**Introduction**

Trauma is a leading cause of death and morbidity among all ages and constitutes a major public health problem. This burden is initially directed at stabilizing direct injury, however, post-trauma complications are common and prolong costly ICU stays. Among these complications are acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). While care for these pulmonary complications has now been standardized and prevention continues to improve, the true pathophysiology has not been elucidated. Current evidence suggests that the activation of a pro-inflammatory cascade plays an important role in the pathogenesis of trauma related lung injury. Additionally, there is a novel T-cell response that has been shown to be intricately involved in other non-traumatic lung diseases and multiple inflammatory diseases. With the recent discovery of this novel T-helper subset (Th-17) and the main effector cytokine, IL-17, there is the potential for further categorizing the biologic mechanism leading to ALI and ARDS. By utilizing the discoveries provided by animal models and further investigation into local and systemic cytokine profiles in human trauma victims, the information gained holds promise in the development of unique therapeutic modalities for the treatment and prevention of ARDS following traumatic injury.

**Keywords:** Inflammation, immune, T-Cells, cytokines

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**Introduction**

Trauma is a leading cause of death and morbidity among all ages and constitutes a major public health problem, with the World Health Organization estimating approximately 5.8 million deaths occurring annually worldwide. In America, this burden has been lessened with the institution of an organized and integrated trauma system [1, 2]. While triage and initial care have improved, post-injury complications and disease are still major problems [3]. Among the disease states that play a role following a traumatic injury are acute lung injury (ALI) and acute respiratory distress syndrome (ARDS). With the institution of ARDS Net, the care of those with ARDS has improved with the aid of a standardized approach, however there is still inadequate knowledge pertaining to the pathophysiology and ultimate prevention of ALI progressing to ARDS. The incidence of ARDS varies depending on patient population and disease state. It has been reported that between 10 and 40% of ventilated patients in trauma ICUs meet ARDS criteria upon admission or during the course of their ICU stay [4-7]. An increased transfusion requirement, as well as the presence of sepsis tends to increase the risk of the development of ARDS [6]. Not only does the presence of ALI and ARDS increase ICU days and the associated hospital cost, but mortality is significantly higher (3-4 fold) with the development of ARDS [5].

Given the added morbidity and mortality associated with the development of ARDS, there has been much attention given to the investigation of the clinical management as well as the causative mechanisms. The management of ARDS has improved greatly over the past two decades with the development of the standardized protocol via an intensive research network, but the identification of the exact causative biologic mechanism (and thus an eye at prevention or better treatment algorithms) has been incomplete, especially in the trauma population. Current evidence suggests that the activation of a pro-inflammatory cascade plays an important role...
role in the pathogenesis of trauma related lung injury [8-10]. Additionally, the Th-17 cytokine response has shown to be intricately involved in other non-traumatic lung diseases [11]. By utilizing the discoveries provided by animal models and further investigation into local and systemic cytokine profiles in human trauma victims, the information gained holds promise in the development of unique therapeutic modalities for the treatment and prevention of ARDS following traumatic injury.

Acute lung injury

Acute Lung Injury (ALI) is a pathologic pulmonary state defined by an increase in endothelial permeability, leading to alveolar edema and a resultant dysfunction of adequate gas exchange. Acute Respiratory Distress Syndrome (ARDS) represents a progression along this continuum leading to even poorer gas exchange with subsequent fibroproliferation and eventual lung remodeling. In the clinical setting, these disease states are diagnosed by the radiologic findings in association with ventilation status [12]. In 1994, a consensus was made to define ARDS as the presence of an oxygenation abnormality (a PaO2/FIO2 ratio ≤ 200) and a chest radiograph with bilateral infiltrates compatible with pulmonary edema. The diagnosis is exclusive of pulmonary edema secondary to cardiac dysfunction (pulmonary artery wedge pressure ≥ 18 mm Hg) and has an acute onset. Inciting factors for the development of ARDS can be either direct (primary), resulting from direct traumatic injury to the lung or they can be indirect (secondary) as a result of extra-pulmonary illness or injury. It has been well established that significant traumatic injury, hemorrhage, and burn are all associated with an up regulated immunoinflammatory reaction and it has been hypothesized that subsequent indirect pulmonary injury is due to the activation of systemic inflammation. In many instances of trauma related lung injury, a direct injury to the lung is apparent prior to the onset of ALI and related decompensation, however, there is a select population that has no direct lung injury and later develops ARDS. Given the elevated blood cytokine levels and other biochemical and cellular mediators following traumatic injury and the significant blood flow through the pulmonary vasculature, it follows that this late local injury is at least in part due to the remote systemic response.

