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T Cell Suppression in Burn and Septic Injuries

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1. Introduction

The mechanism responsible for initiating and controlling burn-induced immunosuppression remains unknown. Accumulating experimental and clinical data indicates that burn injury promotes suppressed immune function, predisposing the host to infectious complications (Moss NM, 1988). Skin plays an indispensable first line of defense against microorganisms; the disruption of this primary barrier in burn injury leaves patients greatly susceptible to invasion by pathogens and increases their morbidity and mortality. Severely burn-injured patients exhibit classical signs of suppressed immune function such as loss of delayed-type hypersensitivity responses, prolonged skin allograft survival and reduced T-cell proliferation to polyclonal and antigen-specific stimulation (Ninnemann JL, 1994, Lederer, JA, 1999, Faist E, 1996). The disturbances in T-cell mediated responses include low T-helper 1 (Th-1) type cytokine production and reduced Th-1 type antibody isotype secretion (Kelly, JL, 1999). There is a rising incidence of nosocomial infections accompanied by burn-induced adaptive immunosuppression (Baker, CC, 1979, Angele MK, 2002). This shift of adaptive immune response towards a counter-inflammatory phenotype takes place in the presence of proinflammatory innate immune response (Harris, BH, 1995). An estimated 40, 000 adults are admitted to hospitals in USA with burns each year (Salinas J et al, 2008, White CE, 2008). Severe burn-injury stimulates a massive release of cytokines into the bloodstream leading to shock, immune dysfunction, and multiorgan failure. Serum levels of interleukin (IL)-8, tumor necrosis factor-α, IL-6, and granulocyte-macrophage colony stimulatory factor (GM-CSF) peak within first week postburn. In addition to shock, this rush of cytokines triggers a hypercatabolic state, with muscle wasting and immunosuppression. Eventually, this immunosuppression follows multiorgan dysfunction, sepsis and heralds death.

2. SIRS-CARS (Figures 1-5)

This paradigm is currently accepted by the investigators in the field of burn, shock and trauma. Extensive tissue destruction following burn-injury predisposes patients to consequences of different and dysregulated inflammatory immune responses (Saffle, JR, 1993, Baue, AE, 1998, Still, JM, 1993). Following the initial resuscitation period, patients develop systemic inflammatory response syndrome (SIRS), which leads to multiple organ dysfunction syndrome (MODS) which is associated with high mortality. If the patients do not develop early MODS and survive SIRS they characterize suppressed immunity and resistance to infection, which is termed as compensatory anti-inflammatory response syndrome (CARS). Baue et al, 1998 supports the theory that interactions between the innate

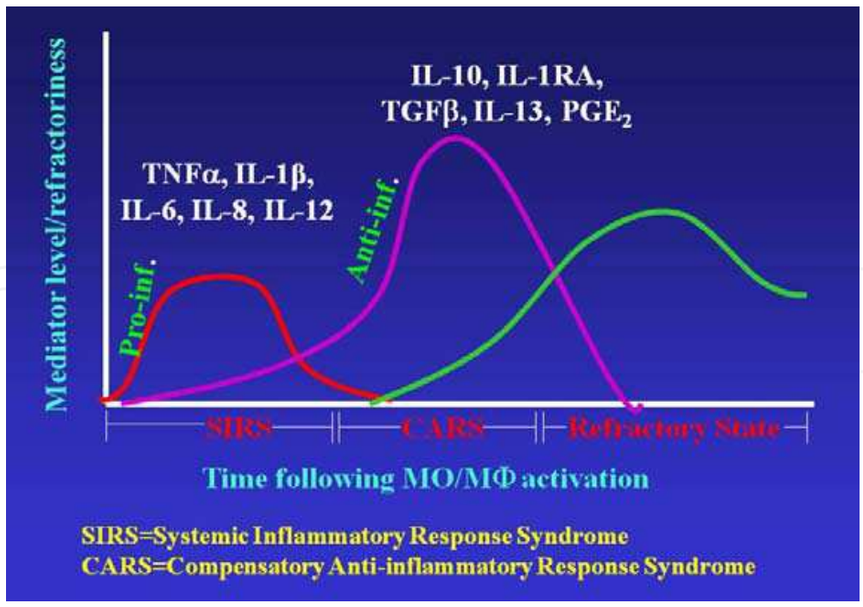

Fig. 1. A schematic drawing of mediators released during different phases of immune response following burn injury. X-axis show levels of mediators released against time (y-axis) following monocyte/macrophages activation. Mediators released during the early pro-inflammatory phase (Systemic inflammatory response syndrome (SIRS) are TNFα, IL-1, IL-6, IL-8 and IL-12 followed by anti-inflammatory phase where IL-10, IL-1RA, TGFβ, IL-13, PGE2 are released. Mixed antagonistic response syndrome (MARS) with both pro-and anti-inflammatory components has not been in literature since year 2000. At the meantime a refractory state is also initiated which continues even after compensatory anti-inflammatory response syndrome (CARS) is over.

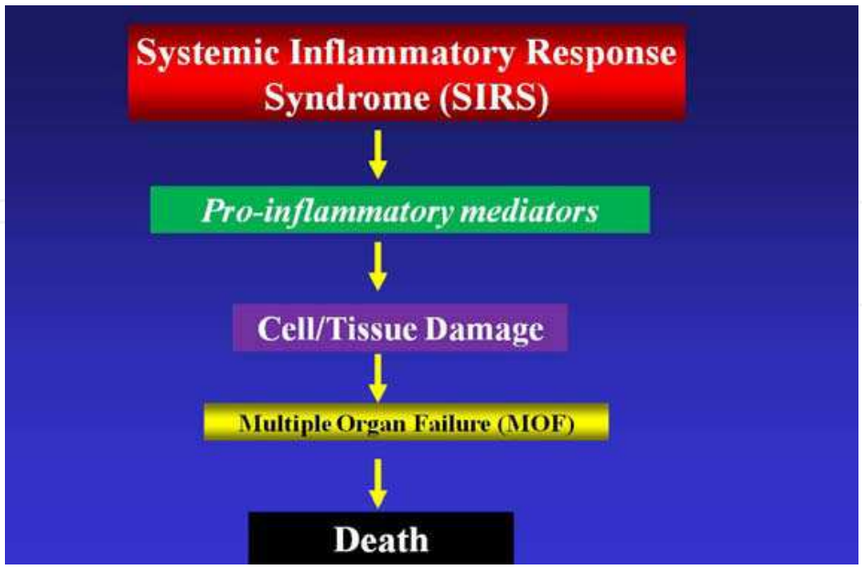

Fig. 2. Systemic inflammatory response syndrome (SIRS) leading to release of pro-inflammatory mediators; leading to cell/tissue damage; leading to multiple organ failure; leading to death.

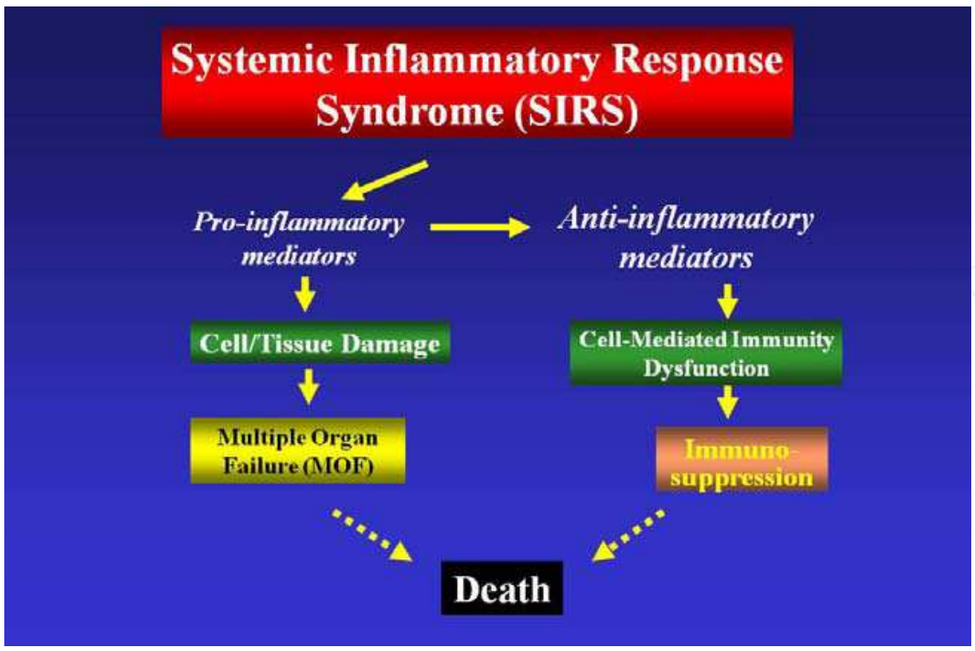

Fig. 3. A schematic drawing of cascade of events (first scenario) where both pro-inflammatory as well as anti-inflammatory immune responses are initiated, eventually leading to mortality. In this scenario anti-inflammatory mediators cause dysfunction of cell-mediated immunity (CMI) leading to death via immunosuppression.

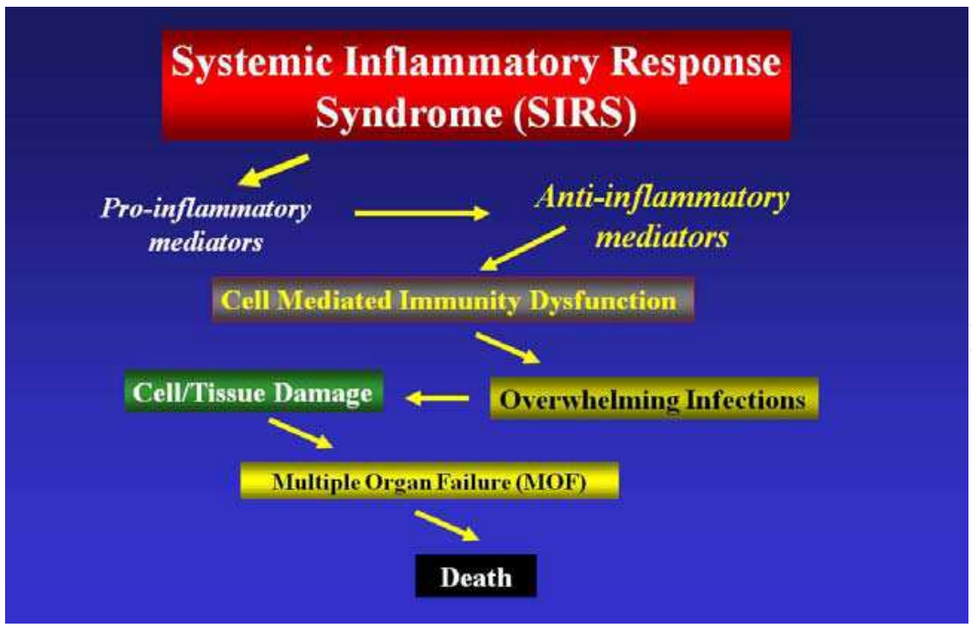

Fig. 4. A schematic drawing of cascade of events (second scenario) when SIRS is complicated by overwhelming infections following dysregulated cell-mediated immunity, leading to mortality. In this case dysfunction of cell-mediated immunity leads a way to overwhelming infections and then classical pathway of cell and tissue damage responsible for multiple organ failure (MOF) paves the way to mortality.

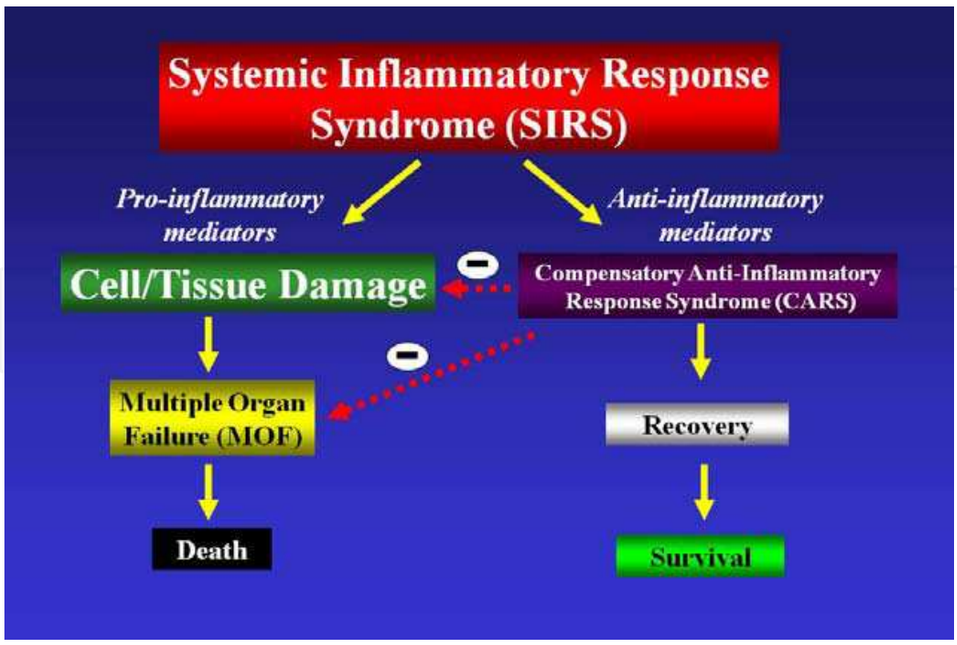

Fig. 5. A schematic outcome of compensatory anti-inflammatory response syndrome (CARS) in a beneficial outcome of recovery leading to survival (third scenario). In this alternative sequence of events anti-inflammatory mediators set the stage up for a compensatory anti-inflammatory response syndrome (CARS) which down regulates cell and tissue damage and halts multiple organ failure thus positively influence the outcome of (SIRS) towards a recovery phase.

and adaptive immune systems are important in the induction of CARS and SIRS. Burn-induced immune dysregulation is a continuously changing process and evolves over time and goes into a refractory state.

3. Locally released inflammatory mediators (Figure 6-7)

Pro-inflammatory cascade of cytokine released immediately after injury is a harbinger of subsequent immune dysfunction, sepsis and multiple organ failure (Meakins, JL, 1990). The cells of innate immune system including macrophages, fibroblasts, natural killer (NK) cells, activated T-cells release pro-inflammatory cytokines i.e., interleukin-1 (IL-1), tumor necrosis factor–α (TNF-α), IL-6, transforming growth factor–β (TGF-β), reactive nitrogen intermediates (RNI), prostaglandin E2 (PGE2) (Ogle, CK, 1994). These cytokines and other mediators are triggered by both non-infectious and infectious stimuli (Figures 6 and 7). The inflammatory SIRS response is known to be caused by stimuli other than sepsis in contrast to CARS that follows invasive infection. Marano MA, 1990 and Gamelli RL, 1995 documented increased systemic levels of these inflammatory mediators following burn injury altering the functional capacity of their parent cells. This elevated production of inflammatory mediators has thus been implicated for post-burn sepsis (Schwacha MG, 1998, Yang L, 1992, O'Riordain, MG, 1992). Locally released inflammatory mediators, i.e, C3a, C5a, PG, LT, O_2^-, NO, TNFα, IL1, IL6, IL8, IL10, TGFβ act on different circulating cells (leukocytes/platelets) and other tissues (endothelium, epithelium and parenchymal cells) and neuro-endocrine axis to enhance different effector responses.

