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REVIEW ARTICLE



# Roles of matrix metalloproteinases (MMPs) in SM-induced pathologies

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**ABSTRACT**

Dysregulation of matrix metalloproteinases (MMPs) is now considered as one of the main toxicity effects of sulfur mustard (SM). Numerous studies have found overexpression of MMPs, but the mechanism is unclear. Accumulation of leukocytes, downregulation of tissue inhibitors of metalloproteinases (TIMPs), increase of pro-inflammatory mediators, as well as massive production of reactive oxygen species (ROS) and oxidative stress (OS) are possible mechanisms by which SM induces MMPs expression long-years after exposure. We aim to discuss cellular and molecular mechanisms of SM toxicity, the importance of MMPs and mechanisms by which SM enhances expression of these proteases in SM-victims.

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## Introduction

Sulfur mustard (SM) is a lipophilic chemical compound which has been used as a warfare agent (Shahriary *et al.* 2017). Although it is developed and used during World War I (Ghabili *et al.* 2011), the highest unconventional application of SM was conducted in Iran–Iraq war (1980–1988) which injured more than 100 000 Iranians (Shahriary *et al.* 2017). Unfortunately, about 40,000 of victims are still suffering from late effects of SM even long-term after exposure (Kehe and Szinicz 2005, Namazi *et al.* 2009). The mechanism of SM action on tissue injuries at the chronic phase is not well-elucidated. Recent investigations have proposed that cytotoxicity effect of SM at the acute phase of injury is mainly because of its direct interaction with cellular components such as DNA, proteins and lipids or induction of free radicals production and oxidative stress (OS) (Tahmasbpour *et al.* 2015). Furthermore, increased expression and hyperactivity of some proteases is considered as one of the other significant mechanisms by which SM induces severe damages at the chronic phase of injury (Shohrati *et al.* 2014b). In the following sections, we will discuss general complications of SM toxicity, as well as mechanisms of its action and possible mechanisms by which SM induces severe abnormalities either at the chronic or acute phases of injury.

## Pathological effects of sulfur mustard

Many studies reported various pathological findings of SM exposure in different organs, especially eyes, pulmonary system and skin either in chronic or acute phases (Balali 1984, Vijayaraghavan 1997, Khateri *et al.* 2003, Hassan *et al.* 2006). A large pathologic findings such as dermal injuries, immunological and hematological abnormalities, neuropsychiatric changes, reproductive and developmental failure, gastrointestinal problems, post-traumatic stress disorder (PTSD), mental and sleep disorders have been reported in SM-exposed patients (Shohrati *et al.* 2007, Namazi *et al.* 2009, Rowell *et al.* 2009, Ghabili *et al.* 2010, Ghanei and Harandi 2011). These abnormalities can cause long-term social and economic effects to injured patients and their families (Rowell *et al.* 2009).

Eyes, skin and lungs are the primary targets for SM either at the chronic or acute phases of injury. A previous study on 236 SM-exposed patients revealed respiratory tract (78%), CNS (45%), skin (41%), and the eyes (36%) problems between 2 and 28 months after exposure (Balali-Mood and Hefazi 2005). In another comprehensive study on 34 000 Iranians, 13–20 years after SM exposure, lungs (42.5%), eyes (39%), and the skin (24.5%) were found as the most common complications in these patients (Khateri *et al.* 2003).

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Eyes are the most sensitive organs to SM exposure because of its direct contact with the corneal and conjunctival epithelium (Mahmoudi *et al.* 2005). The maximum incidence usually occurs 15–20 years after initial exposure. Ocular irritation, lacrimation, redness, burning pain, swelling of the eyelids, photophobia, blepharospasm and corneal damage are the most signs and symptoms (Khateri *et al.* 2003, Shohrati *et al.* 2007).