Th-17 T-cells: a novel T-cell population

A recent discovery of a novel T cell population may provide the foundation for the basis that this systemic inflammatory cascade is the necessary precursor to the development of trauma related lung injury. The Th-17 immune response and its novel cytokine family, the interleukin (IL)-17 cytokine family, including IL-6, IL-17, IL-22, and tissue growth factor [TGF]-β, provide a new pathway for crosstalk between adaptive and innate immunity [13]. The specific set of mediators up-regulated during the immunoinflammatory response of ALI and ARDS (γδ T-cells, IL-6, TGF-β) are very similar to those seen in the more frequently studied auto-immune related Th-17 responses [14]. The ability for Th-17 cells and their mediators to participate in both arms of the immune response, in addition to the evidence that the Th-17 response is involved in host self injury, uniquely positions this response to lead the inflammatory disregulation often seen following trauma.

There are three separate lineages of CD4+ T cells. The Th-1 and Th-2 responses have been well classified over the past three decades and until recently provided a comprehensive view of the cell-mediated response. However, with the discovery of the Th-17 response, a new horizon was opened for the investigation of inflammatory diseases and the immune system as a whole. This more recently identified lineage of T-helper cells, the Th-17 group, is separately classified according to its unique cytokine profile, including IL-17. IL-17 has been implicated to play a central role in not only defensive strategies against bacterial infections but also in several models of immune-mediated tissue injury [13, 15]. While over the last six years there has been a significant amount of work categorizing the specific role of the Th-17 cytokine response, including its role in inflammatory lung disease and autoimmune diseases such as arthritis, multiple sclerosis, and inflammatory bowel disease [14, 16]; there is a lack of knowledge in the setting of trauma.

Th-17 cell lineages

T-helper cells may also be classified according to their cytokine profile. Th-1 cytokines, namely IL-2 and IFN-γ, play a role in the cell-mediated immune response. Th-2 cytokines, IL-4 and IL-10, play an anti-inflammatory role and are cen-
tral in a humoral immune response [9]. However, it is the cytokine environment to which naïve T-helper cells are subjected, mainly IL-12 and IL-10 that directs the differentiation of specific T-helper cell phenotypes, Th-1 or Th-2 respectively. TGF-β in combination with IL-6 or IL-21 is necessary for the differentiation of naïve CD4+ T cells into Th-17 cells [15, 17-19]. IL-21 is produced by NK cells and cytotoxic T-cells in addition to Th-17 cells themselves, creating a positive feedback loop, even in the absence of IL-6 [20]. This feedback loop acts to amplify the Th-17 response. The independence of the Th-17 response is further increased by the expression of IL-23R, also induced by IL-21 [21, 22]. IL-23 is produced by activated dendritic cells and once bound to IL-23R on Th-17 cells, the propagation may occur in the absence of IL-6 and TGF-β, expanding the Th-17 cells population [17]. Figure 1 shows the relationships between cytokines and T-Cell subsets.

