Anti-TNFα Antibody Mitigates Sulfur Mustard-Induced Lung Injury in Rats

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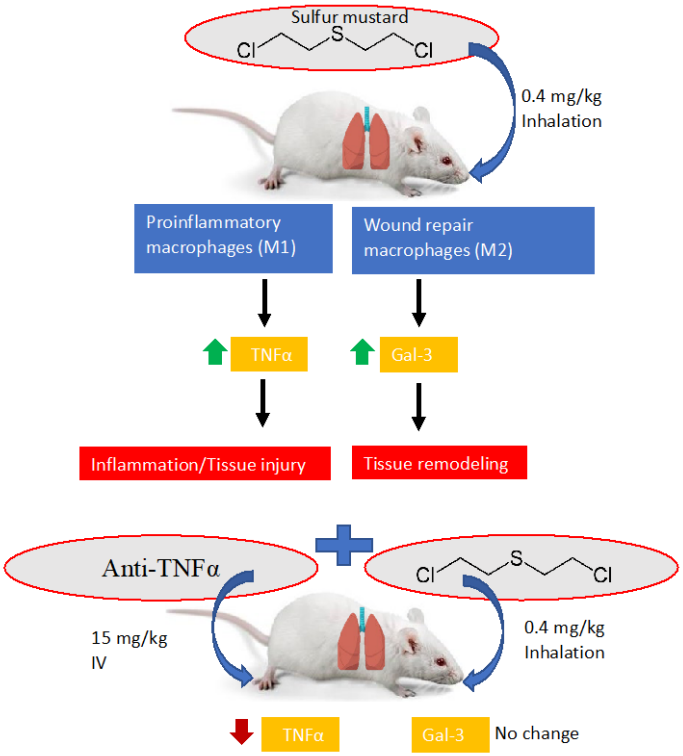
Sulfur mustard (SM) is a vesicating chemical warfare agent that causes severe lung injury when inhaled. Acute sulfur mustard-induced toxicity is due, in part, to persistent accumulation of macrophages in the lung and the release of inflammatory mediators including cytokines, chemokines, eicosanoids and growth factors. The proinflammatory cytokine, tumor necrosis alpha (TNFα), is released from activated macrophages; it has been shown to contribute to lung injury by promoting inflammatory cell accumulation in tissues and stimulating the release of other inflammatory mediators. This leads to oxidative stress, airway hyperresponsiveness, and tissue remodeling. In these studies, we tested the hypothesis that anti-TNFα antibody treatment would mitigate mustard induced acute lung inflammation and injury. Male Wistar rats were exposed to SM vapors (0.4 mg/kg) or air control and treated with either monoclonal anti-TNFα antibody (15 mg/kg) or vehicle 15-30 min later. Animals were euthanized 3 days after exposure, bronchoalveolar lavage fluid (BAL) and lung tissue collected. Treatment of rats with SM resulted in lung injury and inflammation as measured by increases in bronchoalveolar lavage fluid (BAL) cell and protein content. SM exposure also resulted in increased numbers of lung macrophages expressing tumor necrosis factor (TNF) α and heme oxygenase (HO)-1 indicating inflammation and oxidative stress. Treatment of rats with anti-TNFα antibody (15 mg/kg, i.v.) 15-30 min after SM inhalation reduced lung injury and inflammation, SM-induced levels of HO-1 and TNFα were also suppressed by anti-TNFα antibody treatment. These data demonstrate that inhibiting TNFα may be an effective approach to mitigating acute lung injury induced by vesicants. *Supported by NIH Grants U54AR055073, R01ES004738, and P30ES005022.*


Sulfur mustard
Cl
S
Cl
0.4 mg/kg
Inhalation
Proinflammatory macrophages (M1)
Wound repair macrophages (M2)
TNFα
Gal-3
Inflammation/Tissue injury
Tissue remodeling
Anti-TNFα
15 mg/kg
IV
Cl
S
Cl
0.4 mg/kg
Inhalation
TNFα
Gal-3
No change