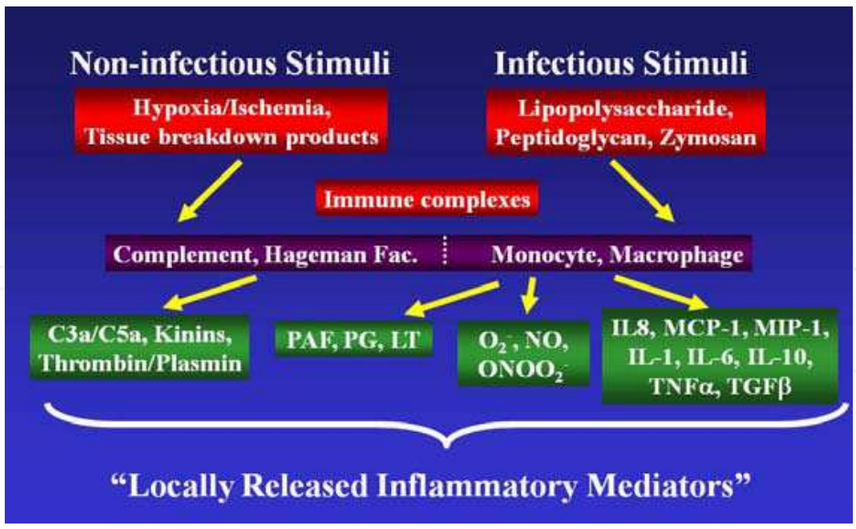

Fig. 6. Locally released inflammatory mediators triggered by both non-infectious vs. infectious stimuli. A list of humoral and cell-derived factors is given which will determine the potential outcome of burn-injury associated tissue damage. In the first sequence of events non-infectious stimuli cause hypoxia/ischemia type of injury and release of tissue breakdown products, mostly initiating a humoral response and a list of modulators causing inflammation. In the event of infectious stimuli LPS, Peptidoglycan activate predominantly a cellular immune response, again triggering release of a list of cytokines and chemokines. These include but do not limit to release of platelet-activating factor (PAF), prostaglandin (PG), lymphotoxin (LT), reactive oxygen species (ROS), reactive nitrogen species (RNI), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1 (MIP-1).

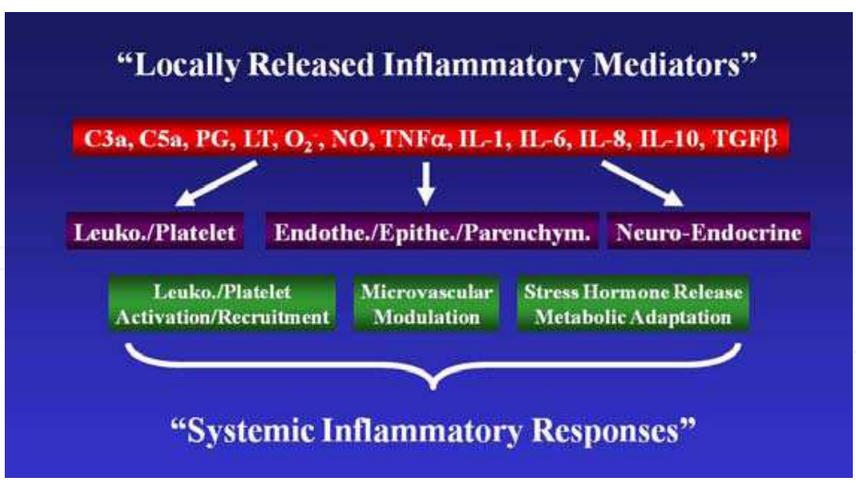

Fig. 7. Locally released inflammatory mediators act on different circulating cells (leukocytes/platelets) and other tissues (endothelium, epithelium and parenchymal cells) and neuro-endocrine axis to enhance different effector responses. Leucocytes and platelets are activated and are recruited to the site of injury. Microvascular changes are brought about by both humoral and cell-mediated factors acting on endothelium, epithelium and parencyhmal cells, and finally, via neuroendocrine axis stress hormones (i.e, cortisol) are released which affect metabolism.

4. Systemically released mediators (Figure 8)

Endogenous mediators related to burn injury include a list, i.e., C-reactive proteins, serum amyloid A, procalcitonin, C3 complement and haptaglobin, etc. These circulating mediators influence endothelial, epithelial and other types of cells. These inflammatory mediators act as double-edged swords (Figure 8).

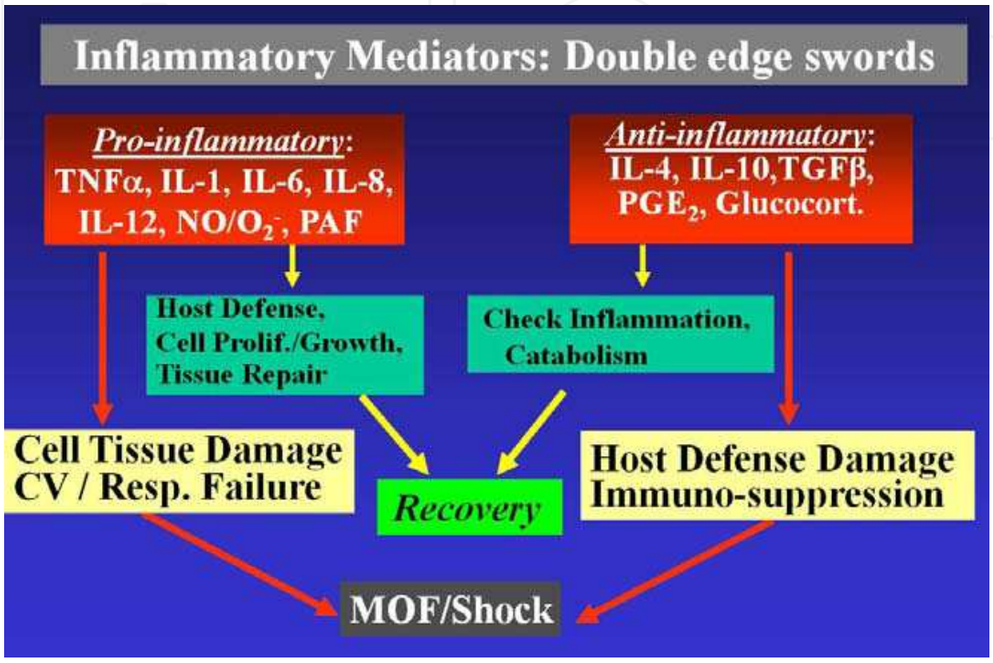

Fig. 8. Inflammatory mediators act like double-edged swords. Cascade of events could either lead to recovery or causing cell tissue damage and/or immunosuppression culminating in multiple organ failure and shock. Pro-inflammatory mediators help in host defense and positively influence cell proliferation/growth and enhance tissue repair-all processes leading to recovery, whereas anti-inflammatory mediators assist in controlling inflammation and limit catabolism thus helping recovery. On the flipside, pro-inflammatory mediators may also culminate in cell/tissue damage, cardiovascular/respiratory failure, and likewise anti-inflammatory mediators decrease host defense via initiating immunosuppression. Thus it acts like a double-edged sword- complementing further multiple organ failure and shock.

5. Pro-inflammatory and anti-inflammatory immune responses (Figures 9-16)

In the midst of burn-injury immune responses pro-inflammatory and anti-inflammatory immune responses elicit different responses. The most notable of pro-inflammatory responses include leukocytosis, enhanced adherence, fever, hypermetablism, activation of HPA axis and acute phase protein response in the liver. Anti-inflammatory immune responses serve to deactivate leukocyte activation, myelosuppression, abrogate hypermetabolism, and suppress tissue repair and most importantly immunosuppression of cell-mediated adaptive immunity. Figures 9-16 explain the dual hit immune response and the details of burn-induced cascade of effector responses leading to infection, sepsis and later complications.

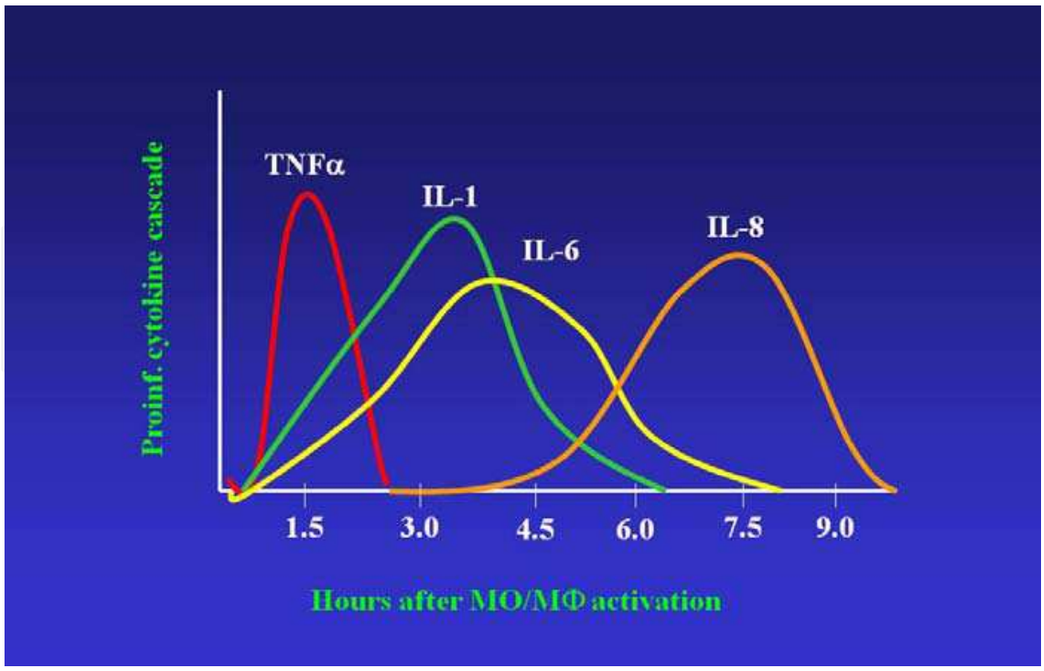

Fig. 9. Timeline of release of pro-inflammatory cytokine cascade in term of hours following their release from activated monocytes and/or macrophages. The first cytokine to appear and peak within hours is TNFα. IL-1 and IL-6 are also initiated but peak when TNFα levels begin to fall down. IL-1 peaks at higher levels than IL-6 and finally IL-8 is among the last to appear in this sequence of cascade of inflammatory cytokines.

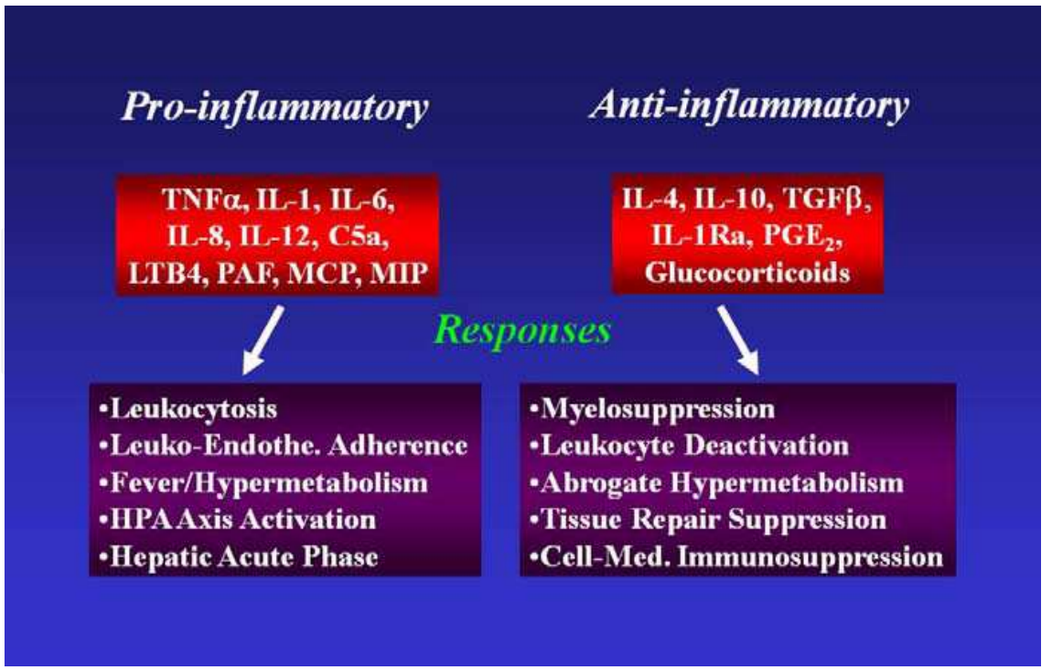

Fig. 10. Pro- and/or anti-inflammatory immune responses are initiated by the respective pro- or anti-inflammatory cytokines leading to two different outcomes as given in this figure.

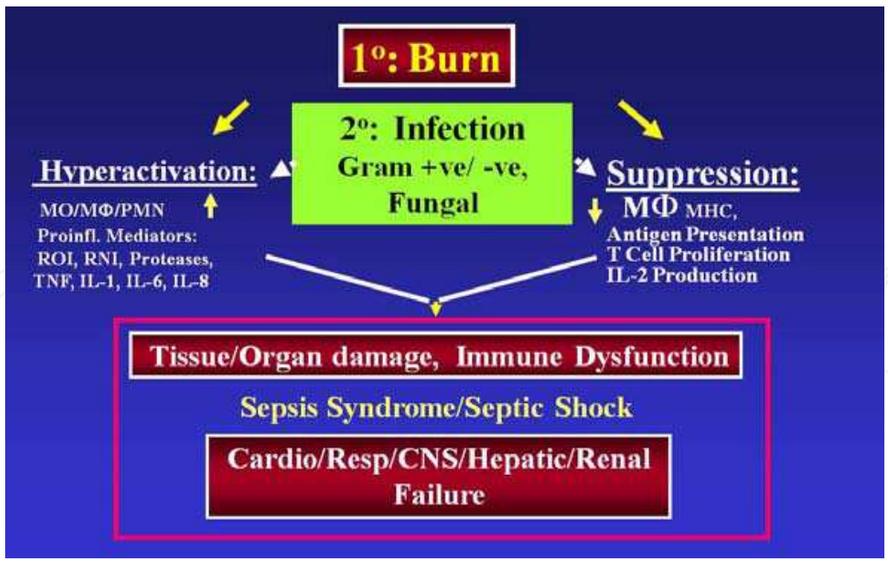

Fig. 11. A two-hit model: Primary hit (burn) when compounded by secondary hit (infection) operates through hyperactivation response (monocytes, macrophages and neutrophil)-mediated or immunosuppression (macrophages, antigen-presenting cells, T cells)-mediated-leading to tissue damage and immune dysfunction. This unregulated immune responses leads to sepsis syndrome/septic shock and multiple organ failure.

