

Systemic Responses to Burn Injury

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Abstract: The major causes of death in burn patients include multiple organ failure and infection. It is important for the clinician to understand the pathophysiology of burn injury and the effects it will have on the pharmacokinetics of a drug. The local and systemic inflammatory response to thermal injury is extremely complex, resulting in both local burn tissue damage and deleterious systemic effects on all other organ systems distant from the burn area itself. Thermal injury initiates systemic inflammatory reactions producing burn toxins and oxygen radicals and finally leads to peroxidation. The relationship between the amount of products of oxidative metabolism and natural scavengers of free radicals determines the outcome of local and distant tissue damage and further organ failure in burn injury. The injured tissue initiates an inflammation-induced hyperdynamic, hypermetabolic state that can lead to severe progressive distant organ failure. Despite recent advances, multiple organ failure (e.g., cardiac instability, respiratory or renal failure) and immune dysfunction remain major causes of burn morbidity and mortality. Further experimental and clinical studies will hopefully lead to a more complete understanding of these pathological processes. From that point it should be then possible to develop improved treatments for burn patients.

Key Words: Thermal injury, multiple organ failure, oxygen radicals, proinflammatory cytokines

Epidemiology

Thermal burns and related injuries are a major cause of death and disability, especially in subjects under the age of 40. Even in developed countries, more than 2 million individuals annually are burned seriously and require medical treatment (1). The average burn patient is 24.4 years old and has a mean burn size of 19% of the total body surface area (TBSA) (2). Most burns are caused by carelessness and appear to be preventable, while the rest of the cases are associated with smoking and alcohol. The face and hands are the most common sites of injury, followed by respiratory damage, with eye damage being the least common injury (3). Men, especially young men, tend to be more prone to burn injury than women (4). Hot or corrosive substances account for two-thirds of all burns, with fire and flame accounting for one-fourth (5). Multivariate analysis revealed that cardiovascular/renal failure, pulmonary failure, extent of burn, age and female sex are the major determinants in mortality. It was also found that patients with failure of 2 or more organ

subsystems had a 98% mortality rate (6), while infection is the major cause in 75% of deaths from burns (7). It is customary to classify burn injuries etiologically as thermal, electrical or chemical in origin (8).

In thermal burns the local wound occurs as a result of heat necrosis of cells. The conductance of involved tissue determines the rate of dissipation or absorption of heat and depends upon several factors. These include the peripheral circulation, water content of the tissue, thickness of the skin and its pigmentation, and the presence or absence of external insulating substances such as hair and skin oil. Among these factors perhaps the most important in determining the degree of injury is the peripheral circulation (8). Electrical burns result from the heat produced by the flow of electrical current through the resistance of body tissues. Factors of primary importance in determining the effect of the passage of an electric current through the human body include the type of circuit, voltage, amperage, resistance of the tissues involved, the path of current through the body and

duration of contact with the current (9). Several chemical agents may be responsible for chemical burns. Most of the chemical agents produce skin destruction through chemical reactions rather than hyperthermic injury. Included among these reactions are coagulation of protein by reduction, corrosion, oxidation, formation of salts, poisoning of protoplasm and desiccation. Acids promote collagen denaturation and subsequent degradations (10-12).

Burn management

Healing of a burn wound is a normal response to injury and the formation of scar tissue is a result of cellular and biochemical processes. Five factors determine the seriousness of a burn: depth, size, area(s) of involvement, age and general health status of the burn victim. Burns are classified as partial-thickness (first or second degree) or full-thickness (third or fourth degree), and the extent of a burn wound is calculated as a percentage of the total body surface area (13).

Initial treatment of the burn patient is aimed to stop respiratory distress, start fluid resuscitation, and prevent burn shock. After the patient is stabilized, drug therapy can be initiated to control pain and prevent infection (14). The application of ice or cold water soaks is effective in decreasing pain in areas of second-degree burn and should be used for analgesic effect if the burns involve less than 25% of the total body surface (15). In the emergency room, fluid resuscitation should be initiated by infusing a balanced salt solution from a peripheral vein underlying unburned skin or underlying the burn wound, or a central vein in that order of preference (15). An arterial blood sample should be obtained from any patient with a major burn injury for the determination of pH blood gases, carboxyhemoglobin, electrolytes, urea nitrogen, glucose and hematocrit. The patient should be weighed, the depth of the burns must be assessed and the extent of the burn should be estimated by the rule of nines (where each upper limb accounts as 9%; each lower limb, 18%; anterior and posterior trunk, each 18%; head and neck, 9%; and perineum and genitalia, 1%) and on the basis of these calculations, the fluid infusion rate is adjusted accordingly. A urethral catheter should be placed in all burn patients requiring intravenous fluid therapy for the measurement of hourly urinary output.

