and respiratory system are the three main targets of this toxic agent. In high doses, this gas can damage proliferating cells in the bone marrow and consequently lead to leukemia and severe immunosuppression [3]. Long-term complications of SM are mainly targeted in the respiratory tract leading to serious problems [6]. Today, a large number of victims are suffering from SM-induced chronic pulmonary complications with a wide range of lung disorders. Despite many studies, current diagnostic, and therapeutic methods have no appropriate efficiency for these patients. Given the unique properties of mesenchymal stem cells (MSCs), numerous studies have focused on the therapeutic effects of these cells in different lung diseases. Their results have been promising the treatment of various diseases [7-11]. Several studies have reported the therapeutic effect of MSCs on SM-induced animal models and victims [10, 12].

The research team of the current paper has gained a lot of experimental and clinical experience in managing SM poisoning. According to recent reports, MSCs are highly tolerant toward SM toxicity in terms of differentiation ability and cell survival; however, SM can affect their migratory activity [13]. We have shown the decreased serum level of stromal cell-derived factor-1α, a chemokine involved in the trafficking and homing of stem cells, in SM-injured patients with long-term pulmonary complications [14]. Therefore, incomplete delivery of MSCs to damaged sites, as a result of decreased MSCs migration or stromal cell-derived factor-1α expression in survivors exposed to SM, is involved in the persistence of long-term complications [14]. Our results have also shown the promising results of adipose-derived MSCs in the treatment of mouse models induced by 2-chloroethyl ethyl sulfide (CEES), a monofunctional analog of SM with similar properties [15]. Therefore, MSCs can be proposed as a new therapeutic candidate for patients with SM-induced complications. Accordingly, this study reviews and discusses the possible therapeutic mechanisms of MSCs in SM-induced lung injuries.

Pulmonary effects of sulfur mustard

The pulmonary system is the main target of SM which is associated with extensive lung injury [16]. SM-induced lung damage is often lethal in the short term or can be a source of ongoing symptoms in survivors. Exposure to SM can lead to upper and lower respiratory damage. Upper airway injury presents as pharyngitis and laryngitis as well as tracheal lesions. Lower airway involvement occurs with shortness of breath and cough [17]. A severe respiratory disorder can be manifested as acute respiratory distress syndrome (ARDS) with high mortality. Mucosal edema is the primary obvious symptom associated with pain and nose or sinus disturbance. The long-term phase resulting from the acute phase leads to persistent effects on pulmonary function, such as obstructive and restricted lung disease and patients experience chronic bronchitis, bronchiolitis, bronchiectasis obliterans, and emphysema [18]. Secondary infections, fibrosis, chronic obstructive pulmonary disease (COPD) symptoms, and lung cancer could be mentioned as long-term effects of SM on the respiratory system [16].

Mechanism of toxicity

SM leads to DNA and cell membrane damage, inflammation, oxidative stress, and caspase activation [19]. DNA alkylation is one of the primary cytotoxic effectsof SM [20]. Poly ADP-ribose polymerase is a nicotinic adenine nucleotide (NAD) dependent enzyme and is involved in DNA repair [21]. SM-induced DNA damage activates this enzyme and reduces NAD and adenosine triphosphate, and considering the importance of adenosine triphosphate in NAD resynthesis, this can lead to cell lysis [21-23]. Induction of oxidative stress is one of the toxic effects of SM, which has destructive effects on cells, including DNA damage and lipid peroxidation [24]. SM also induces the production of inflammatory cytokines and the release of prostaglandins in the acute phase, which is involved in the exacerbation of the disease [25]. In addition, cell death, inhibition of mitosis, mutagenicity, and carcinogenicity are the other toxic effects of SM [25].

Materials and Methods

The PubMed, Google Scholar and Scopus databases were searched, in addition to studies related to SM-induced lung injury. To investigate the possible role of MSC and its therapeutic mechanism in SM poisoning, we reviewed studies associated with a therapeutic approach for this chemical agent using the following terms: mustard gas, sulfur mustard, immune response, immunity, immunology, mesenchymal stem cell, lung, respiratory and pulmonary.

All published articles, regardless of their language, were searched and reviewed. We focused on observations and interventions related to SM or its analogous agents, such as CEES.

Treatment of sulfur mustard-induced pulmonary disorders

Supportive therapies, including administration of oxygen, mechanical ventilation, vaporized moist air, and antibiotic therapy, are used to relieve respiratory symptoms in SM poisoning [26]. Accordingly, a mixture of helium and oxygen with non-invasive positive pressure ventilation might be helpful for victims with chronic shortness of breath [26]. In severe long-term injuries, tracheostomy might be beneficial and bronchodilators, such as salbutamol and anticholinergic like ipratropium bromide improve lung function in these patients [27]. Steroids are used when bronchodilators are ineffective and antibiotics effectively reduce secondary infections [28]. While different medications are suggested for SM toxicity, none of them is considered a practical or specific antidote. The use of such medications has been for immediate treatment and reduction of acute symptoms, and complex protocols should be considered for general and stable treatment. [29]. Therefore, more studies are required to explore new agents for the treatment of the severe complications of pulmonary disorders induced by SM exposure. Specific pharmacological approaches, including immunomodulatory agents, anti-oxidants, and proteinase inhibitors, might replace routine therapies in the future.