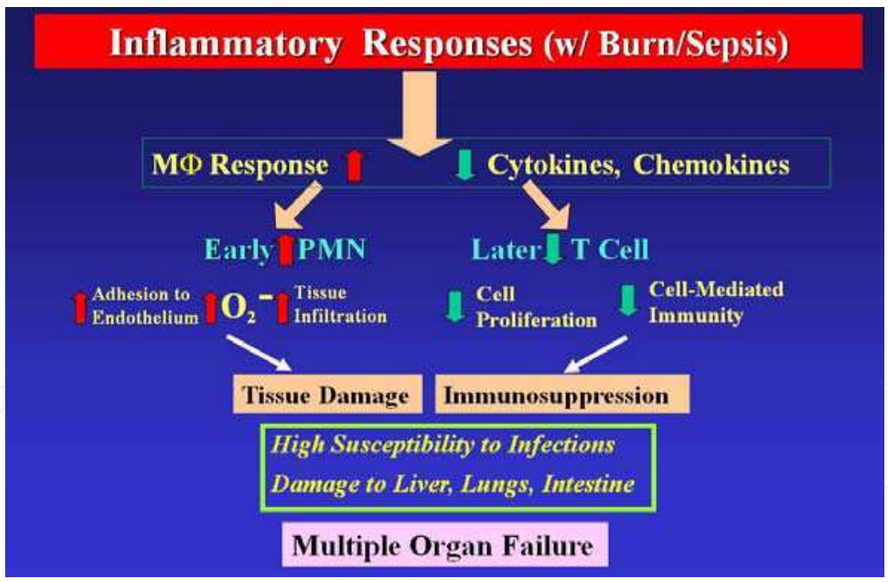

Fig. 12. This figure shows the timeline of burn with sepsis immune response. There is early neutrophil-mediated exaggerated or excessive immune response followed by T-cell mediated immunosuppression. Early PMN-responsible increases adhesion of neutrophils to endothelium, increased tissue infiltration, and increased oxygen radical burst. This heightened PMN response then causes tissue damage to liver, lungs, and intestine, especially compromised intestinal barrier leads to bacterial translocation. A later T cell-mediated response causing immunosuppression (decreased cell proliferation and cell-mediated immunity). These early PMN and late T-cell cause multiple organ failure.

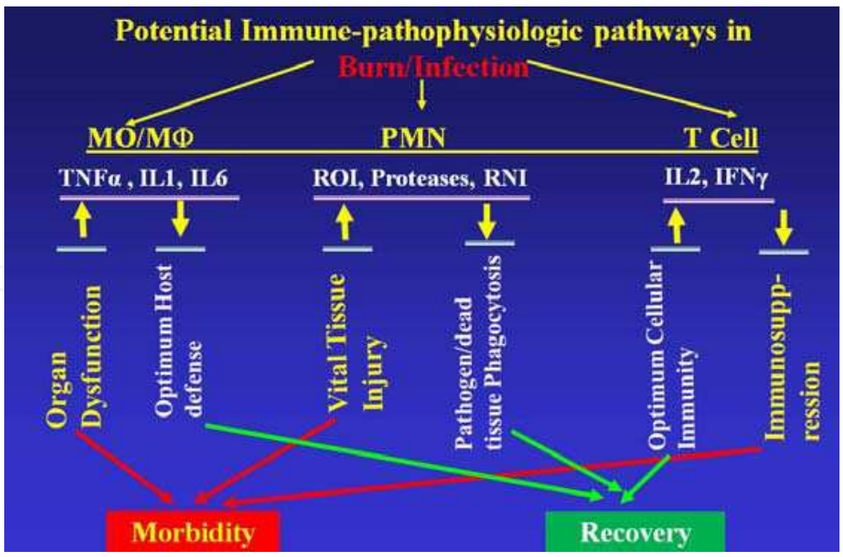

Fig. 13. Sequence of potential immune-pathologic pathways following burn/infection. Organ dysfunction, vital tissue injury and immunosuppression lead to morbidity. Optimal host defense, enhanced phagocytosis/infection control and an optimum cellular immunity leads to recovery. Three probable cells of innate and adaptive immunity are involved in a mixture of positive (recovery) or negative (morbidity) outcome; Firstly, Monocytes and macrophages get activated and release pro-inflammatory cytokines, which have a positive (optimal host defense)-leading to recovery or negative (organ dysfunction)-leading to morbidity. Secondly, PMN release reactive oxygen intermediates (ROI), reactive nitrogen intermediates (RNI), proteases which have a positive (phagocytosis of pathogens)-leading to recovery or a negative (tissue injury to vital organs)-leading to morbidity. Thirdly, T cell-mediated events; positive (optimum cellular immunity)-leading to recovery or negative (immunosuppression)-leading to morbidity.

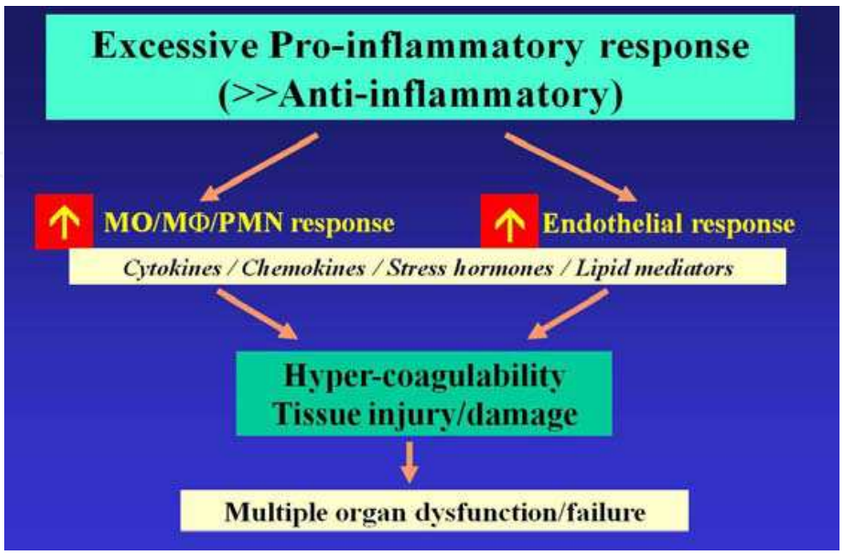

Fig. 14. A possible scenario when pro-inflammatory immune response is stronger than anti-inflammatory immune response.

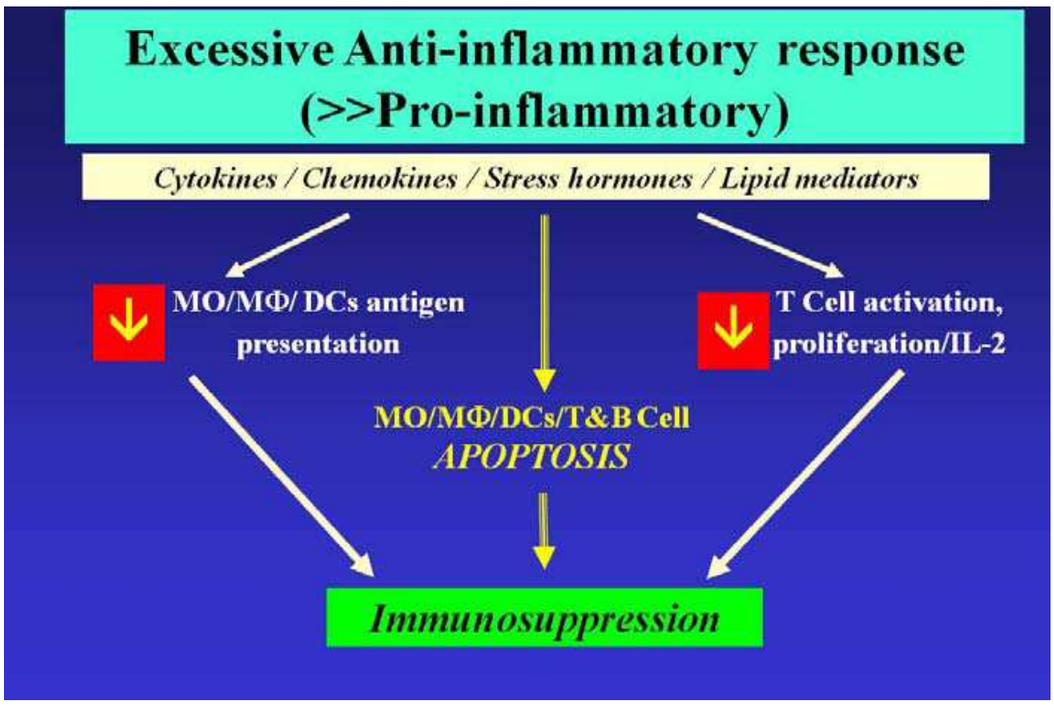

Fig. 15. A possible scenario when anti-inflammatory immune response is stronger than pro-inflammatory immune response.

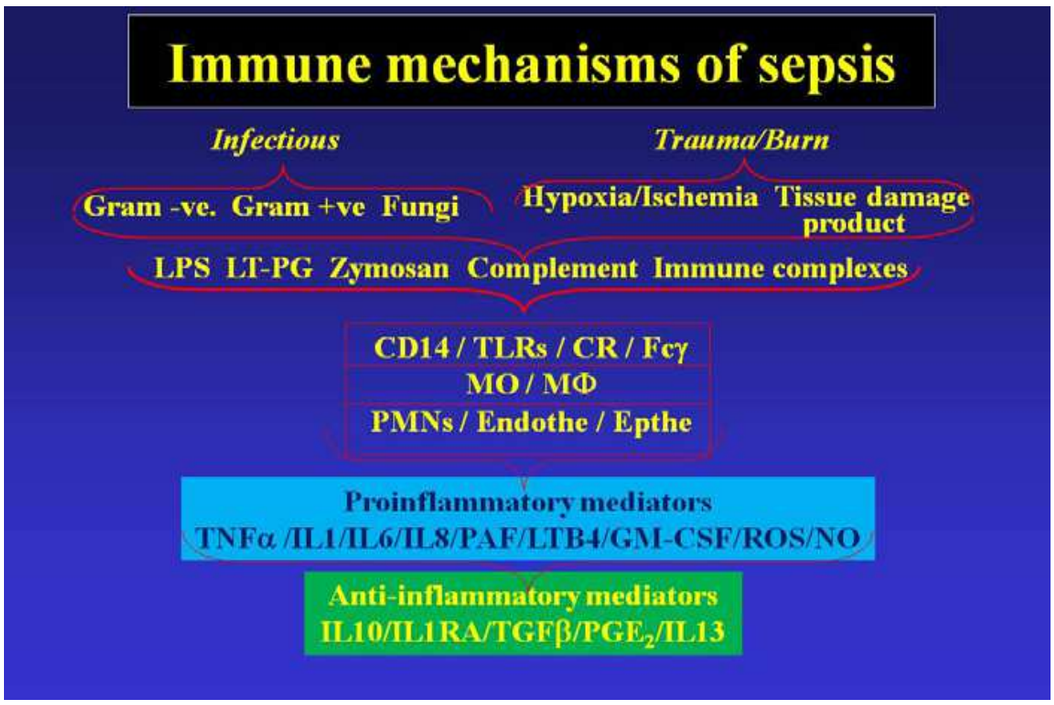

Fig. 16. A flow diagram of immune mechanisms of sepsis involving infectious only, or trauma/burn injury, detailing the list of possible immunomodulators that affect the final outcome leading to immunosuppression.

6. Role of lymphocyte subsets in burn injury and sepsis

The known roles of lymphocyte subsets i.e., natural killer (NK) cells, natural killer T (NKT), gamma-delta (γδ) T cells, and naturally occurring regulatory T cells (Treg) cells in the context of burn and septic injury have recently emerged (Schneider DF, 2007). Jobin et al, 2000 showed that in serum of human burn patient's concentration of sIL-2Ra correlated with intake of fat in diet and inhibition of in vitro NK-cell activity by recombinant sIL-2Ra. Primary mechanisms of NK cell cytotoxicity is known to be via perforin, granzymes, TNF-α, and Fas/FasL. The data obtained from human studies is although inconsistent; and known to be modulated by stress hormones, number of circulating NK cells, presence of IL-4 and IL-10, catalase enzyme, etc. In sepsis, antigen-presenting cells (APCs; macrophages and dendritic cells) recognize antigens or endotoxin and secrete IL-12, which activates NK cells to produce copious amounts of IFN-γ and TNF-α (Medzhitov R, 1998). Burn-induced T cell immunosuppression in a mouse scald burn model along with delayed-type hypersensitivity (DTH) required both CD1d expressing antigen-presenting cells and NK cells (Faunce et al, 2003, Palmer et al, 2006). The role of gamma-delta (γδ) in early burn injury has been elaborated by Schwacha MG 2003, et al, 2000), and has been found to contribute in wound healing, inflammation, and overall survival. However, in other burn studies γδ T cells contributed to neutrophil-mediated tissue damage of lung and small intestine (Toth B et al, 2004, Wu X, 2004). Hence beneficial and harmful effects of γδ T cells are unclear and conflicting, although some researchers have proposed a bimodal response, where they act as proinflammatory in early phases of infection and regulatory in the later phases. CD4+CD25+ regulatory T cells (Treg), overall anti-inflammatory cells are known to comprise 5-12% of CD4+ T cells both in lymphoid and circulatory compartments. In burn model Treg were found to decrease inflammatory cytokine release a week after burn and infectious challenge (Murphy et al, 2005). In a similar burn model Treg were found to inhibit TGF-β and CD4+ proliferation in a cell-to-cell contact (Ni Choileain N, et al, 2006). In contrast a study of polymicrobial cecal-ligation-puncture (CLP) peritonitis model Tregs were found to have protective effects (Heuer JG et al, 2005). The mechanisms by which these small lymphocyte subsets regulate or control remains subject of future studies but final effector responses are modulated through cascade of cytokines, like IFN-γ, IL-4, IL-6, IL-10 and TGF-β.