The clinical course of a burn is a dynamic cascade of pathological changes including hypermetabolism,

hypovolemia and decreased immune function. The major causes of death in burn patients include multiple organ failure and infection. It is important for the clinician to understand the pathophysiology of burn injury and the effects it will have on the pharmacokinetics of a drug. After the initial treatment, the patient must be admitted for further non-operative treatment including resuscitation, nutrition, infection control, ventilation and other burn wound management techniques (16). Ventilatory status should again be assessed to determine the need for endotracheal intubation, oxygen administration and mechanical ventilatory support. The use of clinically effective topical antimicrobial agents developed in the mid-1960s has significantly decreased the occurrence of invasive burn wound infections and burn wound sepsis; thus this effect has been associated with the improved survival of burn patients (17). In particular silver nitrate soaks and silver sulfadiazine are most effective when initiated immediately after burning, before significant microbial colonization has occurred (15).

Pathophysiology of Thermal Injury

The local and systemic inflammatory response to thermal injury is extremely complex, resulting in both local burn tissue damage and deleterious systemic effects on all other organ systems distant from the burn area itself. Although the inflammation is initiated almost immediately after the burn injury, the systemic response progresses with time, usually peaking 5 to 7 days after the burn injury (18-20). Much of the local and certainly the majority of the distant changes are caused by inflammatory mediators (21-23). Thermal injury initiates systemic inflammatory reactions producing burn toxins and oxygen radicals and finally leads to peroxidation. The relationship between the amount of products of oxidative metabolism and natural scavengers of free radicals determines the outcome of local and distant tissue damage and further organ failure in burn injuries (24). The injured tissue initiates an inflammation-induced hyperdynamic, hypermetabolic state that can lead to severe progressive distant organ failure (21-23,25,26).

Cardiovascular Response

Immediately after thermal injury, the changes that occur in the cardiovascular system are of vital importance and require treatment priority in order to limit volume

deficits, prevent the development of burn shock, and achieve maximal salvage (15). The cardiovascular response to thermal injury has 2 separate phases: the first is the acute or resuscitative phase, which immediately follows the burn trauma. It is characterized by decreased blood flow to tissues and organs and is thought to be caused by hypovolemia following injury (27). Hypovolemia may be a direct effect of heat, while the liberation of vasoactive materials from the injured area, which increases the capillary permeability and promotes fluid and protein loss into the extravascular compartment, contributes even more to hypovolemia. Within minutes of burning, cardiac output falls in proportion to burn size in association with an increase in peripheral vascular resistance (28).

The acute phase lasts about 48 h and is followed by a hypermetabolic phase characterized by increased blood flow to the tissues and organs and increased internal core temperature. During the hypermetabolic phase rapid edema formation occurs and this has been attributed to hypoproteinemia, which favors the outward movement of water from the capillary to the interstitium. Secondly, an increase in the water permeability of the interstitial space is evident, which further increases edema formation (29). Patients with acute burn injuries develop a hypermetabolic state with associated catecholamine production and release. Increased adrenergic stimulation is one of the triggers of myocardial infarction and cardiac arrhythmias. In burn patients, end-diastolic volume indices increase while right ventricular ejection fractions decrease, which strongly indicate myocardial dysfunction (30). Cardiac instability in burned patients is associated with hypovolemia, increased afterload and direct myocardial depression. Additionally, the hyperaggregability, hypercoagulability, and impaired fibrinolysis resulting from any acute injury may predispose to myocardial infarction (31-36).