Skin is another significant target for SM exposure which can be associated with skin burning (Balali-Mood and Hefazi 2006), cutaneous lesions, dry skin, local hair loss, extreme itching and erythema, blisters (Firooz *et al.* 2011, Zafarghandi *et al.* 2013), as well as necrosis and inflammation (Hefazi *et al.* 2006, Shahriary *et al.* 2015a). A previous study on 236 Iranian veterans two years after SM exposure revealed late skin effects such as hyperpigmentation (34%), hypo-pigmentation (16%), and dermal scar (8%) (Balali-Mood and Hefazi 2005). Histopathological examination of skin biopsies revealed epidermal atrophy, keratosis, basal membrane hyperpigmentation, nonspecific fibrosis and melanophages (Balali-Mood and Hefazi 2005).

The respiratory system is a primary target for SM toxicity which occurs in a dose-dependent manner from the nasal mucosa to the terminal bronchioles (Ghanei and Harandi 2007, Shahriary *et al.* 2015b, Tahmasbpour *et al.* 2015). SM-induced lung injuries are often lethal in the acute phase, but they are associated with various symptoms and disability such as pain and discomfort in the nose or sinuses, increased nasal secretions, hoarseness, sore throat, a burning sensation of the vocal cords, shortness of breath, hemorrhagic inflammation of the tracheobronchial mucosa, hemoptysis, chest tightness, chest pain, nocturnal dyspnea, generalized wheezing, crackles, decreased lung sounds, clubbing, cyanosis, and necrosis of the mucosa in the chronic phase (Shohrati *et al.* 2008, Akhlaghpoor *et al.* 2011, Mirbagheri *et al.* 2013). Spirometry tests of SM-exposed patients have shown more obstructive spirometric and restrictive injury results (Shohrati *et al.* 2008). For example, a 10-year follow-up survey on Iranian victims who previously exposed to SM illustrated the chronic bronchitis (58%), asthma (10%), bronchiectasis (8%), large airway narrowing (9%), and pulmonary fibrosis (12%), including chronic obstructive pulmonary disease (COPD), as the most delayed destructive pulmonary complications (Balali-Mood *et al.* 2008, Shohrati *et al.* 2008). Chronic bronchitis was reported as the most common chronic effect of SM on respiratory system (Tang and Loke 2012). Pulmonary fibrosis was reported among several Iranian veterans who exposed to SM (Emad and Emad 2007).

Sulfur mustard is also toxic for proliferating cells such as lymphoid and bone marrow cells (Ghanei 2004). Severe leukopenia, hematopoiesis and aplastic anemia were previously reported after acute exposure to SM (Ghanei 2004). Gastrointestinal (GI) problems such as nausea, vomiting, anorexia, abdominal pain and diarrhea were reported in SM-exposed individuals (Emami *et al.* 2014). SM can also affect central nervous system (CNS) and cause neurologic problems such as headache, anxiety, fear of the future, restlessness, confusion and lethargy (Darchini-Maragheh *et al.* 2012). SM may also affect sex hormones. For example, increased level of follicle stimulating hormone (FSH) following with reduced testosterone hormone, impaired spermatogenesis and poor sperm counts were reported after SM exposure (Azizi *et al.* 1995, Amirzargar *et al.* 2009, Ghabili *et al.* 2012, Panahi *et al.* 2013c).

Some studies reported different clinical findings of SM exposure n chronic and acute phases. For instance, a previous study on 213 SM-exposed patients reported leukocytosis (7.2%), leukopenia (3.8%), market lymphopenia (36%), neutrocytosis (38%), eosinopenia (25%), hypochromic anemia (10%), and hypochromic microcytic anemia (5.6%) several days after SM exposure (Tabarestani *et al.* 1990). White blood cell (WBC) counts were reported to be decreased on the third and fourth days after SM exposure (Balali-Mood M *et al.* 1991). Bone marrow biopsies revealed hypocellular marrow and atrophy, fat replacement, nuclear changes such as budding, double nuclear, and kariorrhexis in erythrocyte precursors at the acute phase of injury (Balali-Mood M *et al.* 1991). Increased levels of IgG, IgM and IgE during the first weeks, six-month and even eight years after SM exposure were observed in these patients (Hassan and Ebtekar 2002). A previous study on 40 Iranian veterans indicated higher mean value of IgM even 16–20 years after SM exposure (Ghanei *et al.* 2004). Reduced number of natural killer cells was previously reported 16–20 years after SM exposure (Balali-Mood and Hefazi 2005).