7. Role of antigen presenting cells and T cells

To date, their involvement as critical regulatory molecules responsible for T cell suppression in burn and septic injuries continues to be a subject of extensive studies as evident from reports from several laboratories (Schneider DF, 2007). Recent studies have provided evidence that alterations in costimulatory signaling between APCs (antigen presenting cells) and CD4+ T cells play key roles in disturbing T cell activation and effector responses. For example, altered expression and functions of costimulatory molecules on APCs, CD80/86, CD40, ICOSL, and/or alterations in their interactions with the complementary molecules on T cells, CD28, CTLA-4, CD40L, ICOS can adversely affect T cell activation and responses (Alegre ML, 2001, Okazaki T., 2002, Grohmann U, 2002). Such derangements in APC and T cell interactions may also contribute to burn/sepsis-related down-regulation of CD4+ T cells. Of APCs, dendritic cells (DC) are recognized to be unique not only in effectively activating naïve T cells but also in adversely affecting their functioning. Recent studies have

emphasized the role of induction of indoleamine 2, 3-dioxygenase (IDO) in DCs inhibiting growth and survival of T cells interacting with such DCs (Grohmann U, 2002, Uyttenhove, C, 2003, Mellor, AL, 2003). A derangement in DCs' CD40 interaction with T cell CD40L has also been implicated in T cell functional inhibition (Bingaman, AW, 2001, Straw, AD, 2003). The end effect(s) of alerted co-stimulatory signaling between APCs and CD4+ T cells could be derangements in cell signaling pathways leading to anergy, apoptosis and/or a regulatory T cell (T_{reg}) mediated suppression of CD4+ T cells (Tang, Q, 2003). Our previous studies have assessed individual effects of burn and sepsis as well as of superimposition of sepsis on burn in rats on CD4+ T cell dysfunction and intestinal dysfunction, and animal mortality (Fazal et al, 2000-2010). While burn or sepsis produced low mortality, the combined injury resulted in exacerbation of mortality. The focus in these studies on burn and/or sepsis affords us an opportunity to assess potential sub-lethal versus lethal implications of combined T cell and APC dysfunction. A lack of functional adaptive and innate immunity would lead to high mortality. These studies indicated also that while burn or sepsis suppressed IL-2 production/proliferation without a substantial increase in apoptosis in MLN CD4+T cells, burn-plus-sepsis caused not only suppressed IL-2 production/proliferation but also a substantial increase in apoptosis in CD4+T cells. Our findings also support potential disturbances in interactions between T cells' and APCs' co-stimulatory receptors/ligands contributing to CD4+T cell deficits in burn and/or sepsis injured animals. We hypothesized that CD4+T cell functional inhibition/apoptosis with burn and/sepsis injuries resulted from altered co-stimulatory signaling between the T cell and APC. Recent studies, while indicating immature DC to adversely affect naive T cells have also shown inappropriately activated T cells to adversely affect APCs including DCs and macrophages. Both the DC effects on T cells and the T cell effects on APCs are best understood to be exerted through altered co-stimulatory signaling between T cells and DCs/APCs. These recent findings would seem to support the concept that burn and/or sepsis-related T cell dysfunction may also emanate from DCs defectively activating naïve T cells, and that functionally incompetent T cells in turn adversely affect tissue DCs and macrophages. Such interdependent disturbances in T cell and DC/APC functions can contribute to not only impaired cell mediated immunity but also concurrent increased risk of bacterial infections, and thereby further increase risks for morbidity and mortality in burn and/or sepsis injured hosts.

8. Immune deficits after thermal injury and septic complications

A number of laboratory and clinical studies have shown that extensive thermal injury induces a state of immune-insufficiency, and that the immune-refractoriness predisposes the injured host to critical morbidity and mortality (Toliver-Kinsky, TE, 2002, Kobayashi, M. 2002). The principal outcome of such immune-insufficiency is an increased susceptibility of injured host to opportunistic pathogens causing high risk of death. Both clinical and laboratory studies have shown that immune-insufficiency with burns is characterized by monocyte/macrophage hypoactivity and/or depressed adaptive cell-mediated immunity associated with T lymphocyte functional deficits (Ravindranath, T, 2001). Despite rather extensive studies of T cell functional deficits in animal models of burn injury and in patients (Barret, JP, 2003); the mechanisms of such deficits and a potential role of these deficits in the lethal outcome following burns particularly with the septic complications have remained unknown.

9. Gastrointestinal mucosal immune defense in burn/septic injuries (Figures 17-18)

The intestinal mucosal compartment is presumably the most active regional lymphocyte defense system in the body. It serves as an important first line of defense against pathogenic/non-pathogenic antigens such as those found in ingested food and those derived from the commensal gut bacteria. An early pathophysiologic event following burn as well as sepsis injury, of certain critical magnitude, is a disturbance in intestinal microvascular dynamics which adversely affects the mucosal barrier integrity. Such a loss of barrier integrity has a high probability of grossly increasing the antigen load particularly that derived from the commensal bacteria and potentially aggravating the mucosal lymphocyte defense. There is also the likelihood that the resulting inadequacy of the lymphocytes could exacerbate pathogenic injury to host tissues and organs exacerbating host morbidity and mortality. Thus, by virtue of their location, intestine associated lymphocytes constitute a vulnerable immune defense system, which could be investigated to elucidate the mechanism(s) of immune dysfunction contributing to host morbidity and mortality after burn-plus-sepsis. T lymphocytes are found in the GI tract in the mucosal epithelial layer (intraepithelial T cells), Peyer's patches, and lamina propria. While the intraepithelial T cells are primarily CD8+ cells, the majority of T cells in the lamina propria are CD4+ cells. Peyer's patches contain predominantly B cells and a relatively small population of CD4+ T cells; their lymphoid follicles resemble those in spleens and other lymph nodes. The CD4+T cells in lamina propria are the activated ($CD45RC^{low}$) cells, and have been shown to be derived from the mesenteric lymph nodes (MLN) (Ramirez, F, 2000,

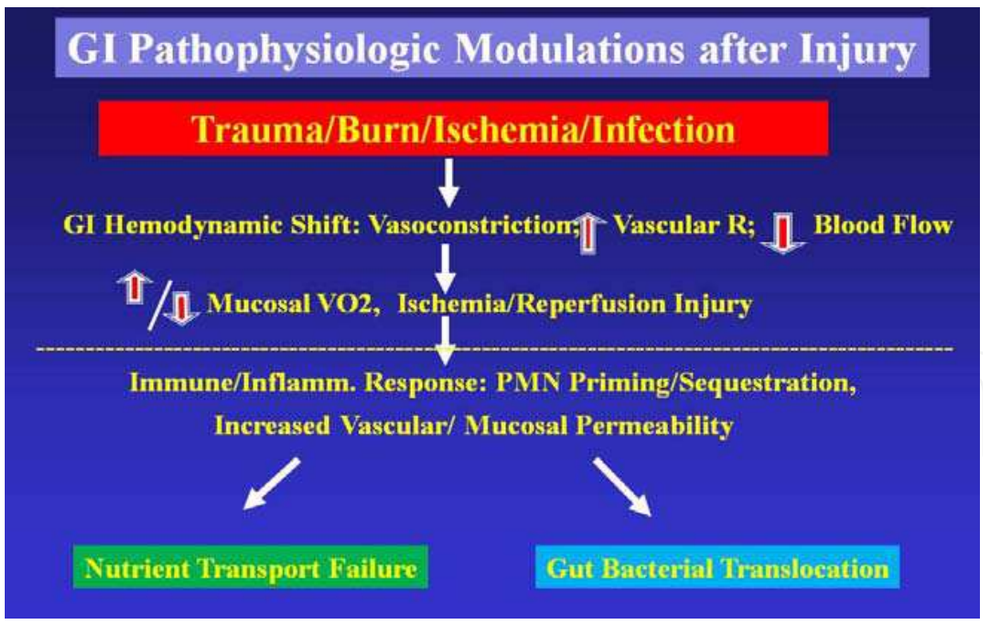

Fig. 17. Pathophysiological gastrointestinal modulations following injury caused by Trauma/Burn/Ischemia/Infection. There are changes in splanchnic blood vessels and mucosal beds mimicking ischemia/reperfusion injury. This leads to chemotaxis of activated neutrophils, increased vascular and mucosal permeability. These vascular and mucosal barrier interruptions cause nutrient transport failure and translocation of bacteria across the gut barrier.

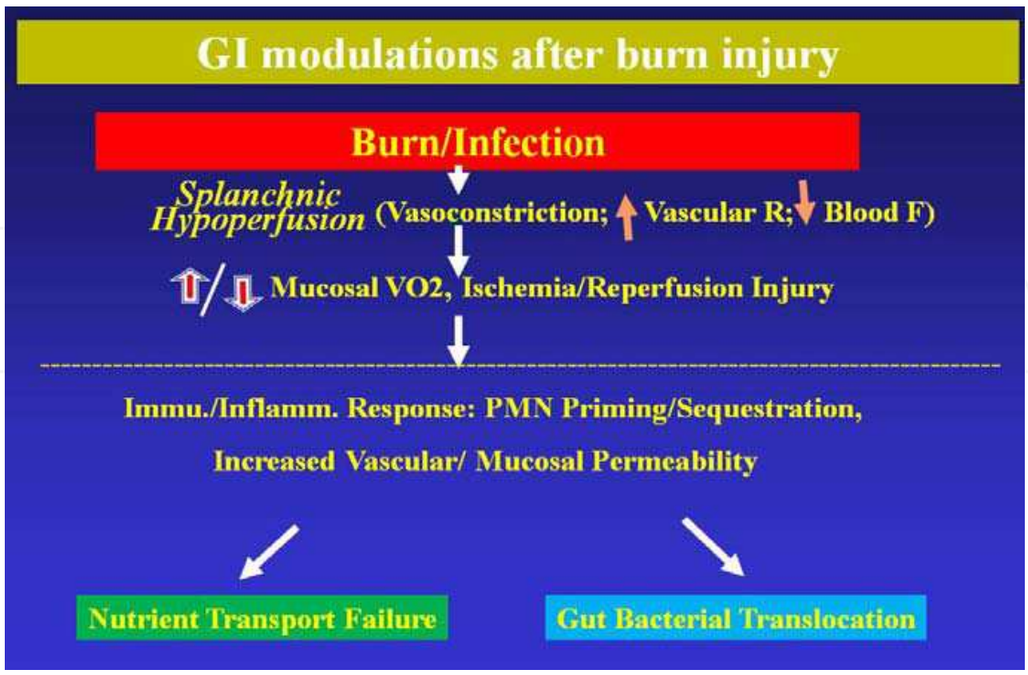

Fig. 18. Gastrointestinal modulations following exclusive burn injury and/or burn/infection. There are changes in splanchnic blood vessels and mucosal beds mimicking ischemia/reperfusion injury. This leads to chemotaxis of activated neutrophils, increased vascular and mucosal permeability. These vascular and mucosal barrier interruptions cause nutrient transport failure and translocation of bacteria across the gut barrier.

Bode U, 2002). The CD4+T cells probably recognized and activated by the antigens presenting cells (APCs) in the MLN (Homann, D, 1999). T cells activated in MLN circulate to intestine as well as other lymphoid tissues including spleen. Previous studies in rats have also shown that activated CD4+T cells originating from MLN recirculate to the intestinal lymphoid tissues and MLN, where they proliferate; their proliferation on restimulation is highest in MLN. The proliferation of CD4+ cells in the MLN was also higher than that of CD8+ cells. Whereas MLN contained both naïve T cells (CD45RC ^{high}) and activated/memory cells (CD45RC ^{low}), lamina propria and PP have been shown to contain mostly activated T cells. Recent studies in rodents including rat have emphasized the importance of dendritic cells (DCs) as exclusive antigen presenters and activators of naïve T cells in the draining lymph nodes (Turnbull, E, 2001). Moreover, in the intestine of rat, DCs play a prominent role in presenting self tissue antigen, such as derived from apoptotic intestinal epithelial cells, to presumably induce tolerance in the lymph node T cells. In rats, such tolerogenic DCs appear to be CD4-, while immunogenic DCs are CD4+ cells.

10. Roles of proliferation and apoptosis in T cell homeostasis/dyshomeostasis (Figures 19-20)

While proliferation and subsequent differentiation of T cells is essential for antigen-specific defense against pathogens, T cell apoptosis is an essential cell death process for the maintenance of T cell homeostasis. Apoptosis is required also for the deletion of overactivated/autoreactive cells and thereby provides for a control of an excessive immune

response (Banz, A. 2002). IL-2 is recognized as a T cell growth factor, but it serves other functions as well (Wells, AD, 1999). T cells, following their interaction with antigen presenting cells, produce IL-2, and express high affinity (~10^{-11} M) IL-2 receptor (IL-2R$\alpha\beta\gamma$). IL-2 acts on the T cells in an autocrine and/or paracrine manner to trigger intracellular signaling through JAK/STAT and PI-3K/Ras pathways, and thereby increase cell concentrations of cell cycle proteins, cyclin D/E, which in turn associate and activate cyclin-dependent kinases (Laliberte, J, 1998, Sakaida, H, 1998). These kinases are known to phosphorylate proteins responsible for the progression of the cell cycle from G1 to the S phase. Thus, IL-2 promotes T cell proliferation. IL-2 also increases production of IFN-γ (responsible for stimulation of macrophages) and IL-4 (responsible for developing Th2 CD4+Tcells, promoting production of antibodies by B cells, and blocking stimulation of macrophages) (Jain, J, 1995). IL-2 also modulates T cell apoptosis. T cells (CD4+ and CD8+) undergo apoptosis via a "passive" and an "active" mechanism. Active apoptosis of T cells occurs after antigen activated T cells, which are producing IL-2 and through IL-2 stimulus are proliferating, are restimulated through TCR. Active T cell apoptosis (antigen/activation-induced cell death, AICD) caused by restimulation restrains T cell expansion due to persistent stimulation of T cells (Zheng, L, 1995). Although recent studies support the concept that IL-2 is a key regulator of AICD, they have not elucidated mechanism in AICD (Boldin, MP, 1995, 1996). Unlike the initial T cell activation which is dependent on TCR and costimulatory CD28 receptor activation, AICD is promoted by TCR signal without the activation of CD28 (Lenardo, M, 1999). The initial event in AICD is expression on the activated T cell surface of FasL/TNF and interactions (in an autocrine or paracrine manner) with constitutively expressed Fas receptor (CD95) (and/or TNF-receptor gene superfamily members, e.g. TNFR-1 and TNFR-2). Such interactions lead to aggregation of cytoplasmic "death domain" of Fas; the components of this complex are: 1) adapter protein, FADD/mort-1, and 2) pro-Caspase8 (Zhang, J, 1998). A subsequent step in AICD release of active Caspase 8 may initiate lethal proteolytic events and activation of caspases including Caspase 3. Caspase 3 has been considered as a primary initiator of DNA fragmentation (Lenardo, M, 1999). Unlike the Fas-FasL mediated apoptosis, TNFR-1 interaction with TNF can signal either apoptosis or cell survival. The antiapoptotic process involves activation of NFκB, which transcriptionally upregulates anti-apoptotic proteins. Recent studies have indicated also that while Fas preferentially controls the death of CD4+ cells, TNFR-1 plays a major role in CD8+T cell death. Passive T cell apoptosis presumably occurs after cessation of antigen interaction with T cells and of IL-2 production. Passive apoptosis involves activation of the mitochondrial apoptotic pathway initiated by a shift in mitochondrial inner membrane permeability causing dissipation of mitochondrial membrane potential, $\delta\psi_{mw}$, and release of cytochrome c from mitochondria. Cytochrome c complexes with the protein, Apaf-1, and the complex serve to activate Caspase 9, which eventually causes activation of Caspase 3 and apoptosis (Clement, MV, 1994, Adachi, S. 1997). Under physiological conditions, AICD would be initiated with antigen restimulation of T cells, and passive apoptosis involving mitochondrial pathway occurs after cessation of IL-2 production. In cases of inadequate activation of AICD, a mechanism seems to exist that allows for an amplification of AICD via activation of the mitochondrial pathway even in the presence of optimum level of IL-2. It is conceivable that in burn/sepsis injury conditions, with suppressed level of IL-2 production by inadequately activated T cells, apoptosis might be occurring via both AICD and mitochondrial pathways (Luo, X, 1998). Previous studies have supported the concept of AICD potentiation via

