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Review

Molecular toxicology of sulfur mustard-induced cutaneous inflammation and blistering

K. Kehe*, F. Balszuweit, D. Steinritz, H. Thiermann

Bundeswehr Institute of Pharmacology and Toxicology, Neuherbergstr. 11, D-80937 Munich, Germany

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ABSTRACT

Sulfur mustard (SM) is a strong alkylating agent, which produces subepidermal blisters, erythema and inflammation after skin contact. Despite the well-described SM-induced gross and histopathological changes, the exact underlying molecular mechanisms of these events are still a matter of research. As part of an international effort to elucidate the components of cellular signal transduction pathways, a large body of data has been accumulated in the last decade of SM research, revealing deeper insight into SM-induced inflammation, DNA damage response, cell death signaling, and wound healing.

SM potentially alkylates nearly every constituent of the cell, leading to impaired cellular functions. However, SM-induced DNA alkylation has been identified as a major trigger of apoptosis. This includes monofunctional SM-DNA adducts as well as DNA crosslinks. As a consequence, DNA replication is blocked, which leads to cell cycle arrest and DNA single and double strand breaks. The SM-induced DNA damage results in poly(ADP-ribose) polymerase (PARP) activation. High SM concentrations induce PARP overactivation, thus depleting cellular NAD^+ and ATP levels, which in consequence results in necrotic cell death. Mild PARP activation does not disturb cellular energy levels and allows apoptotic cell death or recovery to occur. SM-induced apoptosis has been linked both to the extrinsic (death receptor, Fas) and intrinsic (mitochondrial) pathway.

Additionally, SM upregulates many inflammatory mediators including interleukin (IL)-1α, IL-1β, IL-6, IL-8, tumor necrosis factor-α (TNF-α) and others. Recently, several investigators linked NF-κB activation to this inflammatory response.

This review briefly summarizes the skin toxicity of SM, its proposed toxicodynamic actions and strategies for the development of improved medical therapy.

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* Corresponding author. Tel.: +49 89 31682926; fax: +49 89 31682333.
E-mail address: kai.kehe@lrz.uni-muenchen.de (K. Kehe).

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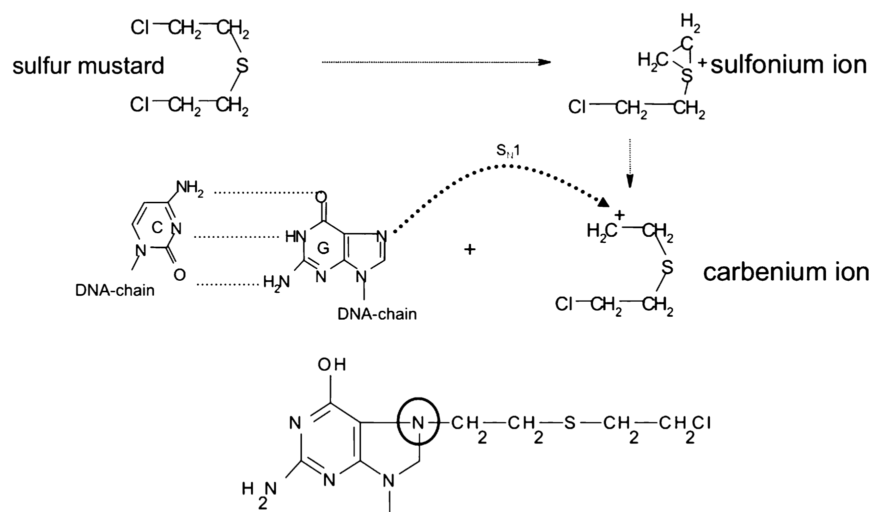

Fig. 1. Reaction of sulfur mustard with N7 in guanine. Sulfur mustard forms an intermediate sulfoniumion that further transforms into a carbeniumion, a strong electrophile capable to react with DNA, such as the N7 in guanine (reprinted with permission from Kehe and Szinicz, 2005).