## Mechanisms of SM toxicity

Although the pathological effects of SM on different organs and systems have been studied extensively, cellular and molecular mechanisms of its action at the chronic and acute phases of injury are still unclear. Nevertheless, several direct and indirect mechanisms have been proposed for the acute and late effects of SM toxicity (Figure 1).

Recent evidences have revealed that pathological effects of SM may be due to its direct interaction with

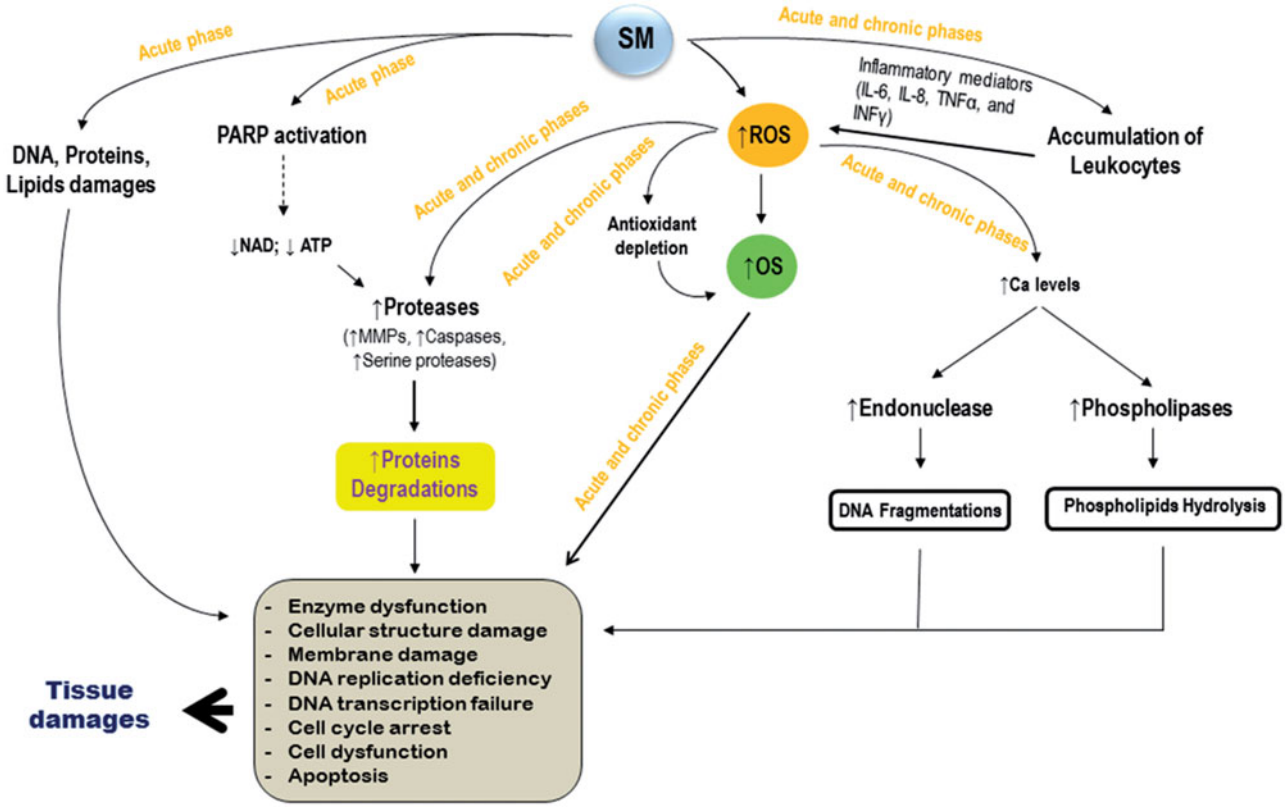


**Figure 1.** Possible mechanisms for the effects of SM action on tissues damage. SM induces tissue damages through the several main mechanisms, including direct alkylating of DNA, proteins, and lipids, as well as, accumulation of leukocytes, depletion of $NAD^+$ and ATP, massive production of ROS, oxidative stress, antioxidants depletion, increases of proteases (e.g. MMPs, Caspases, and Serine proteases) expression, endonucleases, phospholipases, and their activation. SM: sulfur mustard; ROS: reactive oxygen species; OS: oxidative stress.