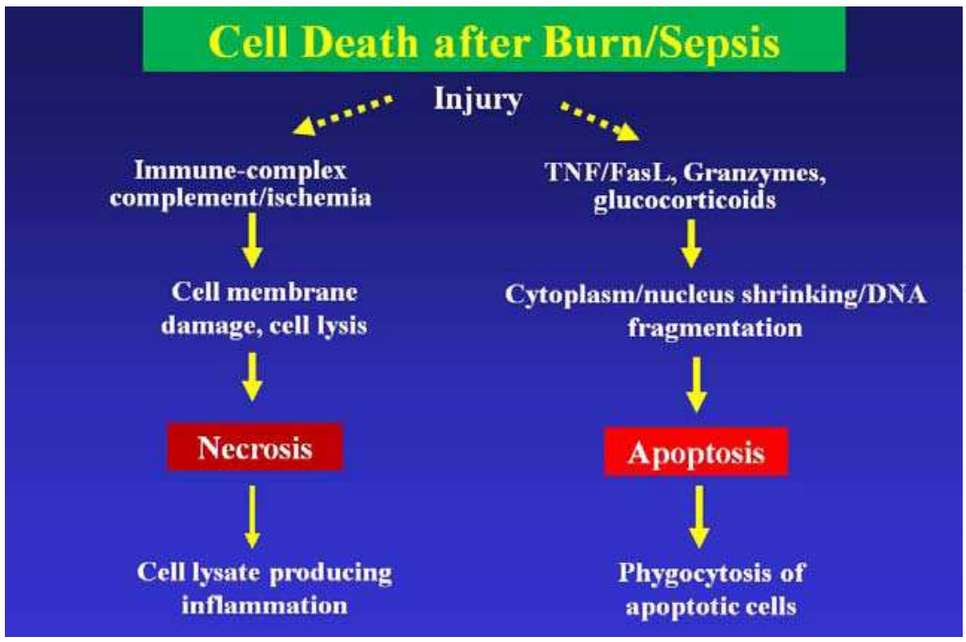

Fig. 19. The mode of cell death following burn- and sepsis-injury. One cascade of events leads to necrosis-mediated inflammation, while another line of events leads to apoptosis. In burn and sepsis injury when humoral factors complicated by immune-complex deposition and ischemia lead to damaged cell membrane and lysis lead to necrosis and inflammation is caused by cell lysate. On the other side TNF/FasL, granzymes and glucocorticoids leading to apoptotic changes in the cytoplasm and DNA fragmentation.

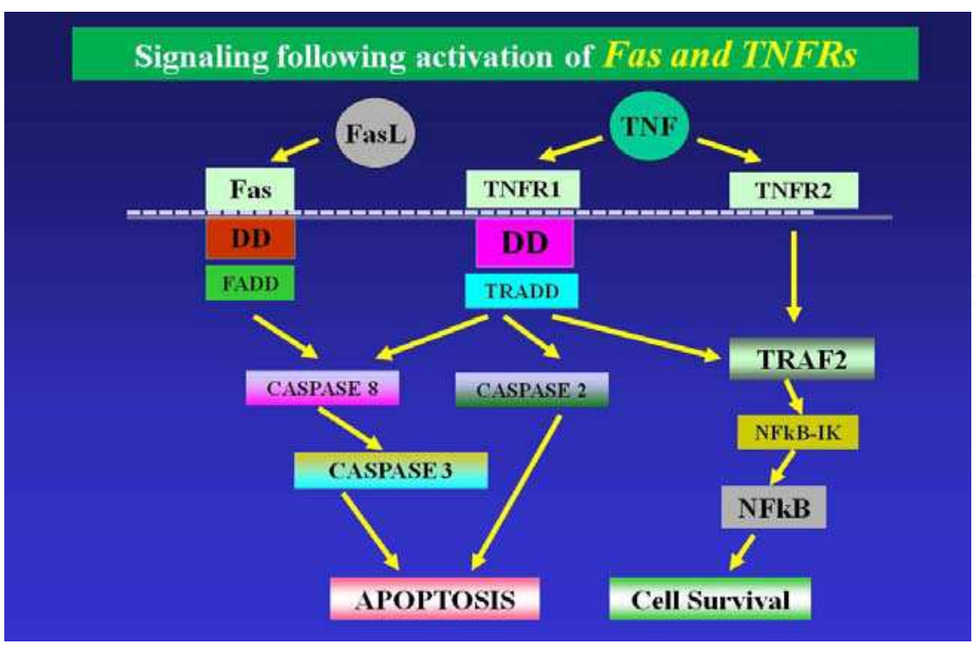

Fig. 20. A schema of signaling pathways following burn injury-mediated FasL and TNF-receptors mediated cell death. Fas and TNF-R1-meditated signaling events lead to apoptosis, while TNF-R2 leads to cell survival.

mitochondrial path subsequent to an over expression of pro-Caspase 3. Other mechanisms of augmentation of apoptosis in T cells with burn/sepsis injury may include that mediated by glucocorticoids and/or reactive oxygen species (ROS), both of which are known to be generated/released in the burn/sepsis conditions (Fukuzuka, K, 2000, Chao, DT, 1995). The glucocorticoids and ROS initiated apoptosis in T cells relies on the mitochondrial pathway (Rathmell, JC, 1999). Although apoptosis via various above-discussed mechanisms is accompanied by activation of the caspase cascade, there is recent evidence that T cells undergo apoptosis independently of the activation of caspases, in vitro. Such caspase-independent cell death primarily involves the activation of the mitochondrial pathway without the involvement of death domain receptors. It is marked, like the caspase-dependent apoptosis, by the loss of $\delta\psi_{mw}$ as well as PS (phosphatidyl serine) translocation from inner plasma membrane leaflet to the outer leaflet but, unlike the caspase-dependent apoptosis, not marked by DNA fragmentation (Rathmell, JC, 1999). Cell death regulatory proteins of Bcl-2 family play a major role in modulating T cell passive apoptosis. Whereas Bcl-2 itself and its homologues, Bcl-xL, Mcl-1 and A1 block apoptosis, others in the family such as Bax, Bak, Bad and Bid are known to promote T cell apoptosis. Bcl-2/Bcl-xL inhibit(s) release of cytochrome c from mitochondria, prevent (s) cytochrome c binding to Apaf-1 and pro-caspase 9, and thereby blocking mitochondrial pathway of apoptosis (Rathmell, JC, 1999). A possible mechanism by which Bad promotes apoptosis after IL-2 withdrawal could be its dephosphorylation and release from its chaperone, in the cytoplasm, followed by its binding to Bcl-2 and thus preventing Bcl-2 from blocking apoptosis (Rathmell, JC, 1999). Bcl-2's antiapoptotic action could also abrogate if Bax or Bak are highly expressed. Activation of Caspase 8 following Fas/FasL interaction can lead to cleavage of cytosolic Bid, and the cleaved product has been implicated in the mitochondrial amplification of apoptosis (Rathmell, JC, 1999).

11. Roles of interactions between APCs and T cells through co-stimulatory ligands and receptors

A variety of receptor-ligand interactions take place between APCs (namely, macrophages, dendritic cells, B cells) and the T cells after antigen presented by APC is recognized by TCR. While some such interactions are 'adhesive' and provide for firm cell-cell positioning, others transduce cell-cell signals that modulate functional responses by T cells and APCs. APC ligands, CD80/86 (B7-1/B7-2), interacting with the CD28 receptor on T cells and causing augmentation of TCR-CD3-initiated T cell proliferation and cytokine production, is a classic example of a co-stimulatory signal transmission from APC to T cells (Wekerle, T, 2001, Zhang, J, 1998). The importance of CD28 co-stimulation is underscored by the observation that in its complete absence, the TCR-mediated cell activation, in vitro, results in T cell anergy typified by inadequate IL-2 production and proliferation, and accompanied by apoptosis. CD28 signaling appears to be involved in both T cell priming and in generation of effector functions in primed T cells; it is, however, critical in T cell priming. Its role in T cell differentiation into effector cells is less clear. While CD28 may promote both Th1 and Th2 responses, it may generate a more exuberant Th2 responses (IL-4 production) than Th1 type (IFN-γ production) (Tang Q, 2003). Recent studies have identified a CD28-related molecule, ICOS (inducible co-stimulator) as a TCR inducible T cell receptor that binds to APC ligand, ICOSL (inducible co-stimulator ligand), a B7 related molecule (B7h) (Lohning, M, 2003,

Okazaki, T, 2002, Villegas, EN, 2002). Like CD28/B7-1&2 interactions, ICOS/ICOSL upregulate T cell proliferation and cytokine production. Unlike CD28, ICOS signaling may be more important in effector cell (Th2 responses) than in CD4+ T cell priming. Unlike CD28 and ICOS, the T cell receptor, CTLA-4 (cytotoxic T lymphocyte associated protein-4), or the recent identified PD-1 (program death-1), both also homologues of CD28, seemingly transmit to T cells inhibitory signals that suppress proliferation and cytokine production in activated cells (Coyle, AJ, 2001). CTLA-4 also interacts with APC's CD80/86 molecules. It, however, binds to these ligands with greater affinity (~20X greater) than CD28 (Egen, JG, 2002), which accounts for the abrogation of the co-stimulatory effects of CD28 in the face of expression of CTLA-4 on activated T cells. CTLA-4 not only interferes with IL-2 production but also causes arrest of T cell cycle in the G1 phase (Alegre ML, 2001). Unlike CD28, which is constitutively expressed and stable, CTLA-4 is induced in activated cells, is relatively unstable, and has a much shorter half life (Egen JG, 2002). The CD40 ligand (CD40L), a member of TNF family, is expressed on activated T cells; its counterpart CD40, a member of TNF-receptor family, is expressed on APCs (Wesa A, 2002). Interactions between T cells' CD40L and B cells' CD40 are important in humoral immunity (Grammer, AC, 2002). In addition, CD40 and CD40L interactions between T cells and other APCs (macrophages, DCs) lead to APCs' upregulation of CD80/86 molecules, and production of IL-12 which is a potent cytokine for generation of Th1 type of T cell responses (Coyle AJ, 2001). T cells' response subsequent to CD40L ligation by anti-CD40 was an early/short-term priming of TCR followed by cytokine production and proliferation, and a later induction of T cell unresponsiveness with upregulation of cytokines, TGFβ and IL-10, and cell cycle disruption (Blair PJ, 2000). The inhibitory effects of CD40L ligation in activated T cells are not clearly understood. Several previous studies produced blockade of CD80/86 ligands by treatment of experimental animals with a soluble CTLA-4-Ig fusion protein, or of blockade in experimental animals of CD40L that prevents CD40 mediated induction of CD80/86 ligands, have shown a resulting a resulting hyporesponsiveness of T cells allowing for acceptance of allotransplanted solid organs by these animals (Honey KS, 1999). Recent investigations have indicated that T cell unresponsiveness produced by CTLA-4-Ig treatment of animals, receiving solid organ transplantation, may not necessarily be due to CD80/86 blockade affecting CD28 co-stimulation but that it could be due to CTLA-4-Ig acting as a CTLA-4 mimic that binds and activates CD80/86 molecules on dendritic cells (Grohmann U, 2002). Such activation apparently leads to activation of dendritic cell intracellular enzyme, indoleamine 2, 3-dioxygenase (IDO), which causes breakdown of tryptophan, and accumulation of the breakdown product kynurenine. Since tryptophan is required in the microenvironment of the T cells for their proliferation and their possible survival, and kynurenine could inhibit T cell proliferation, and promote their apoptosis (Grohmann U, 2002, Uyttenhove, C, 2003, Mellor, AL, 2003), the CTLA-4-Ig mediated induction of IDO could effectively disturb T cell expansion. This action of CTLA-4-Ig on the dendritic cells appears to be mediated by induction of IFNγ, and IFNγ-mediated transcriptional upregulation of IDO. IFNγ presumably acted on DCs in an autocrine/paracrine manner, and activated STAT-1/NF-κB/p38MAPK signaling pathway. As can be surmised from above discussion, studies now support the concept that APC/T cell receptor-ligand molecules allow for a bi-directional transmission of signals between APCs and T cells; CD80/86/CTLA-4 and CD40L/CD40 appear to be operating in this manner. Potential disturbances in CD80/86/CTLA-4 and CD40L/CD40 interactions may play role(s) in the T cell hyporesponsiveness in burn/sepsis injury conditions.

