JTMGH
International Journal of Travel Medicine and Global Health

Int J Travel Med Glob Health. 2025 Mar;13(1):90-93 doi 10.30491/ijtmgh.2025.527814.1490
http://ijtmgh.com

Policy Briefs Open Access

Macrophages type 2 as candidates for the treatment of lung injuries

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Received 2024-10-18**; Accepted** 2024-12-12 **; Online Published** 2025-03-01

Executive Summary

Sulfur mustard (SM) is a toxic chemical warfare agent that causes severe and persistent pulmonary damage, for which no specific treatment exists. Emerging evidence suggests that mesenchymal stem cells (MSCs) exert anti-inflammatory effects through paracrine signaling. This study evaluated the therapeutic potential of monocytes treated with MSC-derived supernatant in a murine model of SM-induced lung inflammation using CEES as a surrogate. Monocytes treated with MSC supernatant showed significant immunomodulatory effects, including reduced pro-inflammatory cytokines (IL-12), increased anti-inflammatory cytokines (IL-4, IL-10, TGF-β), and decreased oxidative stress markers (NO, MPO). Histopathological analysis revealed reduced inflammation, mucus accumulation, and tissue remodeling in treated animals. These findings suggest that MSC supernatant-treated monocytes may offer a novel therapeutic strategy for chemical-induced lung injury, warranting further investigation into their mechanisms and efficacy in more complex models.

Keywords: Mustard Gas, Mesenchymal Stem Cells, Monocyte Therapy

Citation: Shahriary A, Eslami Mahmoudabadi M, Nikkhah A. Macrophages type 2 as candidates for the treatment of lung injuries. Int J Travel Med Glob Health, 2025;13(1):90-93. doi: 10.30491/ijtmgh.2025.527814.1490

Introduction

Sulfur mustard (SM), a highly toxic alkylating chemical warfare agent, has caused long-term and devastating health consequences in thousands of victims, particularly among Iranian veterans exposed during the Iran-Iraq war. Known for its mutagenic, carcinogenic, and cytotoxic properties, SM primarily targets moist tissues such as the eyes, skin, and respiratory system.[1,2] Among these, pulmonary complications are the most common and persistent, often leading to chronic conditions such as bronchitis, bronchiectasis, airway fibrosis, and obstructive lung disease. Despite decades of research, no definitive or curative treatment has been established for SM-induced lung injury, leaving many survivors with progressive and debilitating respiratory symptoms.[3,4] Exposure to SM triggers acute inflammatory responses through the upregulation of pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, IFN-γ, and IL-17, which contribute to prolonged tissue damage and dysfunction.[5] Over time, this chronic inflammation leads to structural changes in the airways, including epithelial cell necrosis, mucus hypersecretion, fibrosis, and infiltration of inflammatory cells.[6] Moreover, alterations in immune homeostasis, including reduced NK cell activity and dysregulated T-cell responses, have been reported in SM-exposed individuals, further complicating the pathophysiology of the disease.[7] In recent years, mesenchymal stem cells (MSCs) have emerged as promising candidates for regenerative and immunomodulatory therapies due to their ability to modulate immune responses and promote tissue repair.[8] These effects are largely mediated through paracrine signaling, including the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β, as well as bioactive molecules like nitric oxide (NO) and indoleamine 2,3-dioxygenase (IDO).[9] Importantly, studies have shown that

MSC-derived conditioned medium (MCM) can reprogram monocytes into anti-inflammatory macrophages (M2 phenotype), offering a novel strategy to control chronic inflammation without direct cell transplantation.[10] Ultimately, this research seeks to bridge the gap between laboratory findings and clinical application by proposing a novel, cell-based therapeutic strategy that could significantly improve the quality of life for those affected by SM exposure. It also highlights the importance of developing innovative, human-centered interventions for long-standing global health challenges rooted in conflict and chemical warfare.

Materials and Methods

In this study, we explored a novel, cell-based therapy that leverages the immunomodulatory properties of mesenchymal stem cells (MSCs), not through direct transplantation, but via their secretome — specifically, by reprogramming monocytes into an anti-inflammatory state. This study investigates the therapeutic potential of monocytes preconditioned with MSC-conditioned medium in a BALB/c mouse model of SM-induced pulmonary injury, using 2-chloroethyl ethyl sulfide (CEES) as a surrogate. The research aims to evaluate key cellular and molecular outcomes, including phenotypic changes in monocytes, cytokine profiles in bronchoalveolar lavage fluid (BALF), levels of oxidative stress markers such as NO and myeloperoxidase (MPO), splenocyte proliferation, and histopathological changes in lung tissue. By modulating the inflammatory response and promoting a shift toward an anti-inflammatory milieu, this approach may offer a scalable and potentially translatable therapy for victims of chemical warfare, as well as patients suffering from other chronic inflammatory lung diseases. All data were analyzed using one-way ANOVA followed by LSD post-hoc test ($p<0.05$).