### The IL-17 cytokine family

The IL-17 family consists of six structurally related effector cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F [15]. IL-17 is one of the main cytokines produced by Th-17 cells, however there are a number of other cells capable of producing an IL-17 response, mainly αβ T cells, γδ T cells, natural killer (NK) cells, and neutrophils. Recent studies have implicated several members of the IL-17 family in multiple inflammatory diseases such as systemic lupus erythematosus (SLE), multiple sclerosis, and collagen-induced arthritis [23-26] as well as chronic pulmonary diseases such as COPD and asthma [11]. It is, at this point, well known that the Th-17 response plays a significant role in the escalation of the inflammatory response. However, whether or not Th-17 cells are the major driving force behind the early response is debatable. As stated previously, NK cells, macrophages, and epithelial cells are all capable of producing members of the IL-17 family of cytokines in an innate-like response [14, 27, 28]. Also, IL-17A and IL-17F have been shown to play a role in the recruitment of neutrophils during lung inflammation[29].

Since its discovery, there has been investigation into the role of the Th-17 response as it relates to auto-immune disease and host auto-destruction. One of the original studies that differentiated the Th-17 response from the prevailing Th-1/Th-2 paradigm also set the stage for further investigation into the true cellular physiology in autoimmune disease. The animal model of experimental allergic encephalitis (EAE), has been a long standing model for cell mediated auto-immunity. In these studies it was discovered that T cells producing IL-17 were able to induce EAE, but T cells producing γ-IFN (the “signature cytokine” of the Th-1/Th-2 paradigm) were not [30]. In addition, administration of antibody to IL-17 lessened the severity of EAE [13, 30]. Stemming from these original studies, there is now suggestion that IL-17 and the Th-17 response play a role in multiple sclerosis as well as rheumatoid arthritis [31-33]. Based on the evidence that IL-23 is a key cytokine involved in the up-regulation and propagation of the Th-17 response, and the work by Duerr et al. showing that IL-23 plays a role as a modulator of inflammatory bowel disease, it is apparent that Crohns Disease and Ulcerative Colitis are modulated by this Th-17 response as well [34].

Additionally, these studies showed that there was reciprocity between Th-1 and Th-17 cell lineages, where Th-1 played an anti-inflammatory role keeping the Th-17 response in check [13]. Therefore, the Th-17 response has been implicated as a pro-inflammatory mediator with a role in host injury when allowed to propagate unchecked.

### The cytokine milieu after injury

A key feature of any immune response is the presence of regulatory mechanisms, be it an
auto-regulatory feedback loop or local chemokine coordination. Much of this regulation is provided by the cytokine milieu in which the response is occurring. The previously categorized Th1/Th2 pathway illustrates the fine coordination between antagonistic responses. Macrophages, being a main cellular component of the innate immune response, have an early opportunity to regulate this Th1/Th2 pathway. They do so by creating a cytokine environment consisting of IL-12 and IL-10, thus influencing the development of naïve Th cells into Th-1 or Th-2 cells respectively. The specific cytokines produced by these separate lineages inhibit the other’s production, thus creating a dedicated and imbalanced response via the original production of IL-12 or IL-10 from macrophages [9]. The more recently introduced Th17 pathway shares many of the feedback mechanisms with the Th1/Th2 pathway. For example, the above mentioned work by Bettelli et al. demonstrated a synergistic relationship of IL-6 and TGF-β in the induction of optimal IL-17 production [13]. Also, in the presence of an active Th1 pathway, the Th17 response is dampened due to the antagonistic effect of IFN-γ and TNF [13]. Given the inter-relationships between the separate T-helper cell pathways, it is important to note that it is the relative excess or deficiency of multiple cytokines that drives the response toward control and resolution versus the unchecked path of host auto-destruction. As the functions of IL-17 become clearer, it may play a central role in perpetuating tissue damage.