12. Signaling through receptor systems in T cells

T cell activation is initiated by triggering TCR with its natural ligand, antigen-MHC complex. The proximal signaling events that follow are activations of Src kinases, Lck, Fyn, and Lyn, associated with the membrane lipid rafts. Activated Src kinases then phosphorylate tyrosine residues in ITAMs (motifs present in the cytoplasmic signaling domains of the TCR-CD3 complex) which become the docking sites for the SH2 domains of the syk kinase, ZAP-70 (Weiss, A, 1994, Chu D, 1998, Weil R, 1994). ZAP-70 is also phosphorylated by the Src kinases. Active ZAP-70 phosphorylate the adapter protein LAT present in the lipid rafts. Phosphorylated LAT is able to recruit several other phosphorylated key molecules, including enzymes and non-enzyme adapter proteins, to its tyrosine-based motifs (Finco, TS, 1998, Zhang W, 1998). Such molecules are: 1) Grb2 (associated with SOS) which Ras (Downward, J. 1996, Henning, SW, 1998), and 2) SLP-76 (associated with Gad). SLP-76 recruits a Tec kinase which activates PLCγ. PLCγ enzymatically cleaves membrane inositol-4, 5 bisphosphate leading to formation of inositol-1, 4, 5 triphosphate (IP-3) and diacylglycerol (DAG) (Berridge, MJ, 1998). Ras couples to distal effector signaling pathways including the activation of MAPKs (Erk, JNK, and p38 MAPK). Erk plays an essential role in the activation of transcription factors, c-Fos and c-myc; c-Fos is involved in the transcriptional regulation of activated protein-1 (AP-1) response element in the IL-2 promoter (Gupta, S, 1994, Rincon, M, 2000). JNK is also involved in the activation of IL-2 promoter but a lesser extent than Erk (Su B, 1994). p38 MAPK is involved in the activation of IFNγ gene expression, as well as playing a role in the induction of T cell apoptosis (Gupta, S, 1994). IP-3, generated after the action of PLCγ, causes release of Ca^{2+} from endoplasmic reticulum storage site. Once the stored Ca^{2+} is depleted from the endoplasmic reticulum, depletion triggers extracellular Ca^{2+} influx through a plasma membrane capacitative Ca^{2+} entry channel (Berridge, MJ, 1998), sustaining high Ca^{2+} concentration required for IL-2 promoter activation by calcineurin, a Ca^{2+}-calmodulin dependent serine phosphatase. Calcineurin dephosphorylates NFAT which translocates to the nucleus and binds in the IL-2 promoter region (Baksh, S., 2000, Penninger, JM, 1999). DAG activates certain isoforms of PKC, also dependent on Ca^{2+} , namely, PKC and certain novel isoforms, PKCδ, ε, ν, and θ, that are not dependent on Ca^{2+} (Mellor H, 1998). In T cells, PKCθ is the only isoform that is recruited to the membrane and is involved in the activation of NFκB (Monks CR, 1997). Src and Syk kinases are thus involved in the activation of distal pathways: 1) Grb2/p21ras/MAPKs, 2) PLCγ/Ca^{2+}/calcineurin, and 3) DAG/PKCθ/NFκB pathways; Src/Syk tyrosine kinases additionally activate phosphatidylinositol 3-kinase (PI-3K) which leads activation of a 4th Vav/Rac-1/PKCθ/Akt/NFκB pathway. PI-3K is recruited through its regulatory SH-2 domain to LAT, and phosphorylates the D-3 position of inositol phosphate (IP) in the membrane. Phosphorylated IPs interact with PH domains of PLCγ, Tec kinase, Vav in the lipid rafts (Viola A, 1999). Vav is a GEF for Rac-1, which activates JNK and cytoskeletal assembly; Vav also recruits PKCθ (Herndon, TM, 2001). PI-3K also activates serine-threonine kinase, Akt (PKB) (Ward, SG, 1996, Bruyns, E, 1998). Both Akt and PKCθ activate NFκB (Alessi, DR, 1998). Nascent NFκB/Rel family proteins, present as dimers, are held in the cytoplasm by IκB. Degradation of IκB by proteasome (dependent on ubiquitination) occurs phosphorylation of IκB by IκB kinase complex (IKK) (DiDonato, JA, 1997, Regnier, CH. 1997), and allows for liberation of NFκB dimmers allows which them translocate to the

nucleus, and bind DNA to transcriptionally upregulate various genes. Co-stimulatory receptor CD28's cytoplasmic tail PR motifs are also involved in the recruitment and activation of Srk kinases, Fyn and Lck, and Tec kinases leading to acticvation of PI-3K, Grb2, and JNK (Su B, 1994, Harhaj, EW, 1998). Although several studies have attempted to evaluate the roles of PI-3K and Grb2 after CD28 costimulation on IL-2 production and proliferation, no definitive information has yet come forth from them (Chan, TO, 1999, Parry, RV, 1997). However, PI-3K activation with co-stimulation has been implicated in the activation of Akt followed by that of NFκB resulting in an upregulation of the anti-apoptotic protein Bcl-xL (Chao, DT, 1995, Boise, LH, 1995). Akt regulation with CD28 costimulation has been shown to possibly induce IL-2 and IFNγ production without affecting IL-4 and IL-5 but remains questionable. Thus, although CD28 costimulation is known to prevent T cell anergy through its effect on IL-2 production and cell cycle progression, the signaling mechanisms of this effect have remained elusive. CD28 stimulation probably exerts its effect on IL-2 mRNA upregulation and proliferation by enhancing tyrosine phosphorylation of TCR, and by decreasing threshold for naïve T cell activation through the assembly of signaling components in the "immunological synapse" housing the TCR/CD3-MHC-peptide/CD28/CD80, 86/SrcKs/PKCθ molecular complex at the T cell and APC interface. Like CD28, CTLA-4 contains in its cytoplasmic tail tyrosine and PR regions. An unphosphorylated tyrosine residue allows for an association between CTLA-4 cytoplasmic domain and the AP50 (medium chain subunit of the clathrin adapter, AP-2) resulting in clathrin-dependent endocytosis of CTLA-4, and thus control over its cell surface retention. After TCR stimulation, the cytoplasmic tyrosine(s) are phosphorylated by Src kinases Lck/Fyn that promotes CTLA-4's surface retention. Crosslinking of CTLA-4 reduces TCR-dependent activation of MAPKs, Erk and JNK, as well as of NFκB, NFAT, and AP-1. Ligation of CTLA-4 during TCR stimulation results in decreased T cell cytokine production and arrest of the cell cycle (Coyle AJ, 2001, Sharpe, AH, 2002). Although an association of SH-2 motif containing tyrosine phosphatase (SHP-2) with CTLA-4's cytoplasmic tyrosine residue is not established, an indirect association of CTLA-4 with SHP-2 might result in dephosphorylation of the CD3 complex and inactivation of TCR signaling mechanism (Walunas, TL, 1996, Marengere, LE, 1996). The available research reports of T cell signaling pathways provide a more extensive characterization of TCR-related signaling than that triggered by co-stimulatory or inhibitory T cell/APC surface molecules. However, it is clear there are redundancies in the pathways activated by the TCR-related and co-stimulatory signals.

13. Conclusion (Figure 21-23)

Attempts to clinically improve immunosuppression following burn and/or sepsis has been largely unsuccessful. Immune dysfunction that normally occurs in such a massive burn injury condition affects both innate and adaptive immune responses, including humoral and especially cell-mediated responses. T-cell or antigen-presenting cell malfunctions occur late. Infection, sepsis, and multiple organ failure take weeks to months to evolve following burn injury. Most of the experimental animal models of burn injury target early adaptive immune response and fail to give the true picture of ensuing immunosuppression. Effective therapy requiring modifying signaling pathways distal to CD3 ligation have been proposed by some while others propose nuclear factor-KB and downstream mediators as potential targets for treating burn-induced immunosuppression.

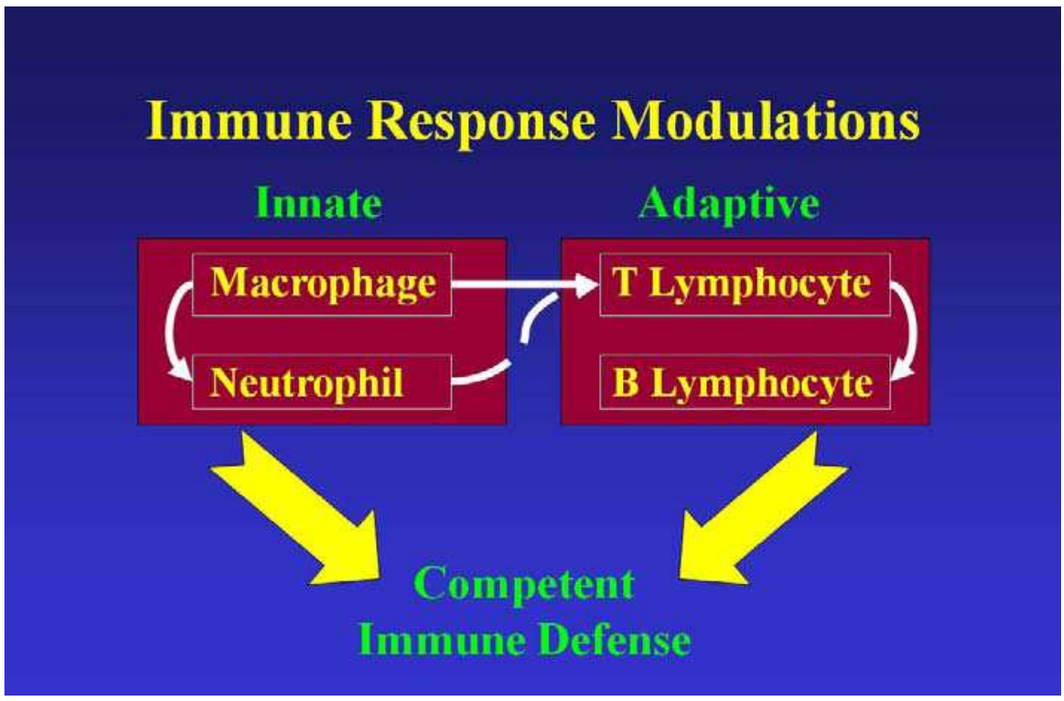

Fig. 21. A summary of events where both inname and adaptive immune response orchestrate complex interaction of cells and their released products to mount a competent immune defense.

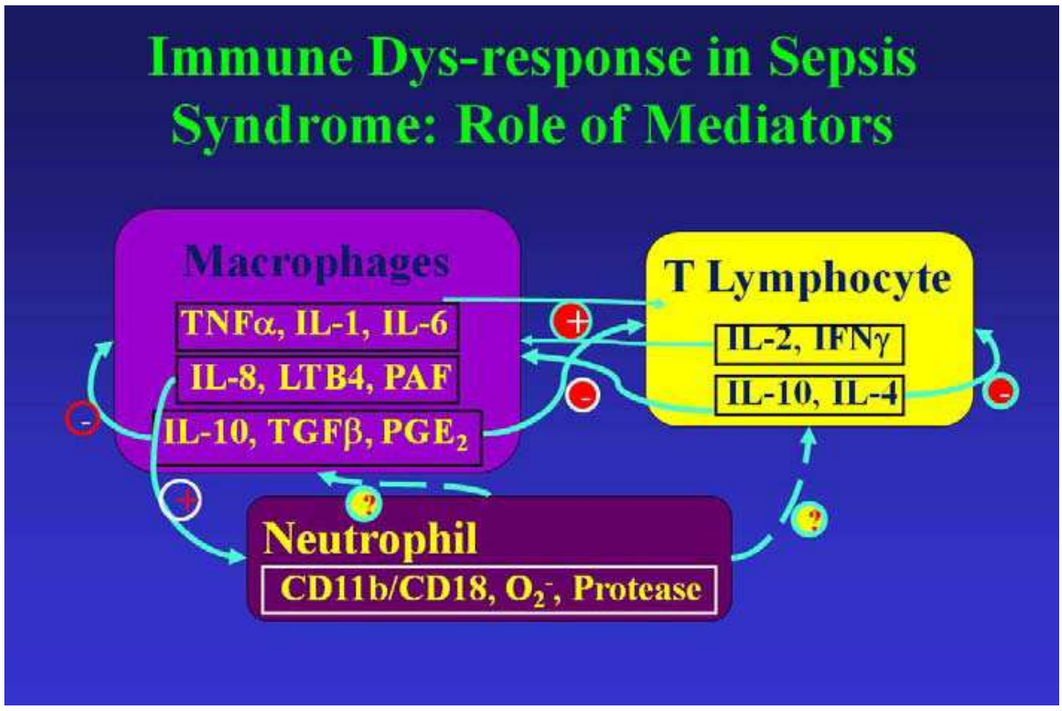

Fig. 22. A flow diagram of possible cellular and humoral factor interactions that occurs in a dysregulated immune response in sepsis.

Fig. 23. A list of potential causes accounting for a failed immunotherapy against clinical sepsis.

14. References

Adachi, S., A. R. Cross, B. M. Babior, and R. A. Gottlieb. 1997. Bcl-2 and the outer mitochondrial membrane in the inactivation of cytochrome c during Fas-mediated apoptosis. *J Biol Chem* 272:21878.

Alegre, M. L., K. A. Frauwirth, and C. B. Thompson. 2001. T-cell regulation by CD28 and CTLA-4. *Nat Rev Immunol* 1:220.

Angele MK, Faist E. 2002. Clinical review: immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care*. Aug; 6 (4):298-305.

Ayala, A., C. S. Chung, G. Y. Song, and I. H. Chaudry. 2001. IL-10 mediation of activation-induced TH1 cell apoptosis and lymphoid dysfunction in polymicrobial sepsis. *Cytokine* 14:37.

Baker CC, Miller CL, Trunkey DD. 1979. Predicting fatal sepsis in burn patients. *J Trauma*; 19 (9):641-8.

Baksh, S., and S. J. Burakoff. 2000. The role of calcineurin in lymphocyte activation. *Semin Immunol* 12:405.

Banz, A., C. Pontoux, and M. Papiernik. 2002. Modulation of Fas-dependent apoptosis: a dynamic process controlling both the persistence and death of CD4 regulatory T cells and effector T cells. *J Immunol* 169:750.

Barret, J. P., and D. N. Herndon. 2003. Modulation of inflammatory and catabolic responses in severely burned children by early burn wound excision in the first 24 hours. *Arch Surg* 138:127.

Baue AE, Durham R, Faist E. 1998. Systemic inflammatory response syndrome (SIRS), multiple organ dysfunction syndrome (MODS), multiple organ failure (MOF): are we winning the battle? *Shock*. Aug;10(2):79-89.

Berridge, M. J., M. D. Bootman, and P. Lipp. 1998. Calcium--a life and death signal. *Nature* 395:645.

Bingaman, A. W., J. Ha, M. M. Durham, S. Y. Waitze, C. Tucker-Burden, S. R. Cowan, T. C. Pearson, and C. P. Larsen. 2001. Analysis of the CD40 and CD28 pathways on alloimmune responses by CD4+ T cells in vivo. *Transplantation* 72:1286.

Blair, P. J., J. L. Riley, D. M. Harlan, R. Abe, D. K. Tadaki, S. C. Hoffmann, L. White, T. Francomano, S. J. Perfetto, A. D. Kirk, and C. H. June. 2000. CD40 ligand (CD154) triggers a short-term CD4 (+) T cell activation response that results in secretion of immunomodulatory cytokines and apoptosis. *J Exp Med* 191:651.

Bode, U., A. Sahle, G. Sparmann, F. Weidner, and J. Westermann. 2002. The fate of effector T cells in vivo is determined during activation and differs for CD4+ and CD8+ cells. *J Immunol* 169:6085.

Boehme, S. A., and M. J. Lenardo. 1993. Propriocidal apoptosis of mature T lymphocytes occurs at S phase of the cell cycle. *Eur J Immunol* 23:1552.

Boise, L. H., A. J. Minn, P. J. Noel, C. H. June, M. A. Accavitti, T. Lindsten, and C. B. Thompson. 1995. CD28 costimulation can promote T cell survival by enhancing the expression of Bcl-XL. *Immunity* 3:87.

Boldin, M. P., E. E. Varfolomeev, Z. Pancer, I. L. Mett, J. H. Camonis, and D. Wallach. 1995. A novel protein that interacts with the death domain of Fas/APO1 contains a sequence motif related to the death domain. *J Biol Chem* 270:7795.

