Inhibition of Matrix Metalloproteinase 9 (MMP9) Suppresses Inflammation and Enhances Wound Healing in Mouse Skin Treated with Sulfur Mustard

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Sulfur mustard (bis(2-chloroethyl) sulfide, SM) is a highly reactive bifunctional alkylating agent that can induce inflammation and blistering in the skin. Effective medical countermeasures against SM-induced cutaneous injury have yet to be established. Overexpression of MMP9 has been implicated in the pathogenesis of SM-induced skin injury. MMP9 is known to degrade basement membrane (BM) and play a role in regulating the migration of macrophages and neutrophils to sites of tissue injury; inhibition of MMP9 reduces inflammatory cell migration and suppresses inflammation in tumors and various wound models. In the present studies, we tested ([N-hydroxy-3-phenyl-2-(4-phenylbenzenesulfonamido) propanamide], BiPS), a specific MMP9 inhibitor, for its ability to suppress inflammation and enhance wound healing following SM exposure using the mouse ear vesicant model. Treatment of male CD1 mouse ear skin with SM (0.08 mg) caused a characteristic cutaneous injury including edema, inflammatory cell infiltration, and the formation of microvesicles at the dermal-epidermal junction (DEJ). Expression of MMP9 mRNA and protein in the skin progressively increased with time 24-168 h following SM exposure. Immunofluorescence studies showed disruption of the BM molecule collagen IV (ColIV), increased expression of COX2, and upregulation of the skin wound marker keratin 6 (K6) in SM induced skin wounds. SM also caused macrophage (F4/80) accumulation in the tissue which persisted up to 168 h post exposure. Pretreatment of ear skin with BiPS reduced SM-induced dermal edema by 60% and maintained the integrity of the DEJ as evidenced by contiguous expression of ColIV. At 168 h post SM exposure, mRNA and protein expression of MMP9 was significantly downregulated in BiPS treated mice. BiPS treatment also suppressed SM-induced inflammation, reducing the number of macrophages accumulating in the tissue; it also suppressed expression of COX2 and downregulated expression of K6. These data indicate that targeting MMP9 by BiPS effectively protected mouse ear skin from SM induced injury. MMP9 inhibitors may be useful as medical countermeasure against SM-induced cutaneous injury. *Supported by NIH grants ES005022 and AR055073.*