Mesenchymal stem cells (MSCs)

The need for new therapeutic strategies for patients suffering from incurable diseases has prompted attention to regenerative medicine [30]. The interest in MSC-based cell therapy, as an essential branch of regenerative medicine with the ultimate goal of tissue homeostasis and regeneration, has increased in the past decade [31]. Preclinical and clinical studies have provided mounting evidence of MSCs as a new therapeutic approach for treating a variety of diseases, such as unmanageable pulmonary illnesses [32]. MSCs are an excellent candidate for cell therapy due to their remarkable properties, such as relative ease of isolation, expansion and differentiation into different cell lineages, availability in many tissues, immunomodulatory capacity and the lack of ethical problems. MSC therapy can be used as an autologous approach using the patient's cells or allogeneic using healthy donors as a source of MSCs for the treatment [33, 34]. MSCs can engraft the damaged tissues and promote tissue repair through differentiation into various cell types needed for tissue repair and secretion of different growth factors and cytokines. In recent years, the clinical applications of MSC-based therapies for the treatment of both acute and chronic pulmonary diseases have been discussed comprehensively [7, 8, 11]. In addition, due to their unique properties through suppressing cell apoptosis, inflammation, and oxidative stress, as significant pathologic mechanisms of SM, MSCs have some attractive therapeutic potentiality, as proved by accumulating preclinical studies [35, 36]. Recently, satisfactory effects of MSCs have been documented in several animal and human models of SM-related studies [10, 12, 37, 38]. While these studies are in the first stages of development and more future research is required, they hold great promise for a new therapeutic approach for SM-induced pulmonary complications. Expanding our understanding of the MSC mechanism governing SM-induced pulmonary injury treatment would be imperative to detect new target opportunities for these victims. Therefore, this review presents the options and therapeutic mechanisms of MSCs in SM poisoning.

Expanding our understanding of the molecular mechanisms governing the immunomodulatory properties of MSCs will enable us to improve significantly their clinical efficacy.

Anti-inflammatory agents

Inflammation in the lung

Inflammation is a nonspecific biological protective response to defend against harmful stimuli and repair tissue [39], because the pulmonary system is continuously exposed to various stimuli, such as inhaled toxins, pathogens, and apoptotic or necrotic cells, a forceful immune response, principally inflammation, is necessary to eliminate damaging inducements as early as possible [40]. During lung inflammation, numerous inflammatory cells release cytokines and mediators to modify the activities of other immune cells. Orchestration of these cells contributes to regeneration by removing the harmful pathogens and debris derived from apoptotic and necrotic cells [40]. Although this inflammatory immune response begins by removing the harmful stimuli and starts the healing process, when it occurs in an uncontrolled manner, it can lead to chronic lung inflammation, which causes problems instead of treating the injuries [41]. Therefore, inflammation and anti-inflammation balance are critical for lung homeostasis. Respiratory homeostasis is mediated by a complex network of tissue-resident cells that control the lung microenvironment, induce tolerance to

harmless inhaled particles, or develop immunity to invading pathogens [33]. Unregulated pulmonary inflammation is involved in different pulmonary disorders, such as ARDS, COPD, asthma and cystic fibrosis [42].

Despite the crucial role of inflammation in the development of lung diseases, traditional therapy does not exert significant effects on respiratory damage caused by the inflammatory response. Accordingly, therapeutic interventions have the goal of attenuating ongoing inflammation and promoting the regeneration of cell function (Figure 1).

The role of inflammation in sulfur mustard toxicity

The pulmonary system is the important organ undergoing chronic injuries among SM-exposed victims [44]. The pathogenesis toxicity of SM in the respiratory system includes a mild to severe inflammatory reaction accompanied by persistent respiratory distress [43]. Acute SM-induced pulmonary symptoms are often non-specific and can contribute development of a characteristic pattern of chronic disease in survivors. This pulmonary damage is mediated by complex inflammatory events, such as the synthesis of destructive enzymes, inflammatory mediators, and alveolar epithelial cell apoptosis, followed by chronic inflammation and eventually resultant pulmonary fibrosis [43]. Acute injury induced by this toxic agent is associated with the premature, sudden and massive release of inflammatory mediators including cytokines (e.g. tumor necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], IL-6 and IL-8), enzymes (cyclooxygenase-2 and inducible nitric oxide synthases [iNOS]), serum amyloid A1 and C-reactive protein as well as reactive oxygen and nitrogen species, which result in severe pulmonary damage [25, 44-47].

The inflammatory markers may persist in circulation long time after SM inhalation [48]. For example, elevated levels of inflammatory cytokines, including IL-1α and β, IL-6, IL-8, IL-12, and IL-13 in bronchoalveolar lavage (BAL) and serum fluids of patients as well as accumulation of neutrophils and macrophages, as a significant source of inflammatory mediators, have been reported from lungs victims [44, 49, 50]. Meanwhile, alterations in serum levels of inflammatory markers, such as cell adhesion molecules (e.g. selectins), IL-6, IL-8 and CRP are correlated with pulmonary symptoms even 20 years after SM exposure [48, 51, 52]. SM-induced pulmonary fibrosis is also associated with elevated levels of inflammatory mediators in BAL, such as IL-1α and -1β, IL-5, -6, -8, -12, IL-13, TNF-α, CCL5 and CCL11 [53, 54].

Similar increases in inflammatory agents, such as accumulation of inflammatory cells, IL-6 and TNF-α in the lung, have also been observed in animal models exposed to SM or CEES, a sulfur mustard analog [25, 55]. Additionally, CEES causes polarization of alveolar macrophages (AMs) toward the inflammatory phenotype (M1 macrophage), which is characteristic of inflammatory mediators production [10, 15].

Due to the essential central role of inflammation in SM toxicity, newer therapeutic approaches have focused on targeting the inflammatory pathway to ameliorate vesicant-induced lung injury, and some anti-inflammatory drugs are summarized in Table 1. For instance, anti-inflammatory drugs, like doxycycline, macrolides, and anti-TNF-α antibodies are protective against SM victims [56]. Also, the therapeutic effects of betamethasone and corticosteroids in improving lung function have been confirmed in both animal models and humans [57, 58]. Research detected that dexamethasone inhibits AM activity after SM exposure [59]. Corticosteroids inhibit the secretion of inflammatory mediators and free radicals by AMs and enhance their anti-inflammatory functions [60]. Although they are significant in bronchitis improvement using them is controversial and some evidence suggests that steroids have no anti-inflammatory effect in patients with persistent symptoms. The results of steroids are non-significant and systemic corticosteroid therapy is only recommended in the exacerbation phase. In addition, the protease-anti-protease is another mechanism of SM-induced pulmonary damage in which steroids have no vital role in a protease-anti-protease imbalance [61, 62].