DNA, lipids and proteins at the acute phase (Jowsey *et al.* 2012), which in turn associated with inhibition of nucleic acid and protein biosynthesis, ATP depletion, cell cycle arrest, cells death and apoptosis (Rao *et al.* 1999, Hefazi *et al.* 2005).

Nicotinamide adenine dinucleotide (NAD) depletion is another possible mechanism of SM-induced toxicity at the acute phase. During SM-induced DNA damages, several DNA repair systems such as Poly (ADP-ribose) polymerase (PARP), base excision repair, nucleotide excision repair, non-homologous and joining are activated (Figure 1). DNA strand breaks induce PARP activation that lead to $NAD^+$ or ATP depletion and stimulation of the $NADP^+$ dependent hexosemonophosphate shunt, which in turn enhances synthesis and release of several proteases such as Caspases (Gross *et al.* 1985). Overexpression of these proteases can be associated with cell death and tissue damage (Papirmeister *et al.* 1985).

Several studies have considered calmodulin and increase in intracellular $Ca^{2+}$ levels as one the other mechanisms by which SM induces cells injury at the chronic and acute phases (Simbulan-Rosenthal *et al.* 2006, Shohrati *et al.* 2007, Ruff and Dillman 2010). Calmodulin and increased intracellular $Ca^{2+}$ level are believed to play a significant role in apoptosis and cell death (Figure 1). High levels of cytosolic $Ca^{2+}$ not only decline proteases activity, but also induce phospholipases and endonucleases activities which in turn degrade cellular proteins, lipids and DNA (Orrenius *et al.* 1989).

Rapid inactivation of sulfhydryl (SH)-containing proteins and peptides, especially glutathione (GSH), is another potential mechanism of SM-induced cell injury at the acute phase (Tahmasbpour *et al.* 2015). However, glutathione depletion is also reported in Iranian veterans long-years after SM-exposure. Glutathione is thought to be crucial in reducing reactive oxygen species (ROS) in cells and preventing OS and loss of membrane integrity (Shohrati *et al.* 2014c) (Figure 1). GSH depletion at the chronic phase of injury may be because of OS.

It is now elucidated that OS induced by excessive production of ROS is a significant mechanism of SM toxicity either at the chronic or acute phases of injury (Tahmasbpour *et al.* 2016). SM induces OS through

either an increase in ROS production or a decrease in antioxidant capabilities (Jost *et al.* 2015). The resulted OS then, in turn, damage DNA leading to chromosome instability, modification of gene expression, genetic mutation which may result in cell death and tissue damages (Gerecke *et al.* 2009, Najafi *et al.* 2014). OS may be associated with lipid peroxidation, which can generate highly reactive electrophilic lipid peroxidation end products, and protein oxidation, which can modify the functional activity of enzymes and structural proteins (Brimfield *et al.* 1998) (Figure 1). Therefore, cytotoxicity from SM may be the result of the direct damage induced by alkylating cellular components or SM-induced ROS production and OS.

Increased activity of different proteases is another significant aspect in the both acute and long-term SM-induced injuries (Ghaffarpour *et al.* 2017). The main group of these enzymes, which are responsible for the collagen and other protein degradation in extracellular matrix (ECM), are matrix metalloproteinases (MMPs). Recent studies have suggested that MMPs may be involved in the chronic effects of SM toxicity. In the following sections, we will discuss the significance roles of MMPs in SM-induced toxicity in injured victims.

## Biological roles of MMPs

Matrix metalloproteinases are a group of zinc-dependent endopeptidases enzymes responsible for the degradation of most extracellular matrix (ECM) proteins, especially collagen (Sorsa *et al.* 2004). MMPs are also involved in embryogenesis, morphogenesis, tissue remodeling, angiogenesis, bone growth, wound healing and tissue regeneration (Jablonska-Trypuc *et al.* 2016). Recent evidence have revealed that MMPs are critical for cells growth, migration, differentiation, inflammatory processes and apoptosis (Nagase *et al.* 2006). These proteases are expressed in various cells, including fibroblasts, neutrophils, monocytes, macrophages, and endothelial cells (Hrabec *et al.* 2007).