Boldin, M. P., T. M. Goncharov, Y. V. Goltsev, and D. Wallach. 1996. Involvement of MACH, a novel MORT1/FADD-interacting protease, in Fas/APO-1- and TNF receptor-induced cell death. *Cell* 85:803.

Chan, T. O., S. E. Rittenhouse, and P. N. Tsichlis. 1999. AKT/PKB and other D3 phosphoinositide-regulated kinases: kinase activation by phosphoinositide-dependent phosphorylation. *Annu Rev Biochem* 68:965.

Chao, D. T., G. P. Linette, L. H. Boise, L. S. White, C. B. Thompson, and S. J. Korsmeyer. 1995. Bcl-XL and Bcl-2 repress a common pathway of cell death. *J Exp Med* 182:821.

Chu, D. H., C. T. Morita, and A. Weiss. 1998. The Syk family of protein tyrosine kinases in T-cell activation and development. *Immunol Rev* 165:167.

Chung, C. S., G. Y. Song, W. Wang, I. H. Chaudry, and A. Ayala. 2000. Septic mucosal intraepithelial lymphoid immune suppression: role for nitric oxide not interleukin-10 or transforming growth factor-beta. *J Trauma* 48:807.

Clement, M. V, and I. Stamenkovic. 1994. Fas and tumor necrosis factor receptor-mediated cell death: similarities and distinctions. *J Exp Med 180:557*.

Coyle, A. J., and J. C. Gutierrez-Ramos. 2001. The expanding B7 superfamily: increasing complexity in costimulatory signals regulating T cell function. *Nat Immunol 2:203*.

DiDonato, J. A., M. Hayakawa, D. M. Rothwarf, E. Zandi, and M. Karin. 1997. A cytokine-responsive IkappaB kinase that activates the transcription factor NF-kappaB. *Nature* 388:548.

Downward, J. 1996. Control of ras activation. *Cancer Surv* 27:87.

Egen, J. G., and J. P. Allison. 2002. Cytotoxic T lymphocyte antigen-4 accumulation in the immunological synapse is regulated by TCR signal strength. *Immunity 16:23*.

Faist E, Schinkel C, Zimmer S. 1996. Update on the mechanisms of immune suppression of injury and immune modulation. *World J Surg*. May; 20(4):454-9.

Faunce DE, Gamelli RL, Choudhry MA, Kovacs EJ. 2003. A role for CD1d-restricted NKT cells in injury-associated T cell suppression. *J Leukoc Biol*. Jun; 73 (6):747-55.

Fazal, N, Al-Ghoul WM. 2007. Thermal injury-plus-sepsis contributes to a substantial deletion of intestinal mesenteric lymph node CD4 T cell via apoptosis. *Int J Biol Sci*. Sep 12; 3(6):393-401.

Fazal, N, Raziuddin, S, Khan, M, Al-Ghoul, WA. 2006. Antigen presenting cells (APCs) from thermally injured and/or septic rats modulate CD4+ T cell responses of naïve rat. *Biochim Biophys Acta*. ; 1762(1): 46-53.

Fazal, N., Choudhry, M.A., Sayeed, M.M., 2005. Inhibition of T cell MAPKs (Erk 1/2, p38) with thermal injury is related to downregulation of Ca2+ signaling. *Biochim Biophys Acta*. Jun 30; 1741(1-2): 113-9.

Fazal N, Al-Ghoul WM, Schmidt MJ, Choudhry MA, Sayeed MM. 2002. Lyn- and ERK-mediated vs. Ca2+ -mediated neutrophil O2- responses with thermal injury. *Am J Physiol Cell Physiol*; 283(5): C1469-79

Fazal N, Al Ghoul WM, Choudhry MA, and Sayeed MM. 2001. PAF receptor antagonist modulates neutrophil responses with thermal injury, in vivo. *Am J Physiol*. 281:C1310-7.

Fazal, N., Shamim, M., Choudhry, M. A., Ravindranath, T and Sayeed, M.M., 2000. CINC blockade prevents neutrophil Ca2+ signaling upregulation and gut bacterial translocation in burn-injured rats. *Biochim Biophys Acta*; 15; 1535(1): 50-9.

Fazal, N., Shamim, M., Khan, S. S., Gamelli, R.L., and Sayeed, M.M., 2000. Neutrophil depletion in rats reduces burn-injury induced intestinal bacterial translocation. *Critical Care Medicine*; 28(5): 1550-56.

Finco, T. S., T. Kadlecek, W. Zhang, L. E. Samelson, and A. Weiss. 1998. LAT is required for TCR-mediated activation of PLCgamma1 and the Ras pathway. *Immunity* 9:617.

Fukuzuka, K., C. K. Edwards, 3rd, M. Clare-Salzler, E. M. Copeland, 3rd, L. L. Moldawer, and D. W. Mozingo. 2000. Glucocorticoid-induced, caspase-dependent organ apoptosis early after burn injury. *Am J Physiol Regul Integr Comp Physiol* 278:R1005.

Gamelli RL, George M, Sharp-Pucci M, Dries DJ, Radisavljevic Z. 1995. Burn-induced nitric oxide release in humans. *J Trauma*. Nov; 39(5):869-77; discussion 877-8.

Gonzalo, J. A., J. Tian, T. Delaney, J. Corcoran, J. B. Rottman, J. Lora, A. Al-garawi, R. Kroczek, J. C. Gutierrez-Ramos, and A. J. Coyle. 2001. ICOS is critical for T helper cell-mediated lung mucosal inflammatory responses. *Nat Immunol* 2:597.

Grammer, A. C., and P. E. Lipsky. 2002. CD154-CD40 interactions mediate differentiation to plasma cells in healthy individuals and persons with systemic lupus erythematosus. *Arthritis Rheum* 46:1417.

Grohmann, U., C. Orabona, F. Fallarino, C. Vacca, F. Calcinaro, A. Falorni, P. Candeloro, M. L. Belladonna, R. Bianchi, M. C. Fioretti, and P. Puccetti. 2002. CTLA-4-Ig regulates tryptophan catabolism in vivo. *Nat Immunol* 3:1097.

Gupta, S., A. Weiss, G. Kumar, S. Wang, and A. Nel. 1994. The T-cell antigen receptor utilizes Lck, Raf-1, and MEK-1 for activating mitogen-activated protein kinase. Evidence for the existence of a second protein kinase C-dependent pathway in an Lck-negative Jurkat cell mutant. *J Biol Chem* 269:17349.

Harris BH, Gelfand JA. 1995. The immune response to trauma. *Semin Pediatr Surg*. May; 4 (2):77-82.

Henning, S. W., and D. A. Cantrell. 1998. GTPases in antigen receptor signalling. *Curr Opin Immunol* 10:322.

Harhaj, E. W., and S. C. Sun. 1998. IkappaB kinases serve as a target of CD28 signaling. *J Biol Chem* 273:25185.

Herndon, T. M., X. C. Shan, G. C. Tsokos, and R. L. Wange. 2001. ZAP-70 and SLP-76 regulate protein kinase C-theta and NF-kappa B activation in response to engagement of CD3 and CD28. *J Immunol* 166:5654.

Heuer JG, Zhang T, Zhao J, Ding C, Cramer M, Justen KL, Vonderfecht SL, Na S. 2005. Adoptive transfer of in vitro-stimulated CD4+CD25+ regulatory T cells increases bacterial clearance and improves survival in polymicrobial sepsis. *J Immunol*. Jun 1; 174(11):7141-6.

Homann, D., A. Holz, A. Bot, B. Coon, T. Wolfe, J. Petersen, T. P. Dyrberg, M. J. Grusby, and M. G. von Herrath. 1999. Autoreactive CD4+ T cells protect from autoimmune diabetes via bystander suppression using the IL-4/Stat6 pathway. *Immunity* 11:463.

Honey, K., S. P. Cobbold, and H. Waldmann. 1999. CD40 ligand blockade induces CD4+ T cell tolerance and linked suppression. *J Immunol* 163:4805.

Huang, F. P., C. F. Farquhar, N. A. Mabbott, M. E. Bruce, and G. G. MacPherson. 2002. Migrating intestinal dendritic cells transport PrP(Sc) from the gut. *J Gen Virol* 83:267.

Huang, F. P., N. Platt, M. Wykes, J. R. Major, T. J. Powell, C. D. Jenkins, and G. G. MacPherson. 2000. A discrete subpopulation of dendritic cells transports apoptotic intestinal epithelial cells to T cell areas of mesenteric lymph nodes. *J Exp Med* 191:435.

Jain, J., C. Loh, and A. Rao. 1995. Transcriptional regulation of the IL-2 gene. *Curr Opin Immunol* 7:333.

Jeschke, M. G., J. F. Low, M. Spies, R. Vita, H. K. Hawkins, D. N. Herndon, and R. E. Barrow. 2001. Cell proliferation, apoptosis, NF-kappaB expression, enzyme, protein, and weight changes in livers of burned rats. *Am J Physiol Gastrointest Liver Physiol* 280:G1314.

Jobin N, Garrel DR, Bernier J. 2000. Increased burn-induced immunosuppression in lipopolysaccharide-resistant mice. *Cell Immunol. ;* 200(2):65-75.

Ju, S. T., D. J. Panka, H. Cui, R. Ettinger, M. el-Khatib, D. H. Sherr, B. Z. Stanger, and A. Marshak-Rothstein. 1995. Fas (CD95)/FasL interactions required for programmed cell death after T-cell activation. *Nature* 373:444.

Kell, M. R., O. Shelley, J. A. Mannick, Z. Guo, and J. A. Lederer. 2000. A central role for CD95 (Fas) in T-cell reactivity after injury. *Surgery* 128:159.

Kelly JL, O'Suilleabhain CB, Soberg CC, Mannick JA, Lederer JA. 1999, Severe injury triggers antigen-specific T-helper cell dysfunction. *Shock*; 12(1):39-45.

Kelly, J. L., C. B. O'Suilleabhain, C. C. Soberg, J. A. Mannick, and J. A. Lederer. 1999. Severe injury triggers antigen-specific T-helper cell dysfunction. *Shock* 12:39.

Kobayashi, M., H. Takahashi, A. P. Sanford, D. N. Herndon, R. B. Pollard, and F. Suzuki. 2002. An increase in the susceptibility of burned patients to infectious complications due to impaired production of macrophage inflammatory protein 1 alpha. *J Immunol* 169:4460.

Kung, J. T., D. Beller, and S. T. Ju. 1998. Lymphokine regulation of activation-induced apoptosis in T cells of IL-2 and IL-2R beta knockout mice. *Cell Immunol* 185:158.

Laliberte, J., A. Yee, Y. Xiong, and B. S. Mitchell. 1998. Effects of guanine nucleotide depletion on cell cycle progression in human T lymphocytes. *Blood* 91:2896.

Lederer JA, Rodrick ML, Mannick JA. 1999. The effects of injury on the adaptive immune response. *Shock.* Mar; 11(3):153-9.

Lenardo, M., K. M. Chan, F. Hornung, H. McFarland, R. Siegel, J. Wang, and L. Zheng. 1999. Mature T lymphocyte apoptosis--immune regulation in a dynamic and unpredictable antigenic environment. *Annu Rev Immunol* 17:221.

Li, H., H. Zhu, C. J. Xu, and J. Yuan. 1998. Cleavage of BID by caspase 8 mediates the mitochondrial damage in the Fas pathway of apoptosis. *Cell* 94:491.

Li, P., D. Nijhawan, I. Budihardjo, S. M. Srinivasula, M. Ahmad, E. S. Alnemri, and X. Wang. 1997. Cytochrome c and dATP-dependent formation of Apaf-1/caspase-9 complex initiates an apoptotic protease cascade. *Cell* 91:479.

Li, X. C., Y. Li, I. Dodge, A. D. Wells, X. X. Zheng, L. A. Turka, and T. B. Strom. 1999. Induction of allograft tolerance in the absence of Fas-mediated apoptosis. *J Immunol* 163:2500.

Li, Y., X. C. Li, X. X. Zheng, A. D. Wells, L. A. Turka, and T. B. Strom. 1999. Blocking both signal 1 and signal 2 of T-cell activation prevents apoptosis of alloreactive T cells and induction of peripheral allograft tolerance. *Nat Med* 5:1298.

Liu, L. M., and G. G. MacPherson. 1995. Rat intestinal dendritic cells: immunostimulatory potency and phenotypic characterization. *Immunology* 85:88.

Liu, L., M. Zhang, C. Jenkins, and G. G. MacPherson. 1998. Dendritic cell heterogeneity in vivo: two functionally different dendritic cell populations in rat intestinal lymph can be distinguished by CD4 expression. *J Immunol* 161:1146.

Lohning, M., A. Hutloff, T. Kallinich, H. W. Mages, K. Bonhagen, A. Radbruch, E. Hamelmann, and R. A. Kroczek. 2003. Expression of ICOS in vivo defines CD4+ effector T cells with high inflammatory potential and a strong bias for secretion of interleukin 10. *J Exp Med* 197:181.

Luo, X., I. Budihardjo, H. Zou, C. Slaughter, and X. Wang. 1998. Bid, a Bcl2 interacting protein, mediates cytochrome c release from mitochondria in response to activation of cell surface death receptors. *Cell* 94:481.

Maloy, K. J., and F. Powrie. 2001. Regulatory T cells in the control of immune pathology. *Nat Immunol* 2:816.

Marano MA, Fong Y, Moldawer LL, Wei H, Calvano SE, Tracey KJ, Barie PS, Manogue K, Cerami A, Shires GT, et al. 1990. Serum cachectin/tumor necrosis factor in critically ill patients with burns correlates with infection and mortality. *Surg Gynecol Obstet*. Jan; 170(1):32-8.

Marengere, L. E., P. Waterhouse, G. S. Duncan, H. W. Mittrucker, G. S. Feng, and T. W. Mak. 1996. Regulation of T cell receptor signaling by tyrosine phosphatase SYP association with CTLA-4. *Science* 272:1170.

Martin, E., B. O'Sullivan, P. Low, and R. Thomas. 2003. Antigen-specific suppression of a primed immune response by dendritic cells mediated by regulatory T cells secreting interleukin-10. *Immunity* 18:155.

Meakins JL. 1990. Etiology of multiple organ failure. *J Trauma*. Dec; 30(12 Suppl):S165-8.

Medzhitov R, Janeway CA Jr. 1998. Innate immune recognition and control of adaptive immune responses.*Semin Immunol*. Oct; 10 (5):351-3.

Mellor, A. L., B. Baban, P. Chandler, B. Marshall, K. Jhaver, A. Hansen, P. A. Koni, M. Iwashima, and D. H. Munn. 2003. Cutting edge: induced indoleamine 2, 3 dioxygenase expression in dendritic cell subsets suppresses T cell clonal expansion. *J Immunol* 171:1652.

Mellor, H., and P. J. Parker. 1998. The extended protein kinase C superfamily. *Biochem J* 332 (Pt 2):281.