Signaling pathways, such as NF-κB and AP-1, which are involved in regulating the activity of genes involved in mustard-induced inflammation, are also promising targets [63]. Antagonist agents against these signaling molecules may help reduce lung toxicity caused by these vesicles [64]. However, more extensive research is required, and the therapeutic effects of current results cannot be conclusively decided.

Anti-inflammatory properties of MSCs

Traditional drug intervention does not exert a significant effect on the destructed airway and pulmonary epithelial cells or other pathological damages of the respiratory system caused by the inflammatory response. However, there is already much enthusiasm for the therapeutic potential of MSCs in respiratory inflammatory diseases [33]. MSCs can modulate the proliferation and function of all immune cells that play an essential

role in the pathogenesis of acute and chronic inflammatory lung diseases [65, 66]. These cells exhibit the ability to directly suppress T-cell function or by modulating the antigen-presenting cells. MSCs induce tolerogenic phenotype in DCs by reducing the expression of the costimulatory and major histocompatibility complex molecules and might promote macrophage polarization to the anti-inflammatory phenotype (M2 macrophage) [67, 68]. They can suppress natural killer-mediated cytotoxicity and also modulate the balance between the cytokine network with the cellular and humoral immune systems [69]. In addition to suppressing the detrimental immune response, MSCs have the potential to differentiate into alveolar epithelial cells resulting in the attenuation of ARDS, acute lung injury, asthma, COPD, idiopathic pulmonary fibrosis and COVID-19 [33]. Several already conducted clinical trials suggest that administration of MSCs was well tolerated and a safe therapeutic approach in inflammatory lung diseases [33, 70]

MSC therapy has also been used to treat lung injury induced by SM. MSCs are known to migrate to sites of injury where they function to down-regulate oxidative stress and inflammation to promote tissue repair [56]. The preclinical studies demonstrated the efficacy of both systemic and direct airway injections of MSCs. MSCs are highly resistant to SM in vitro and can alleviate inflammation and promote wound repair in mouse models exposed to SM [10, 13]. MSCs administered in mouse models with SM-induced lung injuries also reduced inflammatory cells and cytokines, as well as improved lung function and regeneration [25]. In our previous study on mice models with long-term respiratory induced by CEES, we demonstrated that adipose tissue-derived MSCs effectively maintain lung hemostasis conditions by restoring the balance between M1/M2 AMs. Accordingly, pulmonary inflammation with the predominance of inflammatory AMs as an M1 phenotype, in response to CEES, was alleviated after MSCs administration by phenotype alteration to anti-inflammatory M2 macrophages [15].

Given the growing evidence that the therapeutic effects of MSCs rely on the release of extracellular vesicles (EVs), EVs may be a better choice for treating SM poisoning by avoiding the administration of live cells, which arouses concern related to tumor formation and long-term safety [71]. Previous studies demonstrated that miR-146a-5p delivered by MSC-EVs, effectively ameliorated SM-induced inflammation and might provide further development therapeutic approaches [71].

Although these results provide a significant basis for further clinical investigations of MSCs in SM-exposed patients with lung injuries, more comprehensive studies are needed to ensure their therapeutic role in SM toxicity.

Oxidative stress and anti-oxidative agents

Role of oxidative stress in lung

Due to their anatomy, location and functions, the lungs are highly susceptible to oxidative damage; therefore, the imbalance between oxidant and anti-oxidant agents, in favor of oxidants, is defined as oxidative stress [72]. Oxidative stress is a dynamic process linked to a wide variety of adverse biological effects, such as pro-oxidant production, promoting inflammation, metabolic deregulation, and reducing the antioxidant defenses [73]. Oxidative stress in the lung happens when the antioxidant capacity is overwhelmed, or depleted by an exogenous source of oxidant agents, such as air pollution, altered oxygen tension, or endogenously through resident or inflammatory cells [73]. Pulmonary responses to oxidative stress include inflammatory activities in the lung, including AMs and lung epithelial cell activation to produce inflammatory mediators and increase the reactive oxygen and nitrogen species (ROS and RNS) production [74]. Increased levels of ROS and RNS are modulated by the antioxidants located in the lung [75]. Increased levels of ROS/RNS modulate redox signals and lead to the irreversible destruction of critical biomolecules such as DNA, lipids, proteins and potentiate pathogenic cellular processes [75]. Overall, these events result in persistent inflammation, chronic oxidative stress, the imbalance between protease and anti-protease, impaired tissue regeneration, and lastly disease progression, including COPD, asthma, acute lung injury and lung cancer [76-78].

The role of oxidative stress in sulfur mustard toxicity

Oxidative stress is one of the important mechanisms of SM toxicity [25]. SM-induced oxidative stress is a consequence of mitochondrial dysfunction, increased activity of ROS-producing enzymes, reduction of intracellular antioxidants, such as glutathione (GSH), 20 years after exposure, and imbalance between production and detoxification of ROS [79]. Leukocyte accumulation and inflammatory response are other factors involved in ROS production. Previous studies have revealed that SM induces macrophages and neutrophil accumulation in damaged tissues. These activated leukocytes release high amounts of ROS and affect the antioxidant defense systems [80]. Alteration in mitochondria is one of the

mechanisms of SM-mediated oxidative stress and recent findings have shown that CEES inhibits the cytochrome P450 reductase enzyme, which is involved in the detoxification of SM in the lung [81].

