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Cytokine Biology-Cytokines at the Interface of Health and Disease

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The basic goal of immune system is to defend the host against pathogenic microorganisms and cancers. However, the immune system must also remain tolerant to mutualistic microorganisms and self-tissues. Therefore a critical balance between the destruction of pathogenic insults, and the limiting of collateral damage, must be maintained by the immune system. Immune system balance, or immune homeostasis, greatly depends upon effective targeting of a pathogenic insult, when encountered, followed by a return to steady state once it has been eliminated. Cytokines, which are low molecular weight proteins secreted by numerous cell types, play a critical role in the initiation of immune responses directed against a pathogenic insult and a subsequent return to steady state [1]. Given the critical importance of cytokine biology in immune system function and homeostasis, we have compiled a special issue of the *Journal of Clinical and Cellular Immunology* entitled: "Cytokine Biology: Cytokines at the interface of Health and Disease." Within this issue we focus not only on the critical need for cytokines to initiate a proper immune response to pathogenic microorganisms and cancers, but also the deleterious effects of dysregulated cytokine signaling.

Cytokine signaling is essential for elimination of pathogens and clearance of cancerous cells [2-4]. However, excessive cytokine signaling is associated with numerous diseases, including type 2 diabetes [5]; hepatitis C virus associated liver damage [6]; and autoimmune diseases [2,6]. Once cytokines bind to their respective cytokine receptors, present on responding leukocytes, a cascade of intracellular events occur, eventually culminating in the eliciting of various effector functions sufficient to eliminate the attacking infectious agent. As cytokine receptors lack intrinsic kinase activity, they are incapable of directly responding to a given cytokine without an assessor molecule possessing tyrosine kinase ability. Cytokine receptors gain kinase activity largely through the Janus kinase (JAK) family of four proteins: JAK1, JAK2, JAK3, and Tyk2. It is widely accepted that conformational changes, mediated through receptor/cytokine interactions, allow docking of JAKs on the intracellular domain of cytokine receptor proteins. JAKs then become phosphorylated allowing them to send phosphorylate Signal Transducing and Activators of Transcription (STAT) molecules which subsequently translocate to the nucleus and mediate the transcription of the necessary cytokine specific molecules. There are currently seven known STAT molecules, whose various interactions with distinct DNA transcriptional regions are thought to mediate the multiplicity of immune responses which generally mediate the elimination of infectious agents, but can also sometimes mediate the onset of autoimmune disease. Significantly, however, how this multiplicity of immune response is obtained remains unclear. In this issue, Johnson et al reviews research supporting a hypothesis that nuclear JAK and STAT molecule specificity is conveyed by accompanying nuclear cytokines such as IFNγ [7].

The skin and mucosal surfaces form a barrier which inhibits entry of microorganisms into our tissues. However, once the critical barriers of the skin and mucosal membranes are breached, cytokines and chemokines are produced which direct immune cells to the location of the breach. Neutrophils, eosinophils, and other cells of the innate immune system proceed to eliminate pathogens, and activate the adaptive immune response. In this issue, Dr. Malter and colleagues examine the role of transforming growth factor beta and interleukin 5 in the function of eosinophils [8]. Cytokines also play a significant role in regulating the maturation, differentiation and activation of T lymphocytes, a major component of the adaptive immune response. Upon activation T lymphocyte subsets produce and respond to various cytokines, depending upon their differentiation state [9]. The cytokine interferon gamma (IFNγ, is the signature cytokine of the T helper1 (Th1) response that is generally associated with cellular immune responses. Cytokines IL4, IL5, and IL6 are produced by T helper 2 (Th2) cells and are involved in humoral immunity. Interleukin 17A (IL17) is the signature cytokine of T helper17 cells, which are involved in the elimination of extracellular pathogens and fungi [10]. A review by Dr. Yu, in this issue, provides detailed insight into the distinct T lymphocyte phenotypes [11]. Also in this issue, Dr. Isakov reviews recent findings surrounding the involvement of protein kinase C theta (PKθ) in T cell differentiation [12], which in turn regulates subsequent cytokine production.

Type 1 Diabetes (T1D) is a T cell mediated autoimmune disease whereby the insulin producing B cells of the pancreas are destroyed, resulting in the inability to regulate blood sugar [13]. Whereas IFNγ production has been strongly associated with T1D onset and progression, the role of IL17A remains unclear [14-17]. In this issue, Vuckovic and colleagues compare IL17 levels and antigen presenting cell numbers between diabetic children and their siblings [18]. Beyond the debilitating and potentially life-threatening scenarios that can be presented by the inability to regulate blood glucose levels, diabetes is often also associated with potentially debilitating complications. In this issue, Dr. A Steven provides commentary regarding angiogenic factors and cytokines involved in diabetic retinopathy [19].

Systemic lupus erythematosus (SLE) is a debilitating, multifactorial autoimmune disease possessing varied clinical manifestations including leucopenia, skin pathologies, and glomerulo-nephritis [20]. SLE onset in patients is due largely to the cumulative effects of auto-antibody production [21], dysregulated pro-inflammatory cytokine signaling [22], and decreased regulatory T cell function (Tregs) [23,24]. IFNγ production has been associated with lupus progression in both humans and rodent models [25,26]. In this issue, Dr. Yu characterizes T cell mediated cytokines involved in the pathogenesis of Sjogren's syndrome, a systemic autoimmune disease often associated with SLE, in which the secretory functions of the salivary and lacrimal glands

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are impaired [11]. Moreover, Drs. Jung and Guay describe the role of IL21 in SLE in this issue, reviewing data from both patients and several rodent models of disease [27]. As this issue focusses on cytokines at the interface of health and disease, Niu and Chen examine IL21 from the stand point of cancer clearance and autoimmunity [28]. In addition, Fourati et al. present primary data examining genetic factors contributing to SLE in Tunisian patients [29]. Of note, several cytokine related genes were examined.

Although acute inflammation (production of inflammatory cytokines for a fixed amount of time) is essential for pathogenic clearance, chronic inflammation often leads to self-tissue destruction, and possibly autoimmunity. Berger et al., within this issue, demonstrates the importance of the cytokines IFNγ and TNFα in the prevention of fungus Paracoccidioides brasiliensis induced systemic granulomatous disease [30]. In a commentary, the Chaudhuri group describes the increased clearance of gliomas by T11 target structure glycoprotein treated macrophages, which produced increased amounts TNFα and *VeGF* [31]. Moreover, Dr. Karst describes the role of type 1 interferons in regulating norovirus infections [32]. In contrast, a commentary by Dr. Pyrpasopoulou focusses on the role of TNFα in the development and progression of chronic hepatitis C infection [33]. In summary, these articles focus on the critical role of cytokines in modulating immune responses. Furthermore, these articles suggest that dysregulated immune responses-either ineffective pathogen clearance, or autoimmunity-may be corrected though specific targeting of cytokines.

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Conflict of Interest Statement

The author declares no conflict of interest.

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