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Advanced biotherapy for the treatment of sulfur mustard poisoning

Mingxue Sun[a,1], Yuyan Yang[a,b,1], Wenqi Meng[a], Qingqiang Xu[a], Fengwu Lin[c], Yongchun Chen[a], Jie Zhao[a], Kai Xiao[a,*]

[a] Lab of Toxicology and Pharmacology, Faculty of Tropical Medicine and Public Health, Second Military Medical University, Shanghai 200433, China
[b] You'an Men Community Health Service Center, Beijing 100069, China
[c] China-Japan Union Hospital of Jilin University, Changchun 130033, China

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ABSTRACT

Context: Sulfur mustard (SM), a bifunctional alkylating agent, can react with a variety of biochemical molecules (DNA, RNA, proteins and other cell components) to cause a series of serious health issues or even death. Although a plethora of research has been done, the pathogenesis of SM poisoning has yet to be fully understood due to its high complexity. As a consequence, a specific antidote has not yet been developed and the treatment of SM poisoning remains a medical challenge. In recent years, various biological products and cell transplantation in the treatment of SM poisoning offered a significant clinical treatment progress. By highlighting these and other research studies, we hereby summarize the progress in this field in an effort to provide useful information on the clinical treatment of SM poisoning.

Objective: This review summarizes the major advances of SM poisoning therapy by means of biological products (peptide and protein drugs, polysaccharides drugs, nucleic acid drugs, etc.), and cell transplantation (e.g., bone marrow, limbal stem cells, mesenchymal stem cells), as well as other relevant biotherapeutic approaches.

Method: We searched the database PubMed for published domestic and international articles using web based resources for information on histological, immunochemical, ultrastructural, and treatment features of SM-induced manifestations in both animal models and human tissues. To this end, we applied keywords containing mustard gas, chemical warfare, SM, eye, lung and skin.

Results and conclusion: Our review provides a comprehensive understanding of the advances of available biotherapies in SM poisoning, and its potential for the treatment of SM-induced injuries. Potentially, our review will provide new insights for future research studies in this field.

1. Introduction

Sulfur mustard (SM, bis-2-(chloroethyl) sulfide, CAS number: 505-60-2, American military denotation: HD) represents an agent that causes a major military threat since its reported first use in Ypres (Belgium) in 1917 during World War I. Thousands of casualties have been reported as a consequence of the use of SM. During the Iran–Iraq war, over 100,000 people were injured and more than 30,000 are still suffering from long-term effects of SM [1].Moreover, since SM is fairly easy to synthesize, stockpile, and deploy, it has become an attractive tool for terrorism [2]. Possible accidental leakage, for example from abandoned Japanese chemical munitions in China, may also threaten the lives of innocent people [3]. SM participates in a variety of biotransformation reactions in the body, forming covalent bonds with DNA, RNA, proteins, components of cell membranes, and other macromolecules in the body. This leads to acute and chronic injuries of a variety of organs including eye, skin, lung, gastrointestinal tract and even bone marrow. As a lipophilic substance, SM penetrates the skin or mucosa very quickly, often within a few minutes. Latencies follow by erythema, blisters, ulcers, and healing, often promoting secondary infections after the skin was exposed to SM [4,5]. Eye contact with SM leads to acute injuries, including photophobia, corneal erosions, and severe inflammation of the ocular surface [6]. Steamed SM may also be inhaled, ultimately causing damages to the respiratory system. The trachea and bronchial epithelia may become necrotic and detached from the wall forming pseudomembranes, which may cause the obstruction of the lower airway [7]. SM can also cause gastrointestinal injuries if it is accidentally ingested, though such cases have been reported to be relatively rare. After absorption, SM mainly inhibits the hematopoietic system and suppresses bone marrow regeneration [8]. A

* Corresponding author.
E-mail address: kaixiaocn@163.com (K. Xiao).
[1] Authors contributed equally to this work.

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number of patients have been shown to suffer some long-term sequelae like skin cancer, chronic obstructive pulmonary disease and corneal epithelial defects [9,10].

SM poisoning mainly occurs in war zones (e.g. in World War I and the Iran–Iraq war) or during terrorist attacks (e.g. terrorist attacks in Syria carried out by Islamic State of Iraq and the Levant (ISIL)). The most effective ways to prevent injuries include the use of protective equipment and timely decontamination [11], however, due to frequently sudden SM attacks, limited resources and the lack of professional knowledge, it is generally difficult to protect and decontaminate affected areas in a sufficient manner. Therefore, clinical treatment of affected individuals is often necessary and crucial to reduce damages caused by SM. Sadly, the pathogenesis underlying SM poisoning is complicated and not well understood and there are no specific antidotes or standard treatment methods available for SM poisoning in clinical practice. Current treatment strategies mainly focus on the alleviation of symptoms, promotion of healing, and prevention of infections [12,13]. Specific antidotes and standard treatment strategies are required to minimize mortality and ensure maximum healing. Researchers around the globe are still struggling to develop SM protective drugs. Some therapeutic effect may be achieved by using conventional drugs, but the effects are often limited [14]. Therefore, the development of new approaches to treat SM poisoning remains a critical, albeit unmet, goal in SM research.

Among others, biological treatment involves the use of biological macromolecules. The latter approach has been reported to exhibit a variety of promising benefits including definitive effects, reduced toxicity and side effects compared with traditional therapies. In recent years, biotherapy has attracted more attention in the potential treatment of many critical diseases such as cancer, AIDS, cardiovascular disease, inflammatory ocular disorders, skin diseases, etc. [15–18] Some biological products have been identified to significantly reduce various SM-induced symptoms, and therefore helped improve the quality of life for the victims, although systemic clinical investigation of their overall applicability still needs to be carried out.