Some evidence suggests that SM can target anti-oxidant agents [79]. The SM-induced complication respiratory in exposed victims are accompanied by proof of oxidative stress, such as elevated lipid peroxidation products, including malondialdehyde, in the lung or BAL, and down-regulation of antioxidants agents, such as superoxide dismutase (SOD), thioredoxin reductase, glutathione peroxidase, and glutathione reductase [82-85]. Additionally, excessive expression of ROS-producing enzymes, such as aldehyde oxidase-1, myeloperoxidase, thyroid peroxidase, and eosinophil peroxidase, and up-regulation of cyclooxygenase-2 and 12-lipoxygenase, as an involved enzyme in oxidative stress and inflammation response, have also been reported in lung biopsies of SM victims [86]. The conversion of GSH to SM-GSH metabolite is another mechanism of SM since GSH is a cofactor for glutathione peroxidase, its reduction is associated with increasing ROS content and oxidative stress [87]. Meanwhile, down-regulation of GSH in victims 20 years post-exposure was related to altered pulmonary functioning [4].

In this point of view, antioxidant therapies could be effective for facilitating vesicant-induced lung injury. To confirm this, metalloporphyrin, as a catalyst antioxidant, with high SOD activity, improve the pulmonary symptoms in animal models exposed to CEES [88]. Accordingly, the use of ROS inhibitors or anti-oxidants in SM toxicity indicates the significant character of ROS in the pathogenesis mechanism of this chemical toxic [89]. Recent studies have suggested the probable therapeutic role of some antioxidants, including GSH, vitamin E, flavonoids, SOD and catalase in SM or its analogous induced models (Table 1).

Antioxidant properties of MSCs

Oxidative stress, as an indicator of inflammatory lung disease, plays an essential role in the progression and severity of disease; therefore, the antioxidant agents can be considered a therapeutic option for inflammatory lung diseases [90]. Despite numerous promising preclinical studies related to the antioxidant potential of small molecules, clinical trial results have been disappointing [91].

Recently, anti-oxidant properties of MSCs have received considerable attention in various diseases [92, 93]. MSCs have been demonstrated to reduce DNA oxidation and lipid peroxidation associated with oxidative stress in different disease models [92]. According to the literature, MSCs are resistant to oxidative stimuli due to the expression of heat shock protein 70 and sirtuin [92]. Evidence suggests that MSCs could attenuate oxidative injury in some diseases by the reduction in ROS and oxidative biomarkers. These mechanisms could be justified by inhibiting the free radicals, augmenting the host antioxidant mechanism, modulating the inflammatory response, and enhancing mitochondrial function [92, 94, 95]. The effects of MSCs on ROS production and anti-oxidant levels were shown with the increased level of cellular GSH after treatment of the C3H10T1/2 mesenchymal cell line with adrenaline [95]. Although the antioxidant effects of MSCs have been observed in experimental models, there is limited data in human studies. Nonetheless, promising results in a case study utilizing MSCs to treat victims with SM-induced chronic lung injuries revealed the antioxidant effects of MSCs as evidenced by decreased lipid peroxidation levels in the sputum [12]

Matrix metalloproteinase inhibitor agents

Role of matrix metalloproteinase in the lung

Matrix metalloproteinase (MMP), a family of zinc-dependent endopeptidases, mediates various biological responses in the lung from normal development to destructive [96, 97]. Despite important physiological roles in normal lung function (tissue remodeling, repair, homeostasis, and activating defensins), its overexpression has also been blamed for tissue destruction and lung disease progressions, such as asthma, acute pulmonary damage, COPD, respiratory hypertension, interstitial lung disease, and cancer [97, 98]. MMPs have different mechanisms in various lung diseases and in addition to the destruction of pulmonary parenchyma, are involved in the inflammatory response, vascular apoptosis, excessive mucosal secretion and fibrotic pathway, so have recently emerged as promising novel therapeutic targets in the lung disease [99].

In regular conditions, MMPs' biological activities in response to environmental stimuli, such as infections, toxins, growth factors, and cytokines are regulated by tissue inhibitors of metalloproteinase (TIMPs) and a 2-macroglobulin [100, 101]. MMPs and their inhibitors are produced by bronchial, alveoli, and inflammatory cells [101]. The imbalance between MMPs and their inhibitors is a major event in the development of lung disease [100]. Accordingly, MMP inhibition could be considered a basis for future treatment [96].

Despite the critical role of TIMPs as diagnostic and therapeutic tools in some diseases, including cancer, autoimmunity and cardiovascular disease, only doxycycline is currently approved by the Food and Drug Administration [102]. This is probably due to TIMPs limitation, as a lack of MMPs specificity, adverse events and little information about the biological complexity of the various diseases [103]. The musculoskeletal side effects due to the broad-spectrum inhibitory effects of TIMPs are one of the obvious examples in this field [9]. Another challenge is that several studies have focused on the specific MMPs and TIMPs, while one MMP increase might be parallel to a decrease in the other MMPs. Also, the MMPs' activities might vary during the disease and it is significant to study various MMPs and TIMPs in different stages of the disease [104]. Although animal model studies have shown that TIMPs might be effective in preventing disease, animal models could not reflect the potentiality and mechanisms of human disease [105]. As a result, understanding the biological mechanism of the different conditions and the targeting of effective MMPs are required to address these challenges [103].