Pulmonary Response

Respiratory failure is one of the major causes of death after burn injury. Thermal injury itself, without smoke inhalation, has been shown to produce significant lung changes in numerous animals and in humans (37,38). There is increasing evidence that lung inflammation and lipid peroxidation occur in the first several hours after a local burn injury and these processes are initiated by oxidants, in particular hydroxyl radicals. In accordance with these, we have reported that the levels of the end

products of lipid peroxidation are significantly increased in lung tissues 24 h after burn injury, suggesting that pulmonary injury is dependent upon oxygen radicals (39). On the other hand, systemic activation of the complement may initiate the process (40,41). Lung inflammation and lipid peroxidation are not simply an initial transient response, but persist for at least 5 days after the burn. With early and complete removal of the burn wound, the histologic and biochemical abnormalities resolve, again indicating that the inflammation perpetuates the systemic inflammatory changes (40,42). In addition, lung antioxidant defenses may also be decreased postburn. In the sheep model, lung tissue catalase levels have been reported to be significantly decreased by 3 days postburn, even in the absence of any wound infection, the catalase possibly being inactivated by an early superoxide release (43). Respiratory complications from smoke inhalation have become the primary cause of mortality for burn victims and are attributed to a combination of hypoxemia, and thermal and chemical effects. Typically, the pathophysiological sequence 24-72 h after burn trauma with inhalation injury, includes pulmonary arterial hypertension, bronchial obstruction, increased airway resistance, reduced pulmonary compliance, atelectasis and increased pulmonary shunt fraction. Pulmonary vascular hypertension and altered capillary permeability are exaggerated after an inhalation injury. Arachidonic acid, which is released by disturbed cell membranes, is converted by cyclooxygenase to cyclic endoperoxides, thromboxane A₂, and prostacyclin (PGI₂). Both agents mediate pulmonary hypertension, ventilation and perfusion abnormalities leading to progressive hypoxemia and severe gas exchange disturbances (30).

Renal Response

During the acute phase of burn injury, renal blood flow and glomerular filtration rate (GFR), as measured by creatinine clearance, decrease. In the hypermetabolic phase, creatinine clearance is increased, indicating that both blood flow and GFR are raised; however, tubular function is impaired (44). Diminished blood volume and cardiac output cause a post burn decrease in renal blood flow and glomerular filtration rate. If untreated, the resulting oliguria may progress to acute renal failure. The incidence of acute renal failure (ARF) in severely burned patients ranges from 1.3 to 38% and this complication has always been associated with high mortality rates (73 to 100%). The pathophysiologic