So far, more than 20 mammalian MMPs have been identified which can be categorized into six families, including collagenases (MMP-1, -8, and -13), gelatinases (MMP-2, and -9), stromelysins (MMP-3, -10, and -11), matrilysins (MMP-7 and -26), secreted MMPs (MMP-11, -21, and -28), membrane-type MMPs (MMP-14, -15, -16, -17, and -24), and other non-classified MMPs (e.g. MMP-12, -19, -20, -27) (Jablonska-Trypuc *et al.* 2016). Collagenases degrade type II collagen in cartilage, a process which is associated with the progression of rheumatoid arthritis and osteoarthritis. The expression of these MMPs is enhanced in response to interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) (Vincenti and Brinckerhoff 2002). Gelatinases, which are usually expressed by endothelial cells, degrade type IV collagen in basement membrane (Vincenti 2001). Stromelysins have the ability to degrade a wide range of substrates such as proteoglycan, fibronectin, laminin, and the nonhelical region of collagen (Bord *et al.* 1998). Matrilysins are preferentially expressed by airway cells in a variety of lung diseases such as cystic fibrosis and pulmonary fibrosis (Surendran *et al.* 2004). These MMPs, especially MMP-7, have a proteolytic activity against a variety of extracellular matrix substrates such as collagens, proteoglycans, elastin, laminin, fibronectin, and casein (Adachi *et al.* 1999). Among MT-MMPs, MT1-MMP is the most extensively investigated enzyme that serves as a potent collagenase that degrades not only type I and type II collagen, but also basement membrane components such as laminin and type VI collagen (Shi *et al.* 2008).

Given the broad physiological and pathological functions of MMPs, their expression and activity are strictly regulated in different cell types. Several factors such IL-1, IL-6, TNF-α, transforming growth factor (TGF-β), epidermal growth factor (EGF), and basic fibroblast growth factor (bFGF) increase expression of MMPs, while corticosteroids, retinoic acid, heparin, and IL-4 decrease MMPs expression (Lu *et al.* 2008). Additionally, the proteolytic activity of MMPs is controlled by tissue inhibitors of metalloproteinases (TIMPs). The expression of TIMP is regulated by cytokines and growth factors (Jablonska-Trypuc *et al.* 2016). Therefore, changes in expression and secretion of different pro-inflammatory cytokines and growth factors can subsequently affect TIMPs and MMPs expression and activity.

MMPs dysregulation is shown to be associated with different abnormalities such as cardiovascular disease, diabetes, apoptosis, cancer, renal dysregulation, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, and tumor growth (Lu *et al.* 2008, Thrailkill *et al.* 2009). For example, overexpression of MMPs, especially MMP-2 and MMP-9, was reported in patients with breast cancer (Ren *et al.* 2015). Increased expression of MMPs was found in serum, sputum and bronchoalveolar lavage (BAL) fluids of patients with cystic fibroses (Roderfeld *et al.* 2009). Increased level of MMP-9 was reported in submucosal and epithelial areas of patients with asthma (Hoshino *et al.* 1998). A previous study reported downregulation of MMP-1, MMP-3, and MMP-9 in patients with cardiomyopathic hearts (Batlle *et al.* 2007). Additionally, MMP-2 expression levels were reported to be correlated with the fibrosis levels (Batlle *et al.* 2007). In another study,

