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$\gamma\delta$ T-Cells: Potential Regulators of the Post-Burn Inflammatory Response

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Abstract

Burn injury induces an immunopathological response that can contribute to the development of a systemic inflammatory response (SIRS) and subsequent multiple organ failure. While, multiple immune cells type (T-cells, macrophages, neutrophils) are involved in this response, recent evidence suggests that a unique T-cell subset, $\gamma\delta$ T-cells are central in the response to injury. While $\gamma\delta$ T-cells represent only a small percentage of the total T-cell population, they display specific functional characteristics that uniquely position them in the immune/inflammatory axis to influence a number of important aspects of the body's response to burn injury. This review will focus on the potential regulator role of $\gamma\delta$ T-cells in immunopathological response following burn injury and thereby their potential as therapeutic targets for modulation of post-burn inflammation and healing.

Keywords

wound healing; chemokines; growth factors; organ injury; bisphosphonates

Introduction

Major thermal injury induces a pathophysiological response that has a marked inflammatory component. A wide range of pro-inflammatory mediators [i.e., TNF- α , IL-6, PGE₂, nitric oxide (NO), etc] are released that subsequently contribute to the development of a systemic inflammatory response (SIRS), immune dysfunction and multiple organ failure [1-4]. Recent experimental studies suggest a central role for a unique T-cell subset, $\gamma\delta$ T-cells, in post-burn survival, development of macrophage hyperactivity, initiation of neutrophil-mediated tissue damage and wound healing [5-7]. This review will focus on our current knowledge of the potential role of $\gamma\delta$ T-cells in the initiation and regulation of the inflammatory and immune cascades induced by major burn injury. Particular emphasis will be placed on the potential role of $\gamma\delta$ T-cells in wound healing after burn injury.

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Thermal Injury and T-Cell Subsets

The majority of previous studies evaluating T-cell function after thermal injury have focused on T-cells purified from the spleen [8-10] or the peripheral circulation [11]. These T-cells are almost exclusively of the $\alpha\beta$ T-cell receptor (TCR) lineage and are considered part of the adaptive immune system [12]. Adaptive immunity, by definition, is antigen specific and the central cell in the adaptive immune response is the CD4+ $\alpha\beta$ T helper cell. Alpha/beta T-cells, *via* cytokine production and interaction with other immune cells, drive antigen specific immune responses. In contrast to $\alpha\beta$ T-cells, a T-cell subset expressing the $\gamma\delta$ TCR are present in only small numbers in peripheral lymphoid tissues (i.e., spleen) or blood, but are relatively abundant in the skin epithelia, intestine, uterus and tongue [13]. Nonetheless, the involvement of $\gamma\delta$ T-cells in a wide variety of disease processes is indicative of an important role in both innate and acquired immunity [13]. Gamma/delta T-cells have several features which distinguish them from “traditional” $\alpha\beta$ T-cells [14]. Most $\gamma\delta$ T-cells have a phenotype of spontaneous activation with a rapid turnover rate [15] and they quickly expand upon pathogenic/inflammatory activation [16;17]. Gamma/delta T-cells also influence other T-cell functions *via* regulation of their cytokine responses [14]. Table 1 compares some of the salient characteristics of $\alpha\beta$ and $\gamma\delta$ T-cells.

A critical role for $\gamma\delta$ T-cells in inflammation and tissue repair has been shown [18-20]. Intraepithelial $\gamma\delta$ T-cells produce a number of chemokines for recruitment of other immune cells [21]. They also differ from $\alpha\beta$ T-cells with regards to tissue localization and antigen recognition, [$\gamma\delta$ T-cells recognize antigens directly, with no requirement for processing or presentation [22;23]]. Due to these properties and characteristics[18;19;21-24], $\gamma\delta$ T-cells are considered more a part of the innate immune system, rather than the adaptive immune system, like $\alpha\beta$ T-cells. Recent studies have shown activated $\gamma\delta$ T-cells in the circulation of patients with severe SIRS, suggesting a role for these cells in the early response to injury [25]. Recent findings in a mouse burn model also indicate that circulating activated $\gamma\delta$ T-cells numbers are increased early after injury and are an important source of chemokines [6]. An important role for $\gamma\delta$ T-cells early post-burn is suggested by the finding that high mortality was observed during the initial 48 hr post-injury in mice deficient in $\gamma\delta$ T-cells [5]. It can be speculated that $\gamma\delta$ T-cells trigger responses after burn injury important to immune surveillance, tissue repair, and wound healing.