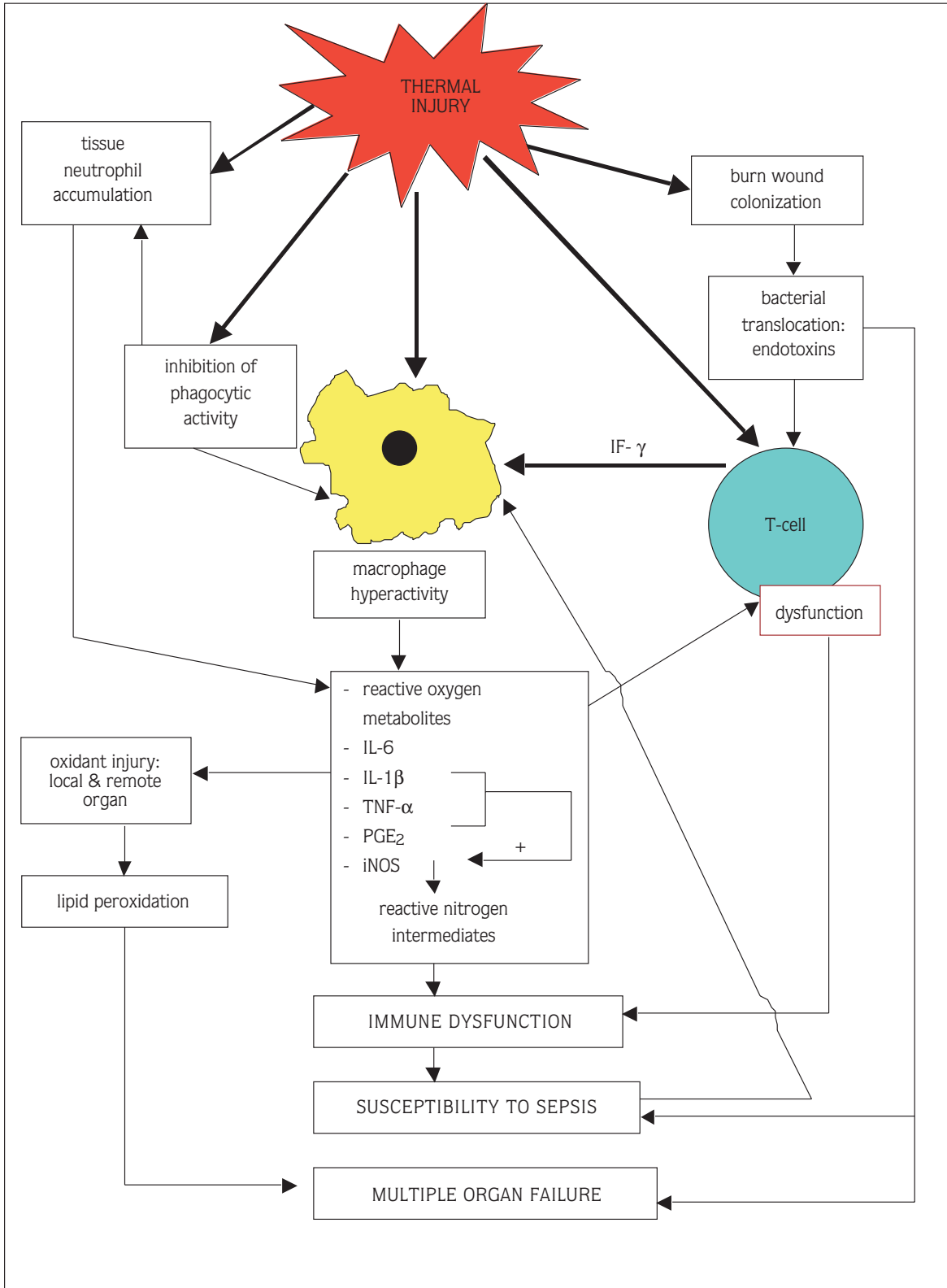


Figure. Immune response to thermal burn injury.

IL: interleukin; PGE₂: prostaglandin E₂; TNF-α: tumor necrosis alpha; iNOS: inducible nitric oxide synthase; IF-γ: interferon gamma.

Table. Systemic responses to burn injury.

| Cardiovascular system | Excretory system | Respiratory system | Gastrointestinal system |
|--|--|--|---|
| Acute (hypovolemia) phase: <ul style="list-style-type: none"> • ↓ blood flow • ↓ cardiac output • ↑ capillary permeability • ↑ peripheral vascular resistance | Acute (hypovolemia) phase: <ul style="list-style-type: none"> • ↓ renal blood flow • ↓ GFR | <ul style="list-style-type: none"> • hypoxemia • pulmonary hypertension • ↑ airway resistance • ↓ pulmonary compliance | <ul style="list-style-type: none"> • adynamic ileus • gastric dilatation • delay in gastric emptying • gastrointestinal hemorrhage • ↑ gastric secretions • ↑ ulcer incidence • ↓ intestinal & colonic motility • ↓ mesenteric blood flow • ↓ nutrient absorption • bacterial translocation • hepatic injury |
| Hypermetabolic phase: <ul style="list-style-type: none"> • ↑ blood flow • edema formation • cardiac arrhythmias • myocardial infarction • myocardial dysfunction/cardiac instability (↑ end-diastolic volume and ↓ right ventricular ejection fraction) | Hypermetabolic phase: <ul style="list-style-type: none"> • ↑ renal blood flow • ↑ GFR • impaired tubular functions • acute renal failure | | |