**Table 1.** Effects of SM on MMPs expression and activity in different study models.

| Study models | Phase of injury | Results | Reference |
|---|---|---|---|
| Human subjects | | | |
| SM-exposed patients | Chronic | ↑MMP-9 activity | Shohrati *et al.* (2014b) |
| SM-exposed patients | Chronic | ↑MMP-9 activity; ↑MMP-9/TIMP-4 complex | Ghaffarpour *et al.* (2017) |
| SM-exposed patients | Chronic | ↑MMP-1 activity; ↓MMP-2 activity | Kiani *et al.* (2013) |
| SM-exposed patients | Chronic | ↑MMPs activity | Pashandi *et al.* (2015) |
| SM-exposed patients | Chronic | ↑MMPs mRNA | Khazdair *et al.* (2015) |
| SM-exposed patients | Chronic | ↑MMP-9 levels | Panahi *et al.* (2014) |
| SM-exposed patients | Chronic | ↑MMP-9 levels | Ghasemi *et al.* (2009) |
| *In vivo* studies | | | |
| SKH-1 hairless mouse | Acute | ↑MMP-9 mRNA | Mouret *et al.* (2015) |
| Rabbit tear fluid | Acute | ↑MMP-9 activity; ↑MMP-2 activity | Horwitz *et al.* (2014) |
| Guinea pigs BAL fluids | Acute | ↑MMPs activity; ↓TIMPs levels | Guignabert *et al.* (2005) |
| Mice | Acute | ↑MMP-9 activity; ↑MMP-2 activity | Kannan *et al.* (2016) |
| Guinea-pigs | Acute | ↑MMP-9 activity; ↑MMP-2 activity | Benson *et al.* (2011) |
| Rat BAL fluids | Acute | ↑MMP-9 levels | Malaviya *et al.* (2010) |
| Guinea-pigs | Acute | ↑MMP-9 activity | Dachir *et al.* (2010) |
| *In vitro* studies | | | |
| Ear skin from mice | Acute | ↑MMP-9 mRNA; ↑MMP-9 protein | Shakarjian *et al.* (2006) |
| Weanling pig skin | Acute | ↑MMP-9 mRNA; | Sabourin *et al.* (2002) |
| Human epidermal keratinocytes | Acute | ↑MT-MMP-1; ↑Serine proteases | Jin *et al.* (2016) |
| SKH-1 hairless mouse skin | Acute | ↑MMP-9 mRNA | Vallet *et al.* (2012) |
| SKH-1 hairless mouse skin | Acute | ↑MMP-9 levels | Jain *et al.* (2011) |

Roach *et al.* (2002) observed that MMP-2 and MMP-9 are strongly upregulated in patients with skeletal muscle ischemia and reperfusion injury. There is also a tight link between MMPs overexpression with OS. Khazdair *et al.* (2015) indicated that up-regulation of MMPs is significantly correlated with increased inflammatory cells recruitment, pro-inflammatory cytokines and tissue injury (Khazdair *et al.* 2015). These data suggest that MMPs regulation is critical for normal function of different tissues and any dysregulation of these proteases by various factors and environmental stimuli such as toxins can be associated with severe abnormalities.

Sulfur mustard is likely a potential stimulator which may affect MMPs expression at the chronic phase of injury. For this reason, a role for MMPs in the pathophysiology of SM-induced injuries is also emerging. In the following sections, we review the literature supporting this hypothesis.

## Roles of MMPs in SM-induced injuries

Sulfur mustard has been shown to stimulates multiple proteases such as MMPs, Caspases and serine proteases and subsequently results in severe damages to different tissues (Jin *et al.* 2016). Increased levels of MMPs can be associated with inflammatory cell recruitment, and as the result overproduction of ROS, OS and tissue injury (Khazdair *et al.* 2015). Therefore, elevated contents of MMPs may be a reason by which SM induces several pathological effects during the chronic phase of injury.