1. Introduction

Sulfur mustard (SM; 2,2′-dichloroethyl sulfide; CASRN: 505-60-2) is a strongly alkylating agent, which can react with all constituents of the skin. Schematically, the process of SM-induced skin pathology can be divided in three overlapping stages: erythema, blister formation and ulceration (Smith et al., 1919). Skin hyperpigmentation is a frequently observed finding accompanying all SM skin lesions (Balali-Mood and Hefazi, 2005). Typical erythema and skin oedema formation occurs several hours after skin contact, which is followed by subepidermal blisters (Aasted et al., 1987). Erythema can frequently be observed 4–8 h after SM exposure at a threshold dose (vapour: 100–300 mg min/m^3, liquid: 10–20 μg/cm^2) while blister formation occurs at higher doses (vapour: 1000–2000 mg min/m^3, liquid: 40–100 μg/cm^2) (Kehe and Szinicz, 2005). The blisters are characterized by small vesicles, which coalesce at a later point in time to gross blisters or large bullae (Balali-Mood and Hefazi, 2006). Exposure to higher concentrations of SM results in ulcers penetrating dermal structures of the skin. These three major skin pathologic findings (erythema, blister, and ulcer) have been linked to a variety of molecular mechanisms (Kehe et al., 2008).

The histopathology of SM affected skin shows vasodilatation and neutrophil infiltrate, which indicates that various vasoactive and chemoattractant mediators are produced in the exposed area (Smith et al., 1997).

The aim of this article is to describe the current knowledge of underlying pathophysiological mechanisms of acute epithelial lesions following SM exposure. Based on this concept rational targets for therapeutical intervention are presented.

2. Tissue destruction (blister and ulcer)

SM-induced blisters are thin-walled and filled with an amber-coloured fluid. A positive Nikolsky sign was frequently described, which means that rubbing of the skin will produce more blistering. Skin blistering may last for several days to weeks after a single SM exposure (Kehe et al., 2004). These blisters are clinical signs of dermal–epidermal separation of skin layers. Histopathologic analysis reveals marked keratinocyte cell death in the basal layer with signs of a massive inflammatory response (Smith et al., 1998).

2.1. DNA damage

SM is a highly reactive chemical, which reacts with nearly all cell constituents. DNA damage is believed to be the most critical lesion (Lodhi et al., 2001). SM reacts with the DNA by forming mono- and bifunctional SM adducts (Lawley and Brookes, 1967). These adducts are formed preferentially at the N7 position of guanine (61%) (Fig. 1), the N1 position of adenine (Ludlum et al., 1994), N3 of adenine (16%) and O6 of guanine (0.1%) (Ludlum et al., 1984, 1986). Even though comparatively rare, O6-(2-ethylthioethyl) guanine is regarded as a critical DNA lesion because human DNA repair mechanism fail to remove the SM adduct at this position (Ludlum et al., 1986). Thus, O6 (2-ethylthioethyl) guanine may be a significant cause of mutagenic effects by SM due to misreplication (Ludlum et al., 1986; Yanagida et al., 1988). Bifunctional SM adducts (intra- or interstrand crosslinks) are observed in nearly 17% of all SM alkylations (Lawley et al., 1969; Lawley and Brookes, 1967). In contrast, nitrogen mustards and its derivates cause only 1–5% interstrand crosslinks (Dronkert and Kanaar, 2001). Interstrand crosslinks are believed to stall replication and finally induce double strand breaks (Andreassen et al., 2006).

Two protein kinases ATM (Ataxia-teleangiectasia mutated protein), a homolog of the yeast checkpoint protein Mec1, and ATR (Ataxia-teleangiectasia and Rad3-related kinase) have been shown to play a major role in the primary recognition of DNA damage and to initiate DNA repair as well as cell cycle arrest (Roos and Kaina, 2006). Both are activated by double strand breaks (Ismail et al., 2005). ATR, but not ATM, is activated by stalled replication forks, then phosphorylates the cell cycle checkpoint kinase Chk1, which in turn destabilizes the cyclin-dependent kinase (Cdk) activator Cdc25A thereby inhibiting Cdk activity (Clarke et al., 2005; Enders, 2008). ATM is activated dependent on the extent of DNA double strand breaks and phosphorylates various downstream proteins such as p53 (Ser15), nibrin (NBS1), Brca1 and Chk2 (Banin et al., 1998; Ismail et al., 2005). Chk2 activates the kinase CDC25, which controls the S-phase checkpoint. Phosphorylation of ATM (Ser1981) has been described to play a role in the intranuclear detection of SM-induced DNA damage. Simultaneously, phosphorylation of H2Ax and accumulation of p53 and p21 was observed (Kehe et al., 2006). The specific role of ATM and ATR in detecting SM-induced DNA damage needs further investigation.

Further cell fate is highly dependent on the amount of SM alkylated DNA. With increasing DNA alkylations cellular responses consists of cell cycle arrest, terminal differentiation, apoptosis, or

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