The role of matrix metalloproteinase in sulfur mustard toxicity

SM could cause severe damage by stimulating various proteases, such as MMPs, caspases and serine proteases [108]. The imbalance between MMPs and TIMPs is one of the SM pathological mechanisms [107]. Numerous studies have evaluated the MMPs in chronic or acute stages of both human and experimental models of SM toxicity [106]. For instance, elevated levels of MMP-9 in serum and BAL samples from victims have been reported. Accordingly, MMP-9 is involved in SM toxicity in various organs, including skin, eyes, and lungs [108, 109]. In our previous study, we evaluated the serum level of some relevant MMPs (MMP1, MMP2, MMP8 and MMP9) and their endogenous inhibitors in exposed subjects with long-term pulmonary complications 20 years after SM exposure. Our result supported that elevated levels of MMP-1 in the serum and decreased MMP-2 activity could be involved in the pathogenesis and persistence of pulmonary damage in these victims [110]. Similarly, increased MMP activities and their association with disease severity have been described in animal models [111-114]. Due to the central role of this enzyme in SM pathogenesis, MMP inhibitors might have hopeful approaches in the future. Studies have shown that the treatment of pig models exposed to SM with doxycycline, a non-specific MMP inhibitor, reduces MMP activity and inflammation and improves lung damage (Table 1) [115]. The effectiveness of ilomastat (a non-selective MMP inhibitor) was evaluated in an SM-induced animal model, and reduced inflammatory cytokines (e.g. IL-1α, IL-13) in lung lavage fluid and lung function improvement were seen in the SM-induced model [116].

Matrix metalloproteinase inhibitory properties of MSCs

In addition to regulating immune responses and inflammatory reactions, MSCs play an essential role in maintaining homeostasis by regulating the balance between proteases and their inhibitors [117]. In inflammatory conditions, MSCs display a secretory profile including cytokines, chemokines, proteases and protease inhibitors [118]. For example, in COPD condition that is characterized by airways and lung parenchyma inflammation and the increased number of inflammatory mediators such as MMP-9 and 12, MSCs can improve the destructive pulmonary function by reducing the levels of MMP2, 9, 12, and -13 that are involved in the degradation of elastin connective fibers and tissue remodeling [119]. MSCs inhibit the MMP pathogenesis effect by increasing TIMP-1 expression in inflammation and hypoxic conditions [120]. TIMP-1 is also involved in the anti-angiogenic effects of MSCs and is considered an imperative factor in the anti-inflammatory properties of these cells. MSCs also express high levels of TIMP-3 [55]. TIMP-3 produced by MSCs has beneficial effects in animal models of traumatic brain injury and some studies identified a new potential marker in clinical settings [54]. Now, due to TIMP secretion, MSCs can protect against MMP-induced tissue damage in various diseases, such as SM toxicity [120]. It was reported that MSC therapy in patients with SM-induced long-term pulmonary complications contributed to a balance between the MMP9/TIMP1 and MMP2/TIMP2 ratio that is necessary for the maintenance of extracellular matrix and lung regeneration [121].

Apoptosis

Role of apoptosis in lung

Apoptosis, as a regulated mechanism for the elimination of unwanted, damaged, or infected cells, is characterized by loss of cell function, rapid morphological changes, and non-inflammatory cell death [122]. Apoptosis proceeds through two intrinsic (mitochondrial) and external (death receptor) pathways. The intrinsic pathway is described by the release of apoptogenic factors from the mitochondria, which contribute to the caspase-9 and caspase-3 activation. The external pathway is activated by cell surface death receptors leading to the acti-

vation of caspase-8 and caspase-10 and cell death [122]. Although apoptosis is a critical physiological process for the development and maintenance of tissue development and homeostasis, such lung dysfunction or disturbance of the balance between apoptosis and cell proliferation are involved in the pathogenic mechanism of lung diseases like emphysema, COPD, acute lung injury, and idiopathic pulmonary fibrosis [123-125].

The pathophysiology mechanism of apoptosis in lung diseases is mediated in two different ways. Firstly, the failure resolution of unwanted cells by apoptosis contributes to prolonging inflammation as a result of releasing their toxic contents. Secondly, excessive apoptosis is a result of the imbalance between apoptosis and regeneration of the structural lung [126].

The Role of Apoptosis in Sulfur Mustard Toxicity

SM is involved in both apoptosis pathways (intrinsic and extrinsic) [127, 128]. The role of SM in the activation of caspase-3 and caspase-8 and mitochondrial-dependent cell death pathways in respiratory cells has also been demonstrated in in vitro studies [128, 130]. In vivo studies have shown that SM-induced pulmonary complication is mediated by different caspase activation (caspase-8, caspase-9, caspase-3 and caspase-6), and caspase localization was reported in epithelium and AMs [4, 25, 131]. Upregulation of the Fas/FasL pathway in epithelial cells occurs in ARDS and is a complication of SM exposure. Evidence suggests that blocking the Fas/FasL system can prevent the advancement of pulmonary complications [132, 133]. Furthermore, the Fas pathway could be an important mechanism in the progression of SM-induced lung disease [133]. Recently, in vitro studies have shown that the use of ribonucleic acid interference against Fas receptor or Fas-antagonistic antibody can reduce SM-induced apoptosis (Table 1) [134-136]. Increased respiratory epithelium apoptosis in response to SM, confirmed by increased levels of Fas and FasL, caspase-3 activation, and accumulation of apoptotic cells in the BAL fluids of victims [137]. Consequently, pharmacological antagonism of the apoptosis pathway could be the goal of a therapeutic approach for SM toxicity.

Anti-apoptotic effects of MSCs

The anti-apoptotic ability of MSCs has been presented in different diseases, including ischemic heart disease, neurological, and pulmonary disorders [7]. Apoptosis inhibition properties of MSCs have been considered a promising therapeutic approach for lung diseases, such as ARDS and idiopathic pulmonary fibrosis [138-140]. In hypoxia, alveolar epithelial cells undergo apoptosis by stimulating hypoxia-inducible factors (HIFs) and ROS pathways. HIF is a transcription factor that might initiate pro-apoptotic pathways [141]. MSCs could protect alveolar epithelial cells from apoptosis due to the down-regulating of ROS pathways and HIF-1α subunit as well as increased expression of B-cell lymphoma 2 (Bcl-2) factor, an anti-apoptotic protein. Also, the anti-apoptotic effects of MSCs are dependent on the secretion of two epithelial growth factors, namely keratinocyte growth factor and hepatocyte growth factor [141]. Recently, other factors have been implicated in the anti-apoptotic activity of MSCs, including IL-6 and insulin-like growth factor-1 (IGF-1) that elevate the levels of secreted frizzled-related protein 2, a central anti-apoptotic mediator in fibroblast-like cells [142].