mechanism may be related to filtration failure or tubular dysfunction (45). Two different forms of acute renal failure have been described in burned patients, differing in terms of their time of onset (45-51). The first occurs during the first few days after the injury and is related to hypovolemia with low cardiac output and systemic vasoconstriction during the resuscitation period or to myoglobinuria, which damages the tubular cells (45,46,50,51). Elevated levels of stress hormones like catecholamines, angiotensin, aldosterone and vasopressin have been reported to be implicated in the pathogenesis of this form of ARF (50). Although this form of ARF has become less frequent than before with aggressive fluid resuscitation, it still is a life-threatening complication in patients with extensive deep burns or with electro-trauma (46,47,51). The other form of ARF develops later and has a more complex pathogenesis. This form has been reported to be related to sepsis and multiorgan failure and is most often fatal. It has been said to occur more often in patients with inhalation injury and is considered the most frequent cause of renal insufficiency in burn patients (49,51). In addition to these mechanisms that support the pathogenesis, we have recently shown that the kidney damage induced by burn injury is dependent upon the formation of oxygen radicals, as evidenced by increased lipid and protein oxidation with a concomitant decrease in renal antioxidant (glutathione) levels (52).

Gastrointestinal Response

Adynamic ileus, gastric dilatation, increased gastric secretion and ulcer incidence, gastrointestinal hemorrhage and local and general distribution of the blood flow with a decrease of mesenteric blood flow are among the effects of thermal injury on the gastrointestinal system (53). A decrease in mesenteric blood flow has been described in a number of burn and smoke inhalation animal models, even in the absence of any evidence of inadequate systemic perfusion (54). The effect of acute burn trauma, produced by hot water scalding in the rat, has demonstrated that there is decreased nutrient absorption (glucose, calcium and amino acids) and DNA synthesis in the small intestine (55). The burn patient has been found to have a high incidence of ulcers. Erosion of the stomach lining and duodenum has been demonstrated in 86% of major burn patients within 72 h of injury, with more than 40% of patients having gastrointestinal bleeding (56). In addition, the process of increased bacterial translocation and macromolecular leak have been well documented after burn injury, being evident in humans as well (57-60). Intestinal ischemia resulting from decreased splanchnic blood flow may activate the neutrophils and tissue-bound enzymes such as xanthine oxidase and these factors destroy the gut mucosal barrier and result in bacterial translocation. These data indicate an early postburn gut barrier leak after the burn, which may be the source of circulating endotoxin (61). Endotoxin, a

lipopolysaccharide derived from the outer membrane of Gram-negative bacteria, translocates across the gastrointestinal tract barrier within 1 h of thermal injury (62). Although the burn wound is initially sterile, plasma endotoxin concentration reaches a peak at 12 h and 4 days postburn (63). Endotoxins are potent activators of the macrophages and neutrophils. This leads to the release of massive amounts of oxidants, arachidonic acid metabolites and proteases, which cause further local and systemic inflammation in burn-induced tissue damage (64).

Chen et al. (65) demonstrated that intestinal and colonic motility in the rat were decreased following burn injury accompanied by a delay in gastric emptying. In a group of studies performed in our laboratory, we observed a marked delay in the intestinal transit of burned animals (66-68). Bombesin, which is known to have a wide spectrum of biological actions in the gastrointestinal tract, was found to ameliorate intestinal inflammation due to burn injury by a neutrophil-dependent mechanism (68). On the other hand, endogenous endothelins were shown to play an important role in the systemic response to burn injury, as observed by a delay in intestinal motility and an infiltration of neutrophils (67).

A 40-50% decrease in effective or nutrient liver blood flow has been described in an ovine burn model, beginning several hours after injury, and persisting even with apparent adequate volume restoration (69). A significant increase in liver malondialdehyde has been reported in the same animal model along with evidence of increased vacuolization of liver parenchymal cells (42,69). In similar studies conducted by our group, burn-induced severe remote organ damage was found in the gastric and hepatic tissues (70,71). Since a significant degree of reduction was observed in the severity of liver and stomach injuries through the inhibition of nitric oxide synthase (NOS) and this reduction was cancelled by adding L-arginine as a precursor of nitric oxide (NO), it is likely that endogenous NO has a significant exacerbatory role in the pathogenesis of burn-induced remote organ injury (71). In another study carried out in our laboratory, the role of cyclooxygenase (COX) inhibition in intestinal motility and in the extent of tissue injury of the small intestine and liver at the early phase of burn injury was investigated. It was concluded that not only COX-2 but also COX-1 inhibition is required for

protection against inflammatory changes in liver and small intestine following burn injury (66). The results of another recent study by our group also showed that a small and local dermal burn results in oxidant injury of the liver, which is still evident on the postburn 5th day (72). This local trauma appears to stimulate the replenishment of hepatic and intestinal Glutathione (GSH) stores, resulting in significant elevations after burn injury, implying that a preconditioning feedback mechanism is involved in triggering GSH synthesis. Thus, the antioxidant capacity of the remote organs to cope with other oxidative challenges appears to be enhanced with the challenge of minor burns.