**IL-17 and trauma related lung injury**

It has been well established for over 25 years that the development of a dysfunctional inflammatory response along with ALI and multiple organ dysfunction syndrome (MODS) hampers the recovery of trauma patients [35, 36]. Although a relationship between trauma and pulmonary dysfunction has been recognized clinically and experimentally, the pathogenesis of this trauma-induced lung injury is only partially understood. Major trauma can induce remote organ injury at sites such as the lung, liver, and small intestines [37-40], and these trauma-induced organ injuries appear to be primarily mediated by neutrophils [39-41]. Tissue injury caused by neutrophils is a central mechanism of host auto-destruction. It is defined by a sequence of events including neutrophil adherence and sequestration, diapedesis, activation, and secretion of toxic compounds, such as oxygen radicals and proteases [42]. These lung disease states are characterized by neutrophil influx and include, asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis [43-45]. The Th-17 inflammatory response has been linked to neutrophil activation and tissue infiltration in the lung in particular [46, 47]. Moreover, IL-17 appears to be central in the regulation of the pulmonary immunoinflammatory response, since excessive or deficient IL-17 production/release leads either to deficient responses or a disease state [48]. Thus, a relationship between the Th-17 immunoinflammatory cytokine response after injury and neutrophil activation appears to be central in the development of pulmonary complications.

**A role for IL-17 in lung immunity and inflammation**

In addition to its role in auto-immune disease and host destruction, IL-17 is also implicated in a multitude of inflammatory lung diseases, both auto-immune and acquired. IL-17A acts directly on epithelial cells within the airways. Given an infectious burden within the airways, members of the IL-17 family (IL-17A, IL-17F, and IL-22) regulate the immune response. These Th-17 effector cytokines induce respiratory epithelial cells to secrete CXCL8, CXCL1, CXCL5, IL-6, G-CSF, and GM-CSF which in turn recruit neutrophils to the airways [48, 49]. This pathways role in protection against pulmonary infection is illustrated by the increased mortality in knockout mice unable to produce functional IL-17RA signaling in the presence of intranasal Klebsiella pneumonia [50]. Similar results have been seen in both mice and humans after challenge with Mycobacterium tuberculosis and Aspergillus fumigatus [51].

**Inflammation in the setting of trauma**

While the Th-17 inflammatory response and IL-17 in particular, have been implicated in the preceding autoimmune diseases and lung inflammatory states, specific inducers and mediators of the response such as IL-6 and TGF-β are also central in the systemic inflammatory complications following severe traumatic injury [15, 52, 53]. This uniquely positions the Th-17 response to influence both aspects of the innate and adaptive immune responses, especially when considering the multitude of other host cells able to innately produce IL-17. This relationship potentially implicates the Th-17 re-
IL-17 and lung injury

Response as the major orchestrator of systemic inflammatory complications in trauma patients. Regardless of the inciting factor, the inflammatory response is initially up-regulated with the goal of responding to the insult, gaining control, and re-instituting homeostasis. The systemic inflammatory response (SIRS) is an innate response induced by any of several insults including major traumatic injury, severe burns, or critical illness such as pancreatitis. It is characterized by the release of pro-inflammatory cytokines such as IL-1, IL-6, IL-8 and TNF-α. The inflammatory response is primarily driven by monocytes and macrophages, however, neutrophils and specific T-cell populations are also recruited and activated creating what is termed as the “inflammatory storm” [9, 54-56]. The response to the upregulation of systemic inflammation is a counter-regulatory balance provided by macrophages and T-cells via the production of IL-4 and IL-10. Under normal conditions these two components of the inflammatory response are tightly regulated resulting in immune homeostasis; however, following major injury this balance is disrupted. This immune imbalance can result in immunosuppression with the subsequent possibility of sepsis and multiple organ failure, following a proposed two-hit theory.

Conclusions

The discovery of a novel T-cell subset, Th-17, has opened the door to understanding a host of inflammatory diseases in a new way. Indeed, multiple auto-immune diseases have been so characterized and new therapeutics are being hypothesized. The multiple disease states that may follow a traumatic injury would also benefit from a more complete understanding, specifically lung injury following trauma and specifically ARDS. The Th-17 cytokine response is known to play a pivotal role in inflammatory diseases, as a strong recruiter of neutrophils, often results in host auto-destruction, and may be expressed by both arms of the immune system. Based on the observations concerning the role of the Th-17 response in inflammation and lung disease, a potentially important and unidentified role for the Th-17 response in immunoinflammatory lung injury after major trauma may exist.

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