Not surprisingly, other immune lymphocyte subsets (independent of $\alpha\beta$ or $\gamma\delta$ T-cells) also appear to be important in the post-burn response that include natural killer (NK) and NK-T cells [26]. In this regard, findings suggest that the post-burn injury defects in T-cell responsiveness that occur subsequent to severe burn injury are not the consequence of global immunosuppression, but rather represent an active form of CD1d/NKT cell-dependent immunological tolerance [27].

$\gamma\delta$ T-Cells and Wound Healing

Proper healing the burn wound site is a critical component of the patient’s successful recovery from burn injury [28;29]. The process of burn wound healing is complex involving a series of overlapping phases [30-32]. This healing process is represented schematically in Fig. 1. During hemostasis, clot formation occurs along with platelet aggregation and the release of chemokines, which recruit immune cells to the injury site [33]. The inflammatory phase is characterized by the infiltration of the injury site with neutrophils, macrophages and lymphocytes [30;34]. The proliferative phase is associated with capillary growth and granulation tissue formation [30]. Cell proliferation and collagen synthesis leads to reepithelialization. Increased deposition of collagen occurs and remodeling of the newly

formed connective tissue persists for months after the initial injury, thus resolving the injury [30;32].

The inflammatory process is instrumental in supplying growth factors, cytokines and chemokines that orchestrate the cell movement necessary for wound repair [35;36]. The cellular components of the immune system appear to peak in the wound in a specific sequence and time frame (Fig. 2) and their migration to the injury site characterizes the different stages of the healing process as outlined in Fig. 1 [34]. Neutrophils are the first immune cells to arrive and their primary role is wound debridement and protection against microbial infection. However, activated neutrophils can also be deleterious by releasing proteases and reactive oxygen intermediates, which can cause significant tissue damage [37]. Macrophages and other myeloid cells (i.e., myeloid suppressor cells, MSC) migrate to the wound within 48 hr and become the predominant immune cell type. Macrophages are essential to successful wound healing, as they cytokines, chemokines and growth factors such as platelet derived growth factor (PDGF) and vascular endothelial growth factor (VEGF), that initiate the formation of granulation tissue [35]. Myeloid suppressor cells (MSC) have been described in a number of mouse systems, including chemo- and radiotherapy [38;39], tumor biology [40;41], immunization [40] and traumatic stress [42]. MSC are thought to function in immunosuppression [43;44]. MSC are also likely to play an important role in wound healing *via* the production of nitric oxide [39;45].

Studies on the role of T-cells in the later phases of wound repair have shown that T-cell depletion leads to a decrease in wound strength and collagen content [34;46]. T-cells in the wound are predominantly of a Th-1 type phenotype [47]. Bernabei et al. [48] observed that active hypertrophic scar tissue was infiltrated by Th1-type T-cells, whereas the Th2-type phenotype was characteristic of the remission phase of hypertrophic scar formation.

Wound healing is a complex process involving many immune cell types; however, the role of $\gamma\delta$ T-cells has received little attention. The majority of T-cells found in the epidermis of normal mice are of the $\gamma\delta$ TCR lineage, and specifically express the invariant V γ 3/V δ 1 TCR [49]. Previous studies have led to the development of the concept that epithelial $\gamma\delta$ T-cells survey for general signs of epithelial injury or stress rather than recognizing specific antigens. Studies have demonstrated that epidermal $\gamma\delta$ T-cells recognize antigen expressed by damaged or stressed keratinocytes and produce chemokines and growth factors upon stimulation [24;50]. More recently, Jameson et al. [51] have shown that mice deficient in $\gamma\delta$ T-cells had defects in keratinocyte proliferation and tissue reepithelialization. *In vitro* studies also demonstrated that the addition of $\gamma\delta$ T-cells to the culture or keratinocyte growth factors restored normal wound healing [51]. These findings by Jameson et al. [51] support the concept that epidermal $\gamma\delta$ T-cells recognize antigen expressed by injured keratinocytes and produce mediators that regulate tissue repair. Recent findings [7;52] suggest that $\gamma\delta$ T-cells may be important to the inflammatory phase of the burn wound healing process. The burn wound from $\gamma\delta$ T-cell deficient mice displayed markedly less inflammation, edema and immune cell infiltration than burn wounds from wildtype mice. Burn wound tissue lysates of $\gamma\delta$ T-cell deficient mice contained decreased levels of fibroblast growth factor (FGF) and platelet derived growth factor (PDGF) supportive of decreased and/or delayed healing processes [52]. These findings [7; 52] support the concept that $\gamma\delta$ T-cells are critical to the proper orchestration of burn wound healing.