The protective effect of MSC-derived exosomes in animal models of SM-induced acute lung injury is mediated through upregulate expressions of anti-apoptotic proteins, such as Bcl-2 and ligand proteins by activating the Hippo-YAP pathway, a signaling pathway involved in cell survival and organ regeneration [143].

Improving the effectiveness of MSCs

MSCs can be considered a targeted therapy for SM toxicity. Nonetheless, several factors can affect the implanted MSCs' ultimate function, such as tissue source, production method, delivery dose, disease stage, and genetics of the patient, which deserves careful investigation before being applied widely to treat patients [67]. In addition, several limitations related to poor cell survival and engraftment restrict the clinical application of MSCs. Therefore, MSCs must be tuned for the intended therapy. Today, ongoing studies are being studied methods for MSCs optimization in which, some of the methods are mentioned in this study (Figure 2).

Considering the stem cell sources' consequences on cell activity, fate, regenerative potential, and safety profile, more research is needed to identify the optimal cell sources with non-invasive methods to design an MSC-based therapeutic approach [67]. Another important aspect to consider is the donor age that is involved in MSCs' efficacy. For example, MSC derived from neonatal tissues exhibit more survival, more comprehensive differentiation, and higher proliferation rate compared to adult tissues [144]. In addition, since individual differences are involved in response to treatment, personalized treatments according to the individual's needs and genetic structure are one of the factors that should be considered [38].

Table 1. Therapeutic effects of different compounds against lung injury of sulfur mustard or its analogous

Variables	Subject	Authors	Drug	Description
Anti-MMP compounds	Animal (guinea pigs)	Guignabert et al. [115]	Doxycycline	Inhibition of MMP-2 and MMP-9 production; decreased inflammation in BAL; decreased histological lesions
	Animal (rat)	Anderson et al. [116]	aprotinin (a serine-protease inhibitor) or ilomastat (a nonselective MMP inhibitor)	Reduction of the total protein and IL-1α and IL-13 in lung lavage fluid; reduction of inflammatory response and lung damage induced by SM
Anti-inflammatory compounds	Animal (guinea pigs)	Calvet et al. [58]	Betamethasone	Tracheal epithelium regeneration mainly derived from basal cells
	Human	Ghanei et al. [57]	Fluticasone propionate, salmetrol, beclomethasone and salmetrol	Improvement of symptoms
	Human respiratory epithelial cells	Gao et al. [151]	Macrolide antibiotic (roxithromycin)	Decreased expression of IL-1β, IL-6, IL-8, and TNF; decreased expression of iNOS
	Airway epithelial cells	Gao et al. [152]	Macrolide antibiotics	Reduced level of iNOS expression and nitric oxide production
	Animal (mouse)	Wigenstam et al. [153]	Dexamethasone	Reduced levels of IL-1 and IL-6 in BALF; diminished the acute airway inflammation
	Monocyte THP-1 cells	Gao et al. [45]	Macrolide antibiotics (azithromycin, clarithromycin, erythromycin and roxithromycin)	Decreased level of proinflammatory cytokines and mediators; Decreased iNOS and NO production
Anti-oxidant compounds	Animal (guinea pigs)	Das et al. [23]	N-acetl-cysteine	inhibit the induction of TNF-α and activation of caspases
	Animal (rat)	McClintock et al. [154]	Liposomes containing catalase and or SOD	Decreased pro-inflammatory mediators in BAL and attenuated CEES-induced lung injury
	Human	Ucar et al. [155]	Melatonin	Decreased level of NO and iNOS and increased SOD activity in the lung
	Human	Ghanei et al. [156]	N-acetyl cysteine	Ameliorate the symptoms of chronic lung injury
	Human	Shohrati et al. [157]	N-acetyl cysteine	Improved spirometric index
	Animal (rat)	Hoesel et al. [158]	Liposome containing glutathione	Decreased lung, hydroxyproline and inflammatory mediators
	Human skin fibroblast cell line (HF2FF)	Saberi et al. [159]	N-acetl-cysteine	Increased GSH level
	Animal (guinea pig)	Mukherjee et al. [160]	Liposome containing N-acetylcysteine	Decreased inflammatory cell accumulation and lipid peroxidation
	Animal (guinea pig)	Mukhopadhyay et al. [161]	Antioxidant liposomes	Decreased IL-1 and IL-6; decreased activation of transcription factor SAF-1/MAZ
	Animal (rat)	O'Neill et al. [89]	Catalytic antioxidant AEOL 10150	Decreased activity of myeloperoxidase in the lung; decreased oxidative stress markers 8-OHdG and 4-HNE in the lung
	Human	Panahi et al. [162]	Curcumin	Decrease serum levels of inflammatory mediators (IL-8, IL-6, CRP, TNF-α)
	Human keratinocyte cell line	Balszuweit et al. [163]	N-acetyl cysteine /GSH	Decreased levels of IL-6 and IL-8
	Human	Panahi et al. [164]	Curcuminoids-piperine	Increased serum levels of reduced glutathione; decreased serum level of malondialdehyde

Variables	Subject	Authors	Drug	Description
Anti-oxidant compounds	Animal (guinea pig)	Gholamnezhad et al. [165]	Vitamin E	Improved lung pathologic symptoms and decreased inflammation in the lung
	Human	Mousavi et al. [166]	Melatonin	Improved respiratory function
Anti-apoptotic compounds	Human keratinocytes	Rosenthal et al. [135]	retroviral vectors expressing CaM1 RNA in the antisense	Inhibition of caspases-3, caspases-6, caspases-7 and suppression of apoptosis
	Human airway epithelial cells	Keyser et al. [134]	Small-interfering RNA	Inhibition of caspase-3 activation; decreased apoptosis and necrosis

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Abbreviations: MMP: Matrix metalloproteinase; BAL: Bronchoalveolar lavage; IL: Interleukin; SM: Sulfur mustard; TNF: Tumor necrosis factor; iNOS: Inducible nitric oxide synthases; SOD: Superoxide dismutase; CEES: 2-chloroethyl ethyl sulfide; GSH: Glutathione; RNA: Ribonucleic acid.

