Sulfur Mustard (SM) is a toxic substance that can cause damage to the DNA. It is otherwise known as "mustard gas" and is used to injure victims in the battle field. Due to its lipophilic properties, it can seep through the skin. Once it reaches the inner layer of the body, it causes stress to specific oxygen molecules which in turn, react and block calcium transport channels. These signals, as well as various other reactions cause by SM, ultimately cause the cells in the body to die (apoptosis). SM poisoning can be extremely detrimental to the body, however; its effects can be reversed when not fully exposed. Certain molecular inhibitors in the body can reduce the body's response to the toxicity.

SM is chemically known as bis [2-chloroethyl] sulfide. Its harmful effects include skin blisters, DNA damages, carcinogen and cytotoxic properties [5]. Due to its hazardous nature, the SM agent has been utilized as a weapon during warfare and is commonly known as "mustard gas" due to its smell and color [2]. Although it is known as a gas, it is not actually a gas. It exist as an oily liquid that can be applied on surfaces. It can vaporize at a high temperature, which is dangerous as it can seep through clothing or wood, and cause a toxic response when inhaled [2]. This agent appeared in World War I, where over a million casualties were caused, giving it the name “King of Battle Gasses.” It is then after known to play a part in the more recent Iran-Iran War [2].

SM mainly damages the skin, eyes, and respiratory tract. Symptoms of skin damages include blisters and inflammation which can lead to infections and in severe cases, apoptosis. SM also has alkylating properties, which enables it to cause damage to DNA molecules to the point of disrepair [2]. Due to the important roles DNA has in the human body, once the molecules start to disrepair, it could lead to a cascade of events which usually results in further damages to even more cells in the body. Prolong exposures to SM can also cause different cellular responses due to the interactions between molecules and proteins, upsetting its natural states and resulting in
necrosis (Figure 1). For example, PARP inhibitors serves the purpose of repairing damages in DNA molecules, calcium ions and calcium ion dependent molecules, and various proteins such as p38. If these chemical reactions in the body get interrupted by the SM toxins, they will not be able to carry out their vital functions. If, however, human exposure to SM is low, the toxicity level can be reduced by inhibiting certain signal molecules to block pathways.

As an alkylating agent, SM can disrupt normal DNA synthesis. Alkylating agents have a high affinity 7-nitrogen group of guanine molecules, which enables it to covalently bind to DNA molecules and inhibit replication [2]. In order to repair this damage, poly (ADP ribose) polymerase will use a substrate called NAD+ to catalyze itself to different nuclear proteins. However, if there was enough damage, it could lead to NAD+ depletion. This is detrimental to cells since ATP would naturally come and attempt to replenish NAD+ [3]. This process was verified by a study done by Papirmeister, who conducted an experiment that exposes nude mice to the SM gas and researched the various levels of skin injury caused. The hypothesis of the experiment was stated that, “accumulation of DNA breaks causes activation of the chromosomal enzyme poly(ADP-ribose)polymerase, which utilizes NAD+ as a substrate to ADP-ribosylate a variety of nuclear proteins and causes a severe lowering of cellular NAD+ (Rankin et al., 1980; Shall, 1982)” [6]. The experiment consisted of applying grafted human skin onto nude mice and exposing them to various levels of SM. The mice would consequence die from the SM toxicity and the human skin was then preserved for study. This can determine the different levels of NAD+ activity in the body in relation to different hours after SM exposures [6]. The experiment concluded that there was a point in which high levels of SM exposure would cause the loss of NAD+ to be irreversible and show signs of severe skin injury (Figure 2) [7]. Along with skin
injury, DNA disrepair could also affect the muscles and heart after it seeps into the skin and infects the cellular pathways within the body.

In order to reduce toxicity of SM exposure, proper steps must be taken. It is stated that, “there is no consensus on medical management of person exposed to mustard gas other than through decontamination and supportive care that could include oxygen therapy, fluid replacement, diuresis, antibiotics” [2]. A way to reduce the toxic responses can be carried out through inhibition of the molecules or changes in mechanisms. For example, in another experiment, p38 was inhibited and tested by treating the exposed normal human epidermal keratinocytes and findings showed a decrease in the SM induced production of molecules by a margin of over 50%, which are all related to inflammatory responses and apoptosis [1]. In addition, this is also a way to treat muscle contraction as well. Increase of muscle contraction is due to increase of calcium ions being built up in the intracellular membrane. In the findings of another experiment, calmodulin-calcineurin inhibition reduces SM-induced toxicity. Furthermore, this is also a way to prevent PARP from depleting NAD+, due to the nature of NAD+ wanting to repair DNA damage. Inhibition could prevent it from phosphorylating or activating. However, in other experimental findings, DNA damage is compromised in the absence of PARP activity. PARP inhibitors and PARP knockout did not protect cells, but sensitized cells to DNA damage, which is more detrimental to treat injuries [2].

The mechanism of SM poisoning is extensive and has some areas that are still inconclusive. However, the mechanisms of how it affects the body and its responses have been derived based
upon various studies. There isn’t a specific treatment for SM induced toxic responses but
detoxification and proper supportive care for the patient will help flush the toxicant out of the
system. To prevent the most detrimental effects and depletion of cell’s energy, over exposure is
best avoided. SM is a chemical warfare agent and most people are not exposed except those in
the battlefield. A small exposure is still treatable but it is best not to come into contact with this
toxicant.
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