Improved understanding of the role of nitric oxide (NO) in biological and pathological responses has had significant impact in the research areas of shock, injury and inflammation. Both clinical and experimental findings have implicated NO in the inflammatory response caused by burn injury [53;54] and altered NO synthesis has been associated with remote organ dysfunction [55-57] and immune dysfunction [8;58-60] under such circumstances. Moreover,

supraphysiological levels of NO metabolites have been detected in thermally-injured tissues and plasma extravasation within the burn wound has been demonstrated to be NO-mediated [61] and inducible nitric oxide synthase (iNOS) has been detected in skin from burned rodents and humans [62-64], thereby implicating iNOS as an important generator of NO post-burn. With regard to $\gamma\delta$ T-cells, they are known to produce mediators, such as IFN- γ , that are associated with macrophage activation [65-67] and previous findings support a role for $\gamma\delta$ T-cells in post-burn macrophage hyperactivity [5]. Jones-Carson et al. [67] have shown that $\gamma\delta$ T-cells enhance macrophage NO production and that $\gamma\delta$ T-cell depletion prevents iNOS expression. Previous studies have also shown that iNOS is important in dermal wound reepithelialization [68], wound closure [69] and collagen deposition [70]. Moreover, fibroblasts isolated from iNOS deficient mice display decreased proliferation, collagen synthesis and contraction of collagen lattices [71] and macrophage angiogenic activity (a critical component of wound healing) is NOS-dependent [72]. Studies suggest that iNOS expression in dermal wounds occurs early post-injury (48-72 hr), whereas arginase expression predominates later [73-75]. Thus, it can be speculated that $\gamma\delta$ T-cells might mediate their effects on wound healing *via* secondary induction/regulation of macrophage iNOS expression.

$\gamma\delta$ T-Cells and Organ Injury

It has been established in both clinical and experimental studies that thermal injury can induce remote organ injury at sites such as the lung, liver, and small intestines [64;76-82]. These burn-induced organ injuries appear to be primarily mediated by neutrophils [56;76;77;82]. Moreover, NO has also been implicated in remote organ damage [55-57]. Boismenu et al. [21] have shown that intraepithelial $\gamma\delta$ T-cells produce a number of chemokines for recruitment of leukocytes to injured tissue. Circulating $\gamma\delta$ T-cells express chemokine receptors and are susceptible to chemotactic gradients and, in this way, can be targeted to damaged tissue [83]. Experimental studies have documented that $\gamma\delta$ T-cell deficient mice have dysfunctional regulation of inflammatory responses in various tissues including the skin, gastrointestinal tract, and lung [84-86]. Since $\gamma\delta$ T-cells can produce chemokines, they may contribute to the recruitment of additional circulating $\gamma\delta$ T-cells to sites of tissue damage [21;83].

Recent findings from our laboratory support a role for $\gamma\delta$ T-cells in neutrophil-mediated remote organ (i.e., lung, small intestine) injury early post-burn that is associated with increased chemokine levels and $\gamma\delta$ T-cell activation [6]. Overall, it is highly likely that activation of $\gamma\delta$ T-cells early post-injury is protective, (even though it is associated with neutrophil-mediated tissue damage in the lung and gut). The protective effect of $\gamma\delta$ T-cell activation post-burn is likely to be related to their role in immune surveillance, tissue repair and wound healing [49; 87;88]. Major burn injury induces mucosal gut atrophy which is associated with disruption of gut epithelial cell homeostasis and increased apoptosis [89;90]. Studies using $\gamma\delta$ T-cell deficient mice have shown that such animals have decreased TNF- α mRNA and apoptosis in the gut following injury [91]. Nonetheless, $\gamma\delta$ T-cell deficiency didn't alter mucosal atrophy post-burn, thereby suggesting that the development of gut mucosal atrophy after a major burn injury is related to multiple factors.

