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Rescuing Macrophage Function Following Severe Thermal Injury

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Commentary

Severe thermal injuries invoke an initial systemic inflammatory response that is followed by a compensatory anti-inflammatory phase [1]. This counterregulatory phase can induce a relative state of immunosuppression that may predispose to the development of septic shock and multiple organ dysfunction syndrome [2]. A key element of this post-burn immune dysfunction involves alteration of macrophage activity including decreased phagocytic abilities [1,3] and decreased major histocompatibility complex (MHC) class II expression with associated increased mortality and other complications [1,4,5]. In addition, increased PGE₂ and decreased IL-12 production by macrophages promote a Th2-mediated humoral response and increased production of the anti-inflammatory cytokines IL-4 and IL-10 [1,6].

Given the significant implications of impaired immunity following severe burns, there is growing interest in modulating the host immune response, in particular through the administration of unmethylated CpG oligodeoxynucleotide motifs (ODN). These DNA motifs are present in higher frequencies in prokaryotic genomes and to a lesser extent in vertebrates and may serve as a “danger signal” to the host immune system during infection by activating germ line-encoded pattern recognition receptors [7]. CpG ODN immunostimulation occurs via activation of Toll-like receptor-9 (TLR9), which is mainly expressed by B lymphocytes and dendritic cells [8]. TLR9 activation results in the proliferation and maturation of natural killer (NK) cells, monocytes, macrophages and T cells [9-11]. CpG ODN also triggers upregulation of MHC class II and costimulatory molecule expression [12] and inflammatory cytokine production including IFN γ , TNF α , IL-1, IL-6, and IL-12 [10,13]. The ability of exogenously administered CpG ODN to induce immune reactions has also led to the investigation of its role as a vaccine adjuvant [14] and immunotherapies for malignancy and hepatitis [15-18].

In the present study, Dr. Yabuki and colleagues investigate the relationship of CpG ODN administration and MHC class II expression by splenic macrophages in a murine burn model. Following generation of 20% full-thickness burns with steam exposure, spleens were harvested up to 21 days later for macrophage isolation. The burn injuries predictably resulted in a progressive decline in macrophage MHC class II expression. *In vitro* treatment of the macrophages with CpG ODN was associated with increased MHC class II expression and production of IL-12, TNF α , IL-6, and IL-1. To evaluate these effects *in vivo*, mice were given intraperitoneal injections of CpG or non-CpG ODN four days following burn injury, and splenic macrophages were harvested ten days later. CpG ODN-treated mice exhibited increased macrophage MHC class II expression compared to non-CpG ODN-treated mice. Combined,

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these data support the hypothesis that CpG ODN administration may augment macrophage MHC class II expression following severe burn injury.

Several questions remain regarding the efficacy of CpG ODN administration following severe burn injuries. It cannot be determined from this observational study whether immunocompetence was restored with increased macrophage MHC class II expression and cytokine production. Furthermore, the optimal timing of CpG ODN dosing in relation of antigen challenge has yet to be defined. CpG ODN upregulation of the immune response may also induce formation of antibodies to “self” molecules [19]. While no adverse clinical sequelae related to this have been observed in previous studies, further monitoring will be necessary. Finally, the potential for adverse effects of iatrogenically stimulating the host inflammatory response with potential for further organ injury and other adverse effects also remains. However, despite these remaining issues, the preliminary data presented in this study justify continued investigation of this potential therapy.

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