Due to the high sensitivity of MSCs to the inhospitable tissue surroundings that contribute to low survival poor engraftment and hampered therapeutic effect of transplanted MSCs, several procedures have been proposed to improve MSCs survival, including preconditioning strategies under sublethal doses of cellular stressors, including hypoxia, temperature stress, and starvation to resemble injured microenvironments which MSCs will be experienced in vivo. Genetic modification to express genes involved in cell survival, apoptosis pathways inhibition, and immunomodulatory factors are other strategies to increase the MSC survival rate [145].

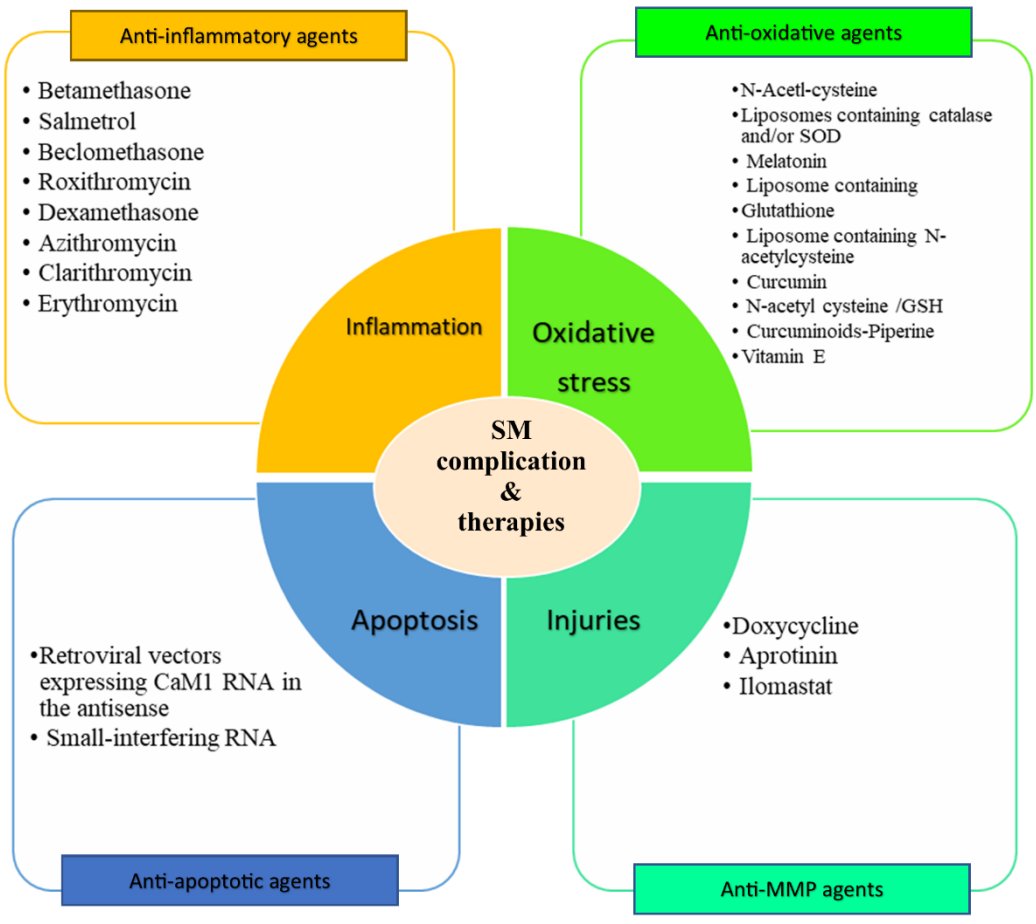

Figure 1. Different treatments of major pulmonary toxicity induced by sulfur mustard and its analogous