Of Men and Mice

An important consideration in experimental studies is that significant differences exist between humans and mice with regard to the dermal T-cell phenotypes found under normal non-pathological conditions. In humans, the predominant dermal T-cell is of the $\alpha\beta$ TCR lineage, whereas in rodents the predominant population in the skin is $\gamma\delta$ T-cells [92;93]. Nonetheless, recent findings by Ebert et al. [94] indicate that human dermal cell suspensions contained significant numbers of V δ 1 T-cells. These cells express the CCR8 chemokine receptor for homing to non-inflamed or normal skin. Upon activation, CCR8 expression is transiently lost

and expression of the CCR7 chemokine receptor is increased. CCR7 promotes homing or migration to sites of inflammation or injury. Thus, human dermal $\gamma\delta$ T-cells are regular and functional constituents of human skin that possess unique homing and migratory patterns. Moreover, in humans under pathological or inflammatory conditions [i.e., systemic lupus erythematosus (SLE), dermatitis herpetiformis, leprosy, leishmaniasis, malignancies], increased numbers of $\gamma\delta$ T-cells are found in the skin and/or dermal lesions [87;95-98]. For example, Robak et al. [96] observed that in patients with SLE that the percentage of $\gamma\delta$ T-cells in the skin of patients was double that of healthy subjects. In contrast, circulating $\gamma\delta$ T-cells in patients was ~50% of that of healthy subjects, suggesting a possible recruitment to the skin tissue. Moreover, a positive correlation between disease activity and $\gamma\delta$ T-cells accumulation in the skin was observed. Thus, $\gamma\delta$ T-cells in human skin appear to be an active immune cell population and, as shown by these studies, their role in dermal pathology is clearly evident.

While the role of $\gamma\delta$ T-cells in the wound healing responses of burn patients remains to be determined, based on wound healing deficits observed in experimental systems with $\gamma\delta$ T-cell deficient mice [7;20;51;52;88] and their role in human dermatological inflammation [87; 95-98], it can be speculated that the healing complications observed in burn patients may be related to a similar deficiency or dysfunction in $\gamma\delta$ T-cells. Therefore, if appropriate clinical studies systematically examining the burn site and other compartments indicate that $\gamma\delta$ T-cells are important to the burn wound healing response, therapeutic applications targeting $\gamma\delta$ T-cells may be effective in decreasing wound healing complications in burn patients.

$\gamma\delta$ T-Cells and Immunotherapy

Gamma/delta T-cells are involved in several physiologic and disease-related processes [99]. These properties of $\gamma\delta$ T-cells may be exploitable in the treatment of various pathological conditions including wound healing. Clinical studies have shown that immunotherapy with $\gamma\delta$ T-cells promoted engraftment of T-cell depleted bone marrow without increased risk of graft vs. host disease [100]. Similar findings were observed in a mouse model [101], indicating the cross application of findings from an experimental mouse system to human patients. Lamb et al. [102] also noted that several patients who received bone marrow grafts depleted of $\alpha\beta$ T-cells developed increased $\gamma\delta$ T-cell numbers, which was associated with improved survival. Recent studies in a preclinical primate model have shown the ability of synthetic phosphoantigens to expand and activate the circulating $\gamma\delta$ T-cell population, thus suggesting a novel immunotherapeutic strategy for a number of pathological conditions [103;104].

We propose the novel concept that immunotherapy with $\gamma\delta$ T-cells might be effective in improving wound healing in human burn patients. Nonetheless, the development of protocols for $\gamma\delta$ T-cell-based adoptive cellular immunotherapy has been impeded by their sensitivity to activation-induced apoptosis. Lopez and co-workers [105;106] have shown a signaling pathway that inhibits apoptosis in human $\gamma\delta$ T-cells. These findings are important, since they permit for the large-scale *ex vivo* expansion of human $\gamma\delta$ T-cells. Since similarities, with regard to inflammation, angiogenesis and healing exist between tumor biology, transplantation and wound healing, immunotherapy with human $\gamma\delta$ T-cells might improve wound healing in burn patients. It should be noted, that even if significant numbers of native $\gamma\delta$ T-cells are not found at the burn site, the adoptive transfer of this cell population might improve the healing process. In fact, a potential lack of $\gamma\delta$ T-cells at the burn site may be causative in the development of post-burn wound healing complications.