Mittrucker, H. W., M. Kursar, A. Kohler, D. Yanagihara, S. K. Yoshinaga, and S. H. Kaufmann. 2002. Inducible costimulator protein controls the protective T cell response against Listeria monocytogenes. *J Immunol* 169:5813.

Miyazaki, T., Z. J. Liu, A. Kawahara, Y. Minami, K. Yamada, Y. Tsujimoto, E. L. Barsoumian, R. M. Permutter, and T. Taniguchi. 1995. Three distinct IL-2 signaling pathways mediated by bcl-2, c-myc, and lck cooperate in hematopoietic cell proliferation. *Cell* 81:223.

Molloy RG, O'Riordain M, Holzheimer R, Nestor M, Collins K, Mannick JA, Rodrick ML. 1993. Mechanism of increased tumor necrosis factor production after thermal injury. Altered sensitivity to PGE2 and immunomodulation with indomethacin. *J Immunol*. Aug 15; 151(4):2142-9.

Monks, C. R., H. Kupfer, I. Tamir, A. Barlow, and A. Kupfer. 1997. Selective modulation of protein kinase C-theta during T-cell activation. *Nature* 385:83.

Moss NM, Gough DB, Jordan AL, Grbic JT, Wood JJ, Rodrick ML, Mannick JA. 1988. Temporal correlation of impaired immune response after thermal injury with susceptibility to infection in a murine model. *Surgery*. Nov; 104 (5):882-7.

Murphy TJ, Ni Choileain N, Zang Y, Mannick JA, Lederer JA. 2005. CD4+CD25+ regulatory T cells control innate immune reactivity after injury. *J Immunol*. Mar 1; 174(5):2957-63.

Muzio, M., A. M. Chinnaiyan, F. C. Kischkel, K. O'Rourke, A. Shevchenko, J. Ni, C. Scaffidi, J. D. Bretz, M. Zhang, R. Gentz, M. Mann, P. H. Krammer, M. E. Peter, and V. M. Dixit. 1996. FLICE, a novel FADD-homologous ICE/CED-3-like protease, is recruited to the CD95 (Fas/APO-1) death--inducing signaling complex. *Cell* 85:817.

Nagasawa, M., I. Melamed, A. Kupfer, E. W. Gelfand, and J. J. Lucas. 1997. Rapid nuclear translocation and increased activity of cyclin-dependent kinase 6 after T cell activation. *J Immunol* 158:5146.

Ni Choileain N, MacConmara M, Zang Y, Murphy TJ, Mannick JA, Lederer JA. 2006. Enhanced regulatory T cell activity is an element of the host response to injury. *J Immunol*. Jan 1; 176(1):225-36.

Ninnemann JL, Fisher JC, Frank HA. 1978. Prolonged survival of human skin allografts following thermal injury. *Transplantation*. Feb; 25(2):69-72.

Ogle CK, Mao JX, Wu JZ, Ogle JD, Alexander JW. 1994. The 1994 Lindberg Award. The production of tumor necrosis factor, interleukin-1, interleukin-6, and prostaglandin E2 by isolated enterocytes and gut macrophages: effect of lipopolysaccharide and thermal injury. *J Burn Care Rehabil*. Nov-Dec; 15 (6):470-7.

Okazaki, T., Y. Iwai, and T. Honjo. 2002. New regulatory co-receptors: inducible co-stimulator and PD-1. *Curr Opin Immunol* 14:779.

O'Riordain MG, Collins KH, Pilz M, Saporoschetz IB, Mannick JA, Rodrick ML. 1992. Modulation of macrophage hyperactivity improves survival in a burn-sepsis model. *Arch Surg*. Feb; 127(2):152-7; discussion 157-8.

Palmer JL, Tulley JM, Kovacs EJ, Gamelli RL, Taniguchi M, Faunce DE. 2006. Injury-induced suppression of effector T cell immunity requires CD1d-positive APCs and CD1d-restricted NKT cells. *J Immunol*. 2006 Jul 1; 177(1):92-9.

Parry RV, Reif K, Smith G, Sansom DM, Hemmings BA, Ward SG. Ligation of the T cell co-stimulatory receptor CD28 activates the serine-threonine protein kinase protein kinase B. *Eur J Immunol*; 27(10):2495-501.

Penninger, J. M., and G. R. Crabtree. 1999. The actin cytoskeleton and lymphocyte activation. *Cell* 96:9.

Ramirez, F., and D. Mason. 2000. Recirculatory and sessile CD4+ T lymphocytes differ on CD45RC expression. *J Immunol* 165:1816.

Rathmell, J. C., and C. B. Thompson. 1999. The central effectors of cell death in the immune system. *Annu Rev Immunol* 17:781.

Ravindranath, T., W. Al-Ghoul, S. Namak, N. Fazal, R. Durazo-Arvizu, M. Choudhry, and M. M. Sayeed. 2001. Effects of burn with and without Escherichia coli infection in rats on intestinal vs. splenic T-cell responses. *Crit Care Med* 29:2245.

Regnier, C. H., H. Y. Song, X. Gao, D. V. Goeddel, Z. Cao, and M. Rothe. 1997. Identification and characterization of an IkappaB kinase. *Cell* 90:373.

Renno, T., M. Hahne, and H. R. MacDonald. 1995. Proliferation is a prerequisite for bacterial superantigen-induced T cell apoptosis in vivo. *J Exp Med* 181:2283.

Riley, J. L., M. Mao, S. Kobayashi, M. Biery, J. Burchard, G. Cavet, B. P. Gregson, C. H. June, and P. S. Linsley. 2002. Modulation of TCR-induced transcriptional profiles by ligation of CD28, ICOS, and CTLA-4 receptors. *Proc Natl Acad Sci USA* 99:11790.

Rincon, M., D. Conze, L. Weiss, N. L. Diehl, K. A. Fortner, D. Yang, R. A. Flavell, H. Enslen, A. Whitmarsh, and R. J. Davis. 2000. Conference highlight: do T cells care about the mitogen-activated protein kinase signalling pathways? *Immunol Cell Biol* 78:166.

Saffle JR, Sullivan JJ, Tuohig GM, Larson CM. 1993; Multiple organ failure in patients with thermal injury. *Crit Care Med*; 21(11):1673-83.

Sakaida, H., S. Kawamata, T. Hattori, and T. Uchiyama. 1998. V3 loop of human immunodeficiency virus type 1 reduces cyclin E expression and induces G1 arrest in interleukin 2-dependent T cells. *AIDS Res Hum Retroviruses* 14:31.

Salinas J, Drew G, Gallagher J, Cancio LC, Wolf SE, Wade CE, Holcomb JB, Herndon DN, Kramer GC. 2008. Closed-loop and decision-assist resuscitation of burn patients. *J Trauma;* 64(4 Suppl):S321-32.

Schneider DF, Glenn CH, Faunce DE. 2007. Innate lymphocyte subsets and their immunoregulatory roles in burn injury and sepsis. *J Burn Care Res*. May-Jun; 28 (3):365-79.

Schwacha MG, Ayala A, Chaudry IH. 2000. Insights into the role of gammadelta T lymphocytes in the immunopathogenic response to thermal injury. *J Leukoc Biol*. May; 67(5):644-50.

Schwacha MG, Samy TS, Catania RA, Chaudry IH. 1998. Thermal injury alters macrophage responses to prostaglandin E2: contribution to the enhancement of inducible nitric oxide synthase activity. *J Leukoc Biol*. Dec; 64 (6):740-6.

Schwacha MG. 2003. Macrophages and post-burn immune dysfunction.*Burns*. Feb; 29(1):1-14.

Sharpe, A. H., and G. J. Freeman. 2002. The B7-CD28 superfamily. *Nat Rev Immunol* 2:116.

Steinman, R. M., and M. C. Nussenzweig. 2002. Avoiding horror autotoxicus: the importance of dendritic cells in peripheral T cell tolerance. *Proc Natl Acad Sci USA* 99:351.

Still JM Jr, Belcher K, Law EJ. 1993. Experience with polymicrobial sepsis in a regional burn unit. *Burns*. Oct;19 (5):434-6.

Straw, A. D., A. S. MacDonald, E. Y. Denkers, and E. J. Pearce. 2003. CD154 plays a central role in regulating dendritic cell activation during infections that induce Th1 or Th2 responses. *J Immunol* 170:727.

Su, B., E. Jacinto, M. Hibi, T. Kallunki, M. Karin, and Y. Ben-Neriah. 1994. JNK is involved in signal integration during costimulation of T lymphocytes. *Cell* 77:727.

Tang, Q., J. A. Smith, G. L. Szot, P. Zhou, M. L. Alegre, K. J. Henriksen, C. B. Thompson, and J. A. Bluestone. 2003. CD28/B7 regulation of anti-CD3-mediated immunosuppression in vivo. *J Immunol* 170:1510.

Toliver-Kinsky, T. E., T. K. Varma, C. Y. Lin, D. N. Herndon, and E. R. Sherwood. 2002. Interferon-gamma production is suppressed in thermally injured mice: decreased production of regulatory cytokines and corresponding receptors. *Shock* 18:322.

Toth B, Alexander M, Daniel T, Chaudry IH, Hubbard WJ, Schwacha MG. 2004. The role of gammadelta T cells in the regulation of neutrophil-mediated tissue damage after thermal injury. *J Leukoc Biol*. Sep; 76 (3):545-52. Epub 2004 Jun 14.

Turnbull, E., and G. MacPherson. 2001. Immunobiology of dendritic cells in the rat. *Immunol Rev* 184:58.

Uyttenhove, C., L. Pilotte, I. Theate, V. Stroobant, D. Colau, N. Parmentier, T. Boon, and B. J. Van Den Eynde. 2003. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2, 3-dioxygenase. *Nat Med* 9:1269.

Varedi, M., M. G. Jeschke, E. W. Englander, D. N. Herndon, and R. E. Barrow. 2001. Serum TGF-beta in thermally injured rats. *Shock 16:380*.

Villegas, E. N., L. A. Lieberman, N. Mason, S. L. Blass, V. P. Zediak, R. Peach, T. Horan, S. Yoshinaga, and C. A. Hunter. 2002. A role for inducible costimulator protein in the CD28- independent mechanism of resistance to Toxoplasma gondii. *J Immunol* 169:937.

Viola, A., S. Schroeder, Y. Sakakibara, and A. Lanzavecchia. 1999. T lymphocyte costimulation mediated by reorganization of membrane microdomains. *Science* 283:680.

Walunas, T. L., C. Y. Bakker, and J. A. Bluestone. 1996. CTLA-4 ligation blocks CD28-dependent T cell activation. *J Exp Med* 183:2541.

Wang, J., E. Guan, G. Roderiquez, and M. A. Norcross. 2001. Synergistic induction of apoptosis in primary CD4 (+) T cells by macrophage-tropic HIV-1 and TGF-beta1. *J Immunol* 167:3360.

Wang, K., X. M. Yin, D. T. Chao, C. L. Milliman, and S. J. Korsmeyer. 1996. BID: a novel BH3 domain-only death agonist. *Genes Dev* 10:2859.

Wang, R., T. L. Ciardelli, and J. H. Russell. 1997. Partial signaling by cytokines: cytokine regulation of cell cycle and Fas-dependent, activation-induced death in CD4+ subsets. *Cell Immunol* 182:152.

Weil, R., and A. Veillette. 1994. Intramolecular and extramolecular mechanisms repress the catalytic function of p56lck in resting T-lymphocytes. *J Biol Chem* 269:22830.

Weiss, A., and D. R. Littman. 1994. Signal transduction by lymphocyte antigen receptors. *Cell* 76:263.

Wekerle, T., J. Kurtz, M. Sayegh, H. Ito, A. Wells, S. Bensinger, J. Shaffer, L. Turka, and M. Sykes. 2001. Peripheral deletion after bone marrow transplantation with costimulatory blockade has features of both activation-induced cell death and passive cell death. *J Immunol* 166:2311.

Wells, A. D., X. C. Li, Y. Li, M. C. Walsh, X. X. Zheng, Z. Wu, G. Nunez, A. Tang, M. Sayegh, W. W. Hancock, T. B. Strom, and L. A. Turka. 1999. Requirement for T-cell apoptosis in the induction of peripheral transplantation tolerance. *Nat Med* 5:1303.

Wesa, A., and A. Galy. 2002. Increased production of pro-inflammatory cytokines and enhanced T cell responses after activation of human dendritic cells with IL-1 and CD40 ligand. *BMC Immunol* 3:14.

White CE, Renz EM. 2008; Advances in surgical care: management of severe burn injury. *Crit Care Med*; 36 (7 Suppl):S318-24.

Wu X, Woodside KJ, Song J, Wolf SE. 2004. Burn-induced gut mucosal homeostasis in TCR delta receptor-deficient mice. *Shock*. Jan; 21 (1):52-7.

Yang L, Hsu B. 1992. The roles of macrophage (M phi) and PGE-2 in postburn immunosuppression. *Burns*. Apr; 18 (2):132-6.

Zhang, J., D. Cado, A. Chen, N. H. Kabra, and A. Winoto. 1998. Fas-mediated apoptosis and activation-induced T-cell proliferation are defective in mice lacking FADD/Mort1. *Nature* 392:296.

Zhang, W., R. P. Trible, and L. E. Samelson. 1998. LAT palmitoylation: it's essential role in membrane microdomain targeting and tyrosine phosphorylation during T cell activation. *Immunity* 9:239.

Zheng, L., G. Fisher, R. E. Miller, J. Peschon, D. H. Lynch, and M. J. Lenardo. 1995. Induction of apoptosis in mature T cells by tumour necrosis factor. *Nature* 377:348.

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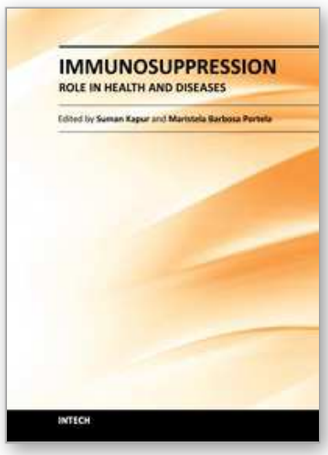

Immunosuppression - Role in Health and Diseases
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A need for a book on immunology which primarily focuses on the needs of medical and clinical research students was recognized. This book, "Immunosuppression - Role in Health and Diseases" is relatively short and contains topics relevant to the understanding of human immune system and its role in health and diseases. Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Therapeutic immunosuppression has applications in clinical medicine, ranging from prevention and treatment of organ/bone marrow transplant rejection, management of autoimmune and inflammatory disorders. It brings important developments both in the field of molecular mechanisms involved and active therapeutic approaches employed for immunosuppression in various human disease conditions. There was a need to bring this information together in a single volume, as much of the recent developments are dispersed throughout biomedical literature, largely in specialized journals. This book will serve well the practicing physicians, surgeons and biomedical scientists as it provides an insight into various approaches to immunosuppression and reviews current developments in each area.

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