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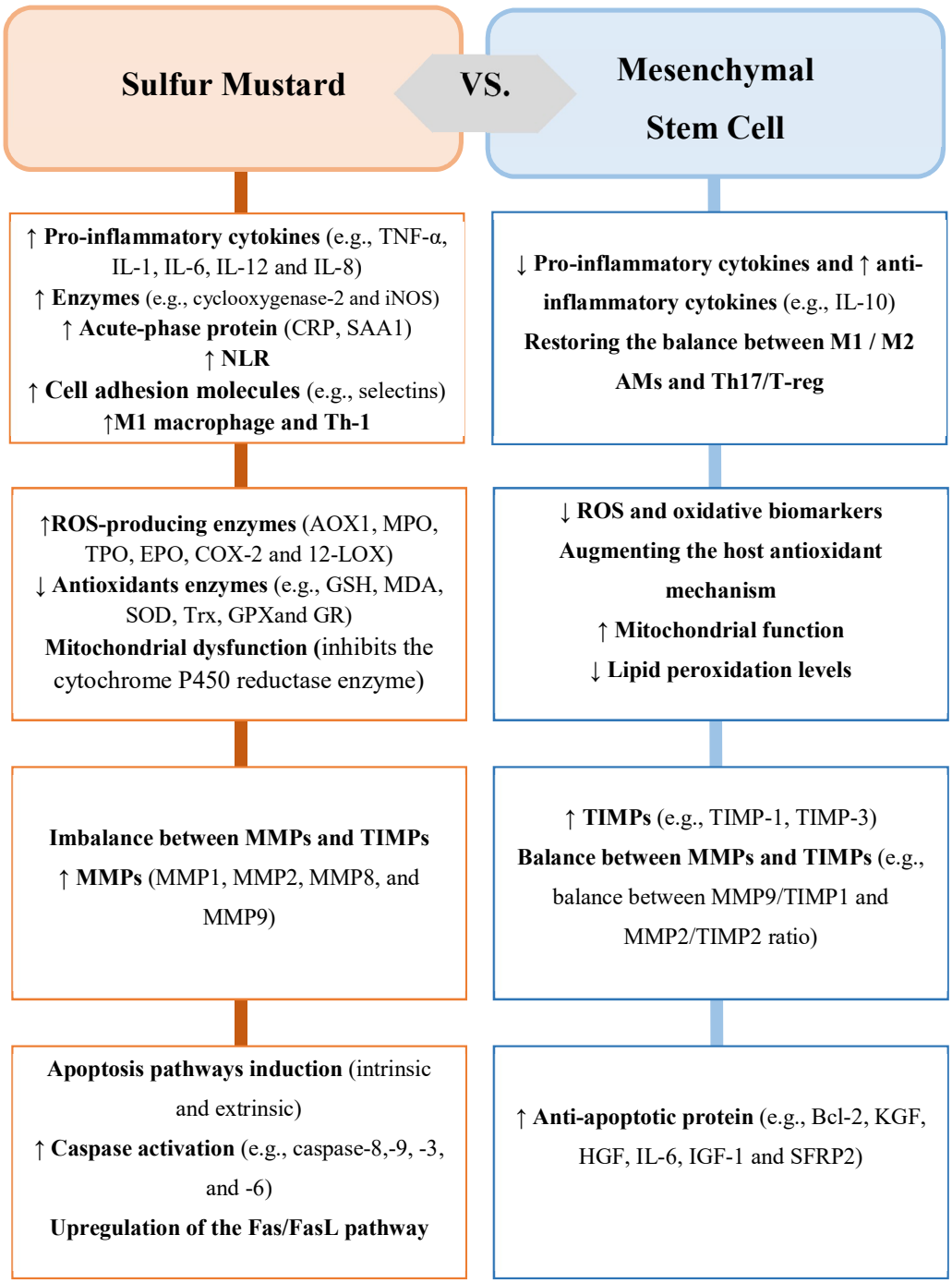

Figure 2. Therapeutic mechanisms of mesenchymal stem cells versus pathologic mechanisms of sulfur mustard
Abbreviations: IL: Interleukin; TNF: Tumor necrosis factor; TIMP: Tissue inhibitors of metalloproteinase; MMP: Matrix metalloproteinase.

Biomaterials could modify these cells to enhance their migration capacity to a targeted area of injury, increase their retention rate in the hostile ischemic microenvironment and promote the secretion of important cytokines for reparative mechanisms, such as neurogenic factors and angiogenic factors.

The fate of MSCs post-administration is considered an essential challenge of these cells in the clinical approach. Since the beneficial effect of cell therapy depends on the appropriate number of cells reaching the target tissue, target delivery of MSCs is another strategy to improve their therapeutic efficiency [146]. Despite the homing

ability of MSCs, this process is not efficient, and due to the low expression level of homing molecules and MSCs heterogeneity, the transplantation rate is often inadequate. Therefore, various strategies, including cell surface manipulation, in vitro priming of MSCs, and using biomaterial scaffolds, radiotherapy, and magnetic, and ultrasound techniques, have recently aroused great interest [147].

The potential risks for tumorigenesis and immunogenicity are other problems with stem cell therapy that can be addressed using acellular treatments, such as stem cells-derived secretomes, cytokines, and exosomes [148]. The mechanism function of stem cells depends more on their secreted soluble factors than on cell-to-cell interactions [15]. Exosomes, as membrane biological nanoparticles, have similar roles to stem cells, such as tissue repair, anti-inflammatory, and immune regulatory properties [149]. The low chance of immune rejection and malignancy, stability, and long-term maintenance are the advantages of exosomes compared to stem cells. Hence, MSCs-derived exosomes could be considered an alternative to cell therapy [150].

Future research should be focused on the development of new strategies related to the standardization of MSC, exosome therapy, and engineering techniques to provide new avenues for the treatment of SM-induced injury.

Conclusion

Pulmonary complications due to exposure to SM a considered a significant health concern even decades after the exposure. Despite numerous clinical studies to find effective treatments for complications of this chemical agent, there is no suitable therapy exists to date. Today, the MSCs-based therapy approaches in respiratory regenerative medicine have evolved rapidly and provide hope to patients with these devastating diseases. Despite available promising evidence of therapeutic potential, there is no comprehensive information relevant to the MSCs' effectiveness in overcoming SM-induced pulmonary complications. The current review study evaluated the possible therapeutic effects of MSCs for SM toxicity and compared them with new approaches through their multiple mechanisms such as anti-inflammatory, anti-oxidant, and anti-apoptotic properties. It seems that, although further studies need to be explored in terms of the standardization of dosing and route delivery, donor source, culture status, manufacturing protocols and applications for the individual case, nevertheless, MSC therapy offers the most innovative strategy for SM-toxicity.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Authors' contributions

Investigation, writing-original draft, review & editing: Somaye Sadeghi and Ali Mohammad Mohseni Majd; Project administration: Somaye Sadeghi; Methodology, Conceptualization, Validation and Supervision: Nariman Mossafa and Tooba Ghazanfari.

Conflicts of interest

The authors declared no conflict of interest.

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