2. Biological products used in research and treatment of SM

2.1. Peptides and proteins

2.1.1. Cytokines

2.1.1.1. Epidermal growth factor (EGF). EGF, composed of 53 amino acids, is a single peptide identified by Cohen in 1960s. It also acts as a cell growth stimulator. According previous studies, external application of recombinant human EGF (rhEGF) could enhance the process of wound healing in animals and patients. EGF has been shown to increase tensile strength of corneal incisions in cats, rabbits, and primates and accelerate the epidermal regeneration of dermatome wounds or partial thickness burns in pigs [19]. rhEGF exerts biological effects through binding to surface receptors existing on the cell membrane. In addition, EGF is a potent chemoattractant that can promote the migration of fibroblasts, endothelial cells and keratinocytes to the sites of injury and induce their proliferation [20]. Hwang et al. demonstrated the therapeutic effects of rhEGF on superficial second-degree burns in 30 patients induced by SM. The healing time of the treated group was shown to be significantly shortened from 12.62 ± 3.10 days to 9.35 ± 1.78 days ($P < 0.05$). However, rhEGF did not exhibit an ideal effect on the treatment of skin damage with infection since the drug itself does not feature any anti-inflammatory effects [21]. Our research group has developed a film combining rhEGF, dexamethasone and tinidazole. This film has been shown to release rhEGF slowly, whereas tinidazole and dexamethasone in the film can inhibit inflammation and prevent local infections. This method significantly promotes healing and protects wounded piglet skin [22]. Meanwhile, we used EGF combined with corneal collagen membrane (CCS) and fibronectin (FN) for SM-induced rabbit corneal damages. We found that the combination of the three components featured a synergistic healing effect compared to a separate use of all three components [23]. This new method provides a new treatment option and a novel technology in SM-induced eye injury. Henemyre et al. also reported that the addition of EGF (1 ng/mL) could significantly shorten the healing time of SM-induced wounds through the mechanism of activating epidermal cell regeneration [24]. Based on these findings, EGF appears to be a potentially promising therapy for SM-induced skin injuries. An optimized combination with other drugs may be achieved in the future in order to slowly release EGF to SM-induced wounds and therefore potentially accelerate wound healing.

2.1.1.2. Basic fibroblast growth factor (bFGF). bFGF represents a polypeptide which transmits cell development signals. It can not only stimulate the proliferation of various cells including granular cells, fibroblast, corneal epithelial cells, adrenocortical cells, and lensepithelial cells, but also directly promotes repairs and growth of the damaged cornea [25,26]. In addition, studies have confirmed that bFGF could promote EGF generation or release, which exhibits a promoting role in SM-induced wound healing as described above. In an animal study carried out in rabbits, bFGF could significantly improve the healing process of the corneal epithelial post SM exposure [27]. However, it should be noted that bFGF was demonstrated to only promote the healing of the corneal epithelium and exhibited no effects on detoxication. Lv et al. have reported that topical application of a recombinant basic fibroblast growth factor (rbFGF) in a cell model could improve the viability of human epidermal keratinocytes [28] and accelerate wound healing of SM-induced cutaneous lesions. After application of rbFGF for one week, the scabbing and healing times were found to be significantly shortened (the treatment group versus control group were 8.25 ± 0.96 and 9.75 ± 1.71 days as well as 14 ± 0.82 and 20 ± 0.82 days for scabbing and healing, respectively) [29]. bFGF features several advantages, including low cost of production, easy use, high efficacy, and feasible mass-production by genetic engineering techniques. Therefore, it may find future application in the treatment of SM-induced corneal injuries.

2.1.1.3. Interferon-gamma (IFN-γ). IFN-γ is the only Type II interferon and is secreted by cytotoxic T cells, T helper cells, mucosal epithelial cells, macrophages and NK cells. According to recent studies, bronchiolitis has become a major long-term sequela in SM exposed patients [30,31]. Ghanei et al. have shown that the level of TGF-β1 (an isoform of TGF-β) was significantly higher in patients with SM exposure compared with veterans not exposed to SM in the Broncho-alveolar Lavage Fluid (BALF) [32]. IFN-γ has been reported to downregulate gene expression of TGF-β and procollagen I and procollage III [33]. Therefore, the researchers in this study tried to observe the 6-month treatment effects of IFN-γ-1b plus prednisolone (a corticosteroid medication) in patients with bronchiolitis caused by SM. The results demonstrated that the efficacy of IFN-γ-1b resulted in a significant improvement in the function of the lungs (e.g, Forced Expiratory Volume in first second (FEV1) and Forced Vital Capacity (FVC)) in patients with bronchiolitis after SM-intoxication ($P = 0.001$) [34]. In another study conducted by Panahiet et al., the administration of IFN-γ exhibited a significantly better effect compared with topical betamethasone on ameliorating SM-induced chronic skin complications including pruritus, erythema, alopeia, and excoriation. These findings indicate that IFN-γ could be considered as an effective medication for the management of SM-induced atopic dermatits [35]. It is interesting to note in this context that the application of recombinant human IFN-γ also improved SM-induced chronic respiratory complications. These effects may at least be partially attributed to its ability to improve serum levels of TNF-α, ILs, TGF-β, CGRP, MMP9, MDA, and both total and reduced glutathione [36]. Taken in concert, IFN-γ has been shown to act as an efficient target for the management of chronic complications post SM exposure.