Immune Response

Severe thermal injury induces an immunosuppressed state that predisposes patients to subsequent sepsis and multiple organ failure, which are the major causes of morbidity and mortality in burn patients (73,74). A growing body of evidence suggests that the activation of a pro-inflammatory cascade after burn injury is responsible for the development of immune dysfunction, susceptibility to sepsis, and multiple organ failure (75). Moreover, thermal injury increases the macrophage activity, thereby increasing the productive capacity for the pro-inflammatory mediators (76). There have been several reports indicating that circulating levels of IL-1 β , IL-6 and TNF- α are increased in patients with burn injury (77).

The immunological response to thermal injury is a depression in both the first and second lines of defense. The epidermis of the skin becomes damaged, allowing microbial invasion; the coagulated skin and exudate of the patient create an ideal environment for microbial growth (78). We have recently demonstrated that even a local burn trauma leads to neutrophil infiltration in the wound site, as well as in the remote organs, the liver and intestines (72). Since much of the local and certainly the majority of the distant changes are caused by inflammatory mediators, these results suggest that a neutrophil-dependent oxidant injury is present both locally and remote to injury during the late phase of a burn wound. Thermal injury also produces a burn-size-related depression of both the cellular and humoral aspects of the immune response (78), and the phagocytic activity of both fixed and blood-borne macrophages and neutrophils is decreased (79,80). Thermal injury initiates systemic inflammatory reactions producing burn toxins

and oxygen radicals and finally leads to peroxidation. Reactive oxygen metabolites lead to destruction and damage to cell membranes by lipid peroxidation. Lipid peroxides have been demonstrated to be increased in burned animal and patient plasma (81). The relationship between the amount of products of oxidative metabolism and natural scavengers of free radicals determines the outcome of local and distant tissue damage and further organ failure in burn injury (24).

Recent evidence suggests that activation of a pro-inflammatory cascade plays an important role in the development of major complications associated with burn trauma (75). With regard to this, macrophages are major producers of pro-inflammatory mediators, i.e. prostaglandin E₂ (PGE₂), reactive nitrogen intermediates, interleukin (IL)-6, and tumor necrosis factor- α (TNF- α) (76,82). Dysregulation of macrophage activity leading to increased release of pro-inflammatory factors appears to be of fundamental importance in the development of post-burn immune dysfunction and additional factors such as T-cell dysfunction, glucocorticoids and T-helper (Th)-2 cytokines are also causative factors in postburn immune dysfunction (83- 86). Previous studies have implicated macrophage hyperactivity (the increased productive capacity for inflammatory mediators) in the increased susceptibility to sepsis following thermal injury (87-89). This concept is explained by Deitch as a "2-hit" phenomenon (90), where the major burn injury is the first hit that "primes" the host to exhibit an abnormal response (i.e. increased pro-inflammatory mediator release) to a second hit (i.e. sepsis) leading to multiple organ failure and death.

The release of pro-inflammatory cytokines (TNF- α , IL-1 and IL-6) is an important mechanism in the regulation of the acute phase responses to injury. TNF- α is a triggering cytokine that induces a cascade of secondary cytokines and humoral factors that then lead to local and systemic sequelae (91). Furthermore, TNF- α is involved in the development of the shock-like state associated with thermal injury and sepsis (92). IL-1 is also a pleiotropic cytokine having a variety of biological activities including the regulation of the inflammatory response by acting as a pyrogen, exerting chemotactic activity and inducing maturation and activation of granulocytes, and T- and B-cells (93,94). Similarly, IL-6 is another pleiotropic cytokine that is of vital importance for B-cell maturation, acute phase protein induction and

regulation of T-cell activation (95). Results of clinical and experimental studies have shown that IL-6 exhibits a significant and consistent elevation after burn injury and sepsis, which correlates with suppressed cell-mediated immunity and increased mortality (96-98). TGF- β is a potent chemoattractant of monocytes, neutrophils and fibroblasts and stimulates many aspects of tissue repair. Additionally, TGF- β acts as an immunosuppressive and suppresses the proliferation and differentiation of B- and T-cells and the expression of cytotoxic T-cells (99-101) and induces splenocyte apoptosis (102-104). TGF- β plasma levels are shown to be elevated 6-8 days postburn.