An alternative approach to immunotherapy with $\gamma\delta$ T-cells might be the use of bisphosphonates. Bisphosphonates are an important part of the therapeutic treatment of benign and malignant metabolic bone diseases, such as Paget's disease, osteoporosis and tumor-associated hypercalcaemia and osteolysis [107]. On mechanism by which bisphosphonates is by

modulation of the immune response. Several nitrogen containing bisphosphonates (N-BPs), such as pamidronate, ibandronate, alendronate, risedronate and zoledronate can induce an expansion of $\gamma\delta$ T-cells, both in vitro and in vivo, primarily through the V γ 9V δ 2 subset [108-111]. In this regard, proliferation of $\gamma\delta$ T-cells and tumor regression in patients with low-grade non-Hodgkin lymphoma has been reported when pamidronate was administered with IL-2 [111]. Interestingly activation of $\gamma\delta$ T-cells by N-BPs requires cell-to-cell contacts with the target (tumor) cell and antigen presenting cells such as macrophages [112]. The N-BP-mediated activation of $\gamma\delta$ T-cells leads to increased cytokine production (TNF- α , IFN- γ etc), which is can regulate tumor killing activity on a number of levels [107]. While, these findings with regard to cancer immunotherapy are exciting, their potential application to other disease states such as regulation of inflammation and wound healing has not been examined and may represent a new and novel approach to address such clinical concerns.

Conclusions

Thermal injury is a significant health problem in the United States with approximately 70,000 people sustaining such injuries requiring hospitalization each year (18). Despite advances, immunosuppression resulting in increased susceptibility to sepsis, wound healing complications, and multiple organ failure remain major causes of burn patient morbidity and mortality. To date, the role of $\gamma\delta$ T-cells in post-burn immunopathology has received little attention. This unique T-cell subset is uniquely positioned in the immune/inflammatory axis to influence tissue repair, inflammation, anti-microbial activity, and overall immune status at the level of neutrophils, macrophages and T-cells.

Based on previous work on the immunoinflammatory response to burn injury and the current understanding of the role of $\gamma\delta$ T-cells in the immune response we propose that that $\gamma\delta$ T-cells are important in wound healing via regulation of the myeloid cell inflammatory response, which is suppressed following burn injury (Fig. 3). We propose that under normal conditions $\gamma\delta$ T-cells are recruited to the dermal wound from surrounding skin and the blood. They are activated in the process to produce chemokines and cytokines. These immunomodulatory factors induce myeloid cell recruitment and activation. The activation of myeloid suppressor cells is critical for wound healing. In burn injury, $\gamma\delta$ T-cell recruitment and activation are suppressed along with subsequent myeloid activation, leading to delayed healing of the burn injury site. Thus, therapeutic approaches which modulate $\gamma\delta$ T-cell activation post-burn may improve healing in such patients and warrant further investigation.

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Figure 1.
Stages of wound healing. Wound healing involves a number of overlapping phases over a period of months that include: hemostasis, inflammation, proliferation and resolution.

Figure 2.

Immune cell content of the healing wound. The cellular components of the immune system in the wound in a specific sequence and time frame.

Figure 3. Schematic of the proposed role of $\gamma\delta$ T-cells in wound healing. Under normal conditions $\gamma\delta$ T-cells are recruited to the dermal wound from surrounding skin and the blood. Burn injury (flame graphics) suppresses this response at multiple steps. See text for details.

Table 1Comparison of $\alpha\beta$ and $\gamma\delta$ T-cells

	$\alpha\beta$ T-cells	$\gamma\delta$ T-cells
Phenotype	Small agranular	Large granular
Location	Primary and secondary lymphoid tissues, circulation	Mucosal epithelial (skin, gut, reproductive organs)
Thymic Selection	Yes	Yes
TCR ^a	Heterodimer, α and β chains 45-50 variable segments Potential diversity $\sim 10^{16}$ Broad repertoire	Heterodimer, γ and δ chains 2-5 variable segments Potential diversity $\sim 10^{18}$ via D segment rearrangement Specific repertoire for bacterial/viral antigens and autoantigens.
CD4, CD8 Subsets	Yes	No. CD8 only on activated cell
Antigen Recognition	MHC ^b restricted. Requires APC ^c	MHC and APC independent. Non-peptide ligands (i.e., phospholipids)
Activation Kinetics	hrs to days	Rapid (min to hrs)

^aTCR: T-cell receptor^bMHC: major histocompatibility class^cAPC: antigen presenting cell