A growing number of studies have considered contents of serum and sputum MMPs after SM exposure either at the chronic or acute phase in both human and experimental models (Table 1). For example, in a cross-sectional study, the serum levels MMP-1, MMP-2, MMP-7, MMP-9, TIMP-1 and TIMP-2 were compared between 25 Iranian patients with pulmonary problems caused by SM (chronic phase) and 25 unexposed participants (Shohrati *et al.* 2014b). Chemically injured group showed significantly higher MMP-9 in their serum compared to normal group, while there was no significant difference in mean of MMP-1, MMP-2, MMP-8, TIMP-1 and TIMP-2 between two groups. In another similar study, MMP-1, MMP-2, MMP-8, MMP-9, TIMP-1, TIMP-2, TIMP-3, and TIMP-4 levels were measured in serum of individuals with lung complications, 20 years after SM-exposure (Kiani *et al.* 2013). Although tissue inhibitors of metalloproteinases (TIMPs) level was not different between SM-exposed and normal groups, increased serum level of MMP-1 and decreased MMP-2 activity was found in SM-exposed individuals. Interestingly, there was a significant relationship between serum level of MMP-1 and severity of lung complications in SM exposed groups (Kiani *et al.* 2013). The authors concluded that elevated serum level of MMP-1 is likely because of pathologic changes affecting alveolar microenvironment in SM exposed patients long-years after exposure. MMP-1 degrades type1 collagen fibrils and converts it to gelatin which, in turn, can be degraded by other MMPs like MMP-9 and MMP-7. In another research, Khazdair *et al.* (2015) suggested that increased expression of MMPs in SM-exposed patients at the chronic phase of injury is contributed to inflammatory cell recruitment, tissue injury and fibrosis.

In a more recent study, Ghaffarpour *et al*. (2017) have considered MMP-9 and TIMPs levels in serum of 372 SM-exposed male patients with pulmonary complications 20 years after exposure. The authors found increased level of MMP-9 in serum of SM-exposed individuals who had moderate or severe pulmonary complications compared to SM-exposed patients with normal lung (Ghaffarpour *et al*. 2017). Furthermore, they reported elevated MMP-9/TIMP-4 complex in SM-exposed group with normal lung compared to its corresponding control group (Ghaffarpour *et al*. 2017). Although MMP-9 and TIMPs did not show any relationship with spirometry findings, increased level of serum MMP-9 was observed in SM-exposed patients with chronic chough and hemoptysis (Ghaffarpour *et al*. 2017). Pashandi *et al*. (2015) demonstrated that elevated serum MMPs activity is involved in development of SM-induced ocular symptoms 30 years after exposure.

There are also several experimental studies that considered role of MMPs after SM-exposure. For example, Mouret *et al*. (2015) investigated the effect of different concentration of SM (0.6, 6 and 60 mg/kg) on skin features and inflammatory biomarkers at the acute phase of injury. They found a dose-dependent increase for mRNA of MMP-9 after SM exposure which was associated with SM-induced blisters formation. In another research, Horwitz *et al*. (2014) measured MMP-9 and MMP-2 activities in tear fluids of rabbit eyes after SM vapor exposure (acute phase). They found high MMP-9 activity and negligible MMP-2 activity in all exposed eyes. Similarly, Vallet *et al*. (2012) found MMP-9 upregulation following cutaneous exposure (acute phase) to SM in hairless mouse SKH-1. The increase in MMP-9 was correlated with upregulation of inflammatory cytokines and macrophage inflammatory proteins (Vallet *et al*. 2012). Shakarjian *et al*. (2006) observed an overexpression of MMP-9 mRNA and protein in ear skin of SM-exposed mice. However, they didn't find a significant increase in expression of MMP-2 mRNA and protein between treated and control ears (Shakarjian *et al*. 2006). Similarly, Sabourin *et al*. (2002) demonstrated that SM exposure increases MMP-9 mRNA levels in porcine skin. A more recent study has suggested that upregulation of MT-MM-1 may be involved in SM-induced skin blistering (Jin *et al*. 2016). Therefore, given the potential effect of MMPs on structural and biochemical units to abrupt microenvironment, regulation of their activity in SM-injured patients is vital for normal tissues function (Ghaffarpour *et al*. 2017).