Experimental and clinical studies have shown elevated systemic nitrate levels after thermal injury (105-108). Inducible NOS (iNOS) activity is an important marker of macrophage hyperactivity postburn. Moreover, other macrophage derived pro-inflammatory factors induced by thermal injury (IL-1, TNF- α , PGE₂) can all positively influence macrophage iNOS activity (76,109-112). Recent studies have also implicated iNOS induction in vascular hyperpermeability and derangement of gut barrier function following thermal injury as well as increased vascular permeability in a combined injury model of burn and smoke inhalation (113-115). In accordance with these observations, we have demonstrated that the inhibition of NO synthesis ameliorates burn-induced gastric and hepatic damage, emphasizing the critical role of NO in burn-induced remote organ injury (71).

Another important immunological aspect of thermal injury is the increased production of eicosanoids, which are metabolites of arachidonic acid (e.g., prostaglandins, leukotrienes, thromboxanes) that have multiple biological effects. In general, prostaglandins, which are elevated in burned patients or in experimental animals, are considered important immunosuppressive mediators (116,117) and macrophages from burned hosts exert an enhanced prostaglandin productive capacity (118-125). Since COX enzyme is responsible for some of the deleterious consequences associated with thermal injury, COX inhibitors are capable of restoring the various aspects of immune function and improve survival after thermal injury (121,126,127).

It has been implied that the elevated production of PGE₂ and NO by macrophages can suppress T-cell activity (128-131) and impaired T-cell function may be the end

point in the development of thermal injury-induced immunosuppression. Several findings suggest a potential dual role for γ/δ T-cells postburn. Although gut barrier function is compromised following thermal injury, increased "early postburn mortality" in mice lacking γ/δ T-cells is suggestive of a role for these cells in maintaining some aspect of gut barrier function following burn injury (125). In a recent study, we investigated whether exogenous leptin, an adipose tissue derived circulating hormone, reduces remote organ injury and burn-induced immunosuppression in rats with thermal burn. In order to assess the impact of leptin administration on burn-induced immune response, the profile of circulating leukocytes and their apoptotic responses in burn injury were evaluated. Moreover, the effect of leptin treatment on tissue neutrophil infiltration, which is known to be a potential source of free oxygen radicals in mediating postburn injury, was also investigated. Our results demonstrate the presence of elevated myeloperoxidase activity in all the studied remote organs, implicating the contribution of neutrophil infiltration. Leptin administration was found to be effective in protecting the liver, kidney and the gut within 24 h of burn injury, while lung injury was not alleviated with by leptin treatment. All the organs that were protected against burn trauma demonstrated a reduction in tissue neutrophil infiltration, suggesting that the protective effect of leptin may involve an inhibitory action on tissue neutrophil accumulation. Furthermore, leptin treatment reduced the burn-induced

death and apoptosis of circulating leukocytes and prevented the apoptosis of both the monocytes and granulocytes (unpublished observations). Since it was previously shown that leptin replacement in mice was protective against susceptibility to endotoxic shock by inhibiting TNF induction (132), our results suggest that leptin ameliorates burn-induced remote tissue injury that appears to be due to its inhibitory effect on the apoptosis of cytokine-producing leukocyte subsets, which may or may not directly involve the inhibition of TNF induction.

Despite recent advances, multiple organ failure (such as cardiac instability, respiratory or renal failure) and compromised immune function, which results in increased susceptibility to subsequent sepsis, remain major causes of burn morbidity and mortality (133). Further experimental and clinical studies will hopefully lead to a more complete understanding of these pathological processes. From that point it should be then possible to develop improved treatments for burn patients.

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