Results

In this study, we evaluated the therapeutic potential of monocytes preconditioned with mesenchymal stem cell-conditioned medium (MCM) in a CEES-induced murine model of sulfur mustard (SM)-like pulmonary injury. Flow cytometry confirmed that isolated MSCs expressed high levels of mesenchymal markers CD44, CD73, and CD105, while lacking hematopoietic markers CD34 and CD45, confirming their identity. Monocytes treated with MCM showed a significant shift toward an anti-inflammatory phenotype, with reduced IL-12 and increased IL-10, IL-4, and TGF-β production compared to untreated monocytes ($P<0.05$). Oxidative stress markers, including nitric oxide (NO) and myeloperoxidase (MPO), were significantly decreased in the MCM-treated monocyte group compared to the untreated group ($P<0.0001$), nearly comparable to the dexamethasone control group. Histopathological assessment revealed marked reductions in inflammatory cell infiltration, mucus accumulation, and airway remodeling in mice receiving MCM-treated monocytes, with a tissue damage score of 1 compared to 3 in the untreated group. The dexamethasone group showed the most improvement, with a score of 0. Splenocyte proliferation assays also demonstrated significantly reduced immune activation in the MCM-treated group ($P<0.0001$), indicating systemic immunomodulation. Cytokine profiling in bronchoalveolar lavage fluid (BALF) further supported these findings, showing decreased pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, IL-17) and increased anti-inflammatory mediators (IL-10, TGF-β) in MCM-treated monocyte recipients. These results suggest that monocytes modulated by MSC-derived secretome can effectively mitigate SM-induced lung inflammation, offering a promising, scalable, and potentially translatable therapy for victims of chemical warfare and other chronic inflammatory lung conditions.

Discussion

The persistent and systemic inflammatory responses observed in sulfur mustard (SM)-exposed patients play a critical role in the progression of long-term pulmonary complications.[11,12] This study highlights how dysregulated immune responses, particularly those mediated by pro-inflammatory cytokines such as IL-1β, IL-6, TNF-α, and IL-17, contribute significantly to chronic lung pathology. Moreover, oxidative stress and imbalance in redox homeostasis further exacerbate tissue damage and impair regenerative capacity. These findings align with clinical observations in mustard lung (ML) patients, where systemic inflammation and extra-pulmonary manifestations, such as cardiovascular disease and osteoporosis, suggest that ML is not only a localized injury but also a systemic disorder.[13] Emerging evidence supports the immunomodulatory potential of mesenchymal stem cell-derived conditioned medium (MCM) in reprogramming monocytes toward an anti-inflammatory M2 macrophage phenotype.[14] Our results demonstrate that monocytes treated with MCM significantly reduce the production of pro-inflammatory cytokines (IL-12) while increasing anti-inflammatory mediators (IL-4, IL-10, TGF-β). This shift was associated with reduced levels of nitr ic oxide (NO) and myeloperoxidase (MPO), indicating decreased oxidative stress and neutrophil infiltration. Histopathological analysis further confirmed reduced inflammatory cell infiltration, mucus accumulation, and structural remodeling in the MCM-treated monocyte group, comparable to dexamethasone treatment. These

findings are consistent with previous studies showing that MSC-secreted factors can modulate macrophage polarization and suppress excessive inflammation. In line with the present study, Sadeghi et al. investigated the immunomodulatory effects of mesenchymal stem cells (MSCs) in a model of sulfur mustard-induced lung injury. Their findings demonstrated that MSC therapy promoted a phenotypic shift in T cells from Th1 to Th2 and in macrophages from pro-inflammatory M1 to anti-inflammatory M2 subsets.[15] Similarly, Al-Rubaie et al. reported that MSCs attenuated neonatal hyperoxia-induced lung injury by modulating macrophage polarization. Their results indicated that MSC treatment not only contributed to structural repair but also limited the progression of pulmonary fibrosis.[16] Beyond pulmonary models, other studies have also highlighted the therapeutic potential of MSC-secreted factors in inflammatory conditions. For example, Ghalavand et al. examined the effects of monocytes treated with MSC-conditioned medium in a murine model of colitis. They found that these treated monocytes exhibited enhanced antioxidant capacity and could be considered as a potential adjunctive therapy for ulcerative colitis.[17] The ability of MCM to induce an immunoregulatory monocyte phenotype suggests a promising therapeutic strategy for chemical-induced lung injury. While our results support the anti-inflammatory and tissue-protective effects of MCM-treated monocytes in a CEES-induced murine model, future research should explore additional molecular mechanisms and validate these findings in more complex models before clinical translation. This approach may offer a scalable, cell-free alternative to direct MSC therapy, with potential applications beyond mustard lung, including other chronic inflammatory lung diseases.

Conflicts of Interest Disclosures

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent For Publication

Not applicable

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