RISING DERM STARS

Silver Sulfadiazine retards wound healing in mice via alterations in cytokine expression

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Background: Silver sulfadiazine (SSD), a broad-spectrum antimicrobial agent, has been the gold standard for burn wound treatment for decades. However, several studies have demonstrated its inferiority when compared to other wound healing adjuvants.[1,2] This study aimed to elucidate SSD's impact on wound healing and suggest mechanisms by which it occurs.

Methods: Thermal burns were induced on the dorsal surface of BALB/c mice; mice were split into two groups: untreated control (n=56) and SSD-treated (n=46) (50μL of 1% SSD cream per wound daily). Daily photographs and Image J software were used to asses change in wound area relative to day 0. Histologic samples were stained using hematoxylin and eosin (H&E), Masson's trichrome, ionized calcium-binding adapter molecule-1(IBA-1) and myeloperoxidase (MPO) to visualize morphology, collagen deposition, macrophages and neutrophils respectively. Burn wounds were harvested for cytokine analysis (n= 10 wounds, 5 animals per group) and tissue samples were analyzed in duplicate for cytokine expression using Mouse Cytokine Antibody Array and cytokine signal intensity was measured using Quantity One Software.

Results: Topical SSD applied to the wound bed significantly delayed wound closure compared to controls. By day 3 post-burn, both controls and SSD-treated wounds expanded compared to day 0, however the extent was significantly greater in the SSD-treated group (49.7 vs 23.8%, $P<0.0002$). By day 10, the SSD-treated group demonstrated 16.3% closure relative to day 0, as compared to 42.1% closure in controls ($p<0.005$) [Figure 1]. Wound histology and immunohistochemistry revealed more and persistent inflammatory granulation tissue and delayed collagen deposition in the wound bed as compared to controls over time, with increased neutrophil and decreased macrophage infiltration identified by myeloperoxidase and IBA-1 staining respectively. Cytokine analysis on day 3 revealed an absence of several pro-inflammatory factors including monocyte chemotactic protein(MCP)-1, macrophage inflammatory protein(MIP)-1α and interleukin-1 receptor antagonist(IL-1ra), which were present in untreated tissue. Expression of interleukin(IL)-1α and macrophage inflammatory protein(MIP)-2 were significantly lower than controls. On day 7, significantly lower levels of IL-1α, IL-1ra, MIP-1α and MIP-2 were noted in the SSD group with complete absence of MCP-1 [Figure 2].

Discussion: Our findings have several implications for the mechanisms by which

SSD impedes wound healing. Treatment with SSD alters the cytokine milieu resulting in aberrant recruitment and activation of macrophages. The inflammatory reaction in wound healing is regulated by a delicate balance between pro- and anti-inflammatory cytokines, with the IL-1 family regulating chemokine production by keratinocytes, fibroblasts and macrophages.[3,4] While expression of the IL-1 family is dependent on the complex interplay between members of the family, given our results, we hypothesize that SSD alters gene expression of IL-1 family genes resulting in impaired downstream cytokine production and ultimately delayed wound healing. While these data suggest a causal relationship by which SSD retards wound healing, further investigations are necessary to fully assess the degree of this effect. This study also underscores the importance of evaluating the immunologic effects of drugs in order to fully understand their mechanism of action.

Figure 1

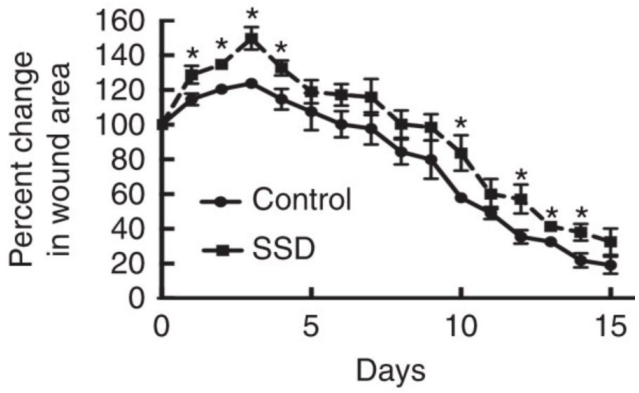
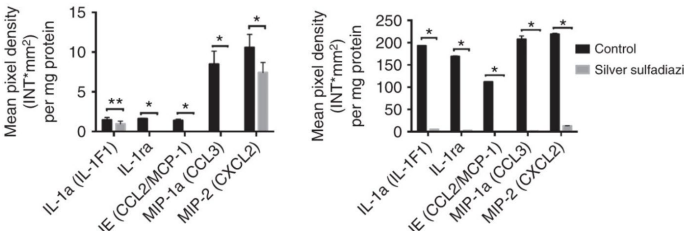


Figure 2



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