Although numerous studies showed a relationship between SM exposure and dysregulation of MMPs, especially MMP-9 and MMP-2, the mechanism in which SM increases MMPs expression and activity either at chronic or acute phases is not well-understood. OS induced by SM may be a main reason for MMPs deregulation, especially in chronic phase. It is now illustrated that OS induced by free radicals is one the major mechanisms for direct effects of SM exposure on different organs in the both chronic and acute phases. Mitochondrial deficiency, hypoxia, upregulation of ROS-producing enzymes, downregulation of several antioxidants, and GSH depletion are the mechanisms by which SM indices ROS overproduction and OS even long-terms after exposure. Recent evidences have indicated that there is a remarkable link between the accumulation of ROS and OS with the increased expression of MMPs (Gencer *et al*. 2013). For instance, Yu *et al*. (2008) showed that increased OS leads to MMP-9 upregulation, blood–brain barrier disruption, and apoptosis. Previous studies reported that MMPs activity, especially MMP-2 and MMP-9, can be regulated by ROS (Alexander and Elrod 2002). Excessive production of ROS, which occurs in SM-exposed individuals, can increase MMP-2 and MMP-9 activity. Activation of endothelial cell MMPs by ROS was also found in cell culture studies (Deem and Cook-Mills 2004).

There are also several *in vitro* studies that showed ROS induce MMPs (e.g. MMP-1, -2, and -9) activity, while decrease TIMP function (Cucullo *et al*. 2008). In a physiological process, there is a precise balance between MMPs and TIPMs. MMPs form a noncovalent complex with TIMPs in a 1:1 ratio (Ghaffarpour *et al*. 2017). TIMP-1 favorably makes a complex with MMP-9, while TIMP-2 preferentially forms complex with MMP-2. Distortion of this balance can be a cause of many pathological conditions such as COPD and pulmonary fibrosis. Recent studies have indicated that SM disrupts this balance (Nejad-Moghaddam *et al*. 2016). Since TIMPs are significant inhibitors of MMPs, downregulation of these proteins in SM-exposed patients can be another reason for MMPs upregulation and tissue damages.

Increased levels of pro-inflammatory cytokines and growth factors are another reason by which SM may enhance MMPs expression. SM can accumulate inflammatory cells, including macrophages and neutrophils with a subsequent release of chemical mediators of inflammation such as interleukins and cytokines that can recruit and activate other leukocytes at the site of tissue injury (Tahmasbpour *et al*. 2015). Numerous studies have shown that SM exposure is associated with the secretion of proinflammatory cytokines, chemokines and growth factors, including TNFα, IL-1α,

IL-1β, IL-6, IL-8, IL-13, IL-15, INF-γ, and macrophage chemotactic protein (MCP)-1 (Jafari and Ghanei 2010, Khaheshi *et al.* 2011, Panahi *et al.* 2013a, Shohrati *et al.* 2014a). Increased levels of IL-1α, IL-1β, IL-5, IL-6, IL-8, IL-12, IL-13 and TNFα were also detected in BAL fluids of SM-exposed individuals (Panahi *et al.* 2013b, Shohrati *et al.* 2014a). Recent evidences have also demonstrated that SM induces IL-17, which in turn increases MMP-1 (Koshy *et al.* 2002, Mishra *et al.* 2012). This phenomenon can explain the reason why MMP-1 level is elevated in serum of SM-exposed patients which is associated with pulmonary complications even 20 years after exposure.

## Conclusions

Sulfur mustard causes tissue injuries and severe abnormalities in victims through the several cellular and molecular mechanisms even long-term after exposure. SM leads to cytotoxicity effects through DNA oxidation, NAD depletion, antioxidants depletion, inflammation, OS and apoptosis. Increased expression and activity of some proteases, especially MMP-2 and MMP-9, is another significant mechanism by which SM induces severe damages even at the chronic phase of injury. Nevertheless, the exact mechanism in which SM increases MMPs expression or activity is unclear. SM-induced OS and massive production of ROS may be a main reason for MMPs and TIMPs deregulation even at the chronic phase of injury. Accumulation of leukocytes at the site of damaged tissues which is associated with increased contents of pro-inflammatory cytokines, interleukins and growth factors, are significant mechanisms that increase expression and activity of MMPs at the chronic phase of injury. Since overproduction of ROS and OS is likely a main reason for increased expression and activity of MMPs, antioxidants therapy may protect tissues against SM-induced damages. However, further clinical trial research are require to investigate the effect of antioxidant therapy on levels of MMPs and TIMPs activity in patients who exposed to SM long years after exposure.

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## Disclosure statement

No potential conflict of interest was reported by the authors.

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