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## Indeed, IL-18 is more than an inducer of IFN $\gamma$ .

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Most immune related studies on IL-18 have focused on its property to induce IFN $\gamma$ . Indeed, Haruki Okamura and coworkers described in 1995 the release of a cytokine from *Propionibacterium acnes*-primed liver macrophages stimulated with LPS 1995 and gave the cytokine the name “IFN $\gamma$  inducing factor” [1]. In this issue of the Journal, El-Darawish reports that recombinant IL-18 primes resting mouse spleen-derived NK cells to transduce effective signals, which allows IL-2 to trigger proliferation and survival of NK cells [2]. The main point of their study is that IL-18 is the driver of signal transduction via PI3/AKT, mTOR, ATG and LC3 in NK cells. IL-18 primed NK cells respond to IL-2 and increase CD25 expression. Using IL-18 deficient mouse NK cells, there is no significant expansion. There is considerable clinical importance to IL-18 in the context of NK cells survival. As described below in this commentary, IL-18 activation of NK cells is consistent with the pathogenesis of the hemophagocytic lymphohistiocytosis syndrome and the related macrophage activation syndrome. However, in their Significance Statement, the authors state “The concept that IL-18 is merely an IFN $\gamma$ -inducer limited research of IL-18 roles in other cellular processes”. We disagree with this view that research on IL-18 was limited to the induction of IFN $\gamma$ . On the contrary, research on IL-18 has been studied extensively during the last 20 years in models of human disease and cellular activation quite independent of IFN $\gamma$ .

The early studies of IL-18 focused on its similarities with IL-1 $\beta$  because the precursor forms of both cytokines require caspase-1 cleavage to convert to active cytokines. However, IL-18 is hardly a recapitulation of IL-1 $\beta$ . The precursor of IL-18 is present constitutively in epithelial cells of the skin, liver, gastrointestinal tract and kidney of healthy humans and healthy mice, whereas IL-1 $\beta$  is not constitutive in health and is not found in epithelial cells [3]. Recent interest in IL-18 comes from missense mutations in NLRP3 where loss of control of caspase-1 cleavage results in a large spectrum of inflammatory diseases termed “autoinflammatory”. In general, manifestations of autoinflammatory diseases are independent of T-cells and IFN $\gamma$ . Mice deficient in IL-18 spontaneously develop metabolic syndrome while eating a standard mouse diet. This study and several others reveal the anti-inflammatory properties of IL-18 as reviewed in [3]. IL-18 also plays a significant role in myocardial suppression, heart failure and atherosclerosis [3]. In heart failure, it is difficult to envision a role for IFN $\gamma$  [4]. Figure 1 lists properties of IL-18, which are independent as well as related to IFN $\gamma$  [3].

The importance of IL-18 as an immunoregulatory cytokine is derived from inducing IFN $\gamma$  from NK cells and T-cells, including CD8 $^{+}$  cytotoxic T-cells. Several human autoimmune diseases are associated with elevated production of IFN $\gamma$  and IL-18 (Figure 1). Diseases such as systemic lupus erythematosus, rheumatoid arthritis, Type-1 diabetes, Crohn's disease, psoriasis and graft versus host disease are mediated, in part, by IL-18 and IFN $\gamma$  production. However, the best example for IL-18 causation in disease can be found in the hemophagocytic lymphohistiocytosis (HLH) syndromes. In HLH syndromes, one can observe the phagocytosis of cells by bone marrow macrophages and hence the adjective "hemophagocytic". Primary HLH is a rare congenital disease, affecting children below the age of 1 year, due to inherited lymphocyte cytotoxicity defects. Secondary HLH occurs in adults complicating infections, lymphoma, or rheumatic diseases, especially systemic juvenile idiopathic arthritis and adult onset Still's disease. Secondary HLH is called Macrophage Activation Syndrome, MAS.

IL-18 levels in the circulation of healthy subjects are low; the mean level in the plasma of 500 healthy Dutch men and women is 163 pg/mL [5]. The increases in circulating IL-18 during sepsis, Crohn's Disease and active lupus are modest. The mean level of IL-18BP in 500 healthy subjects is 2,490 pg/mL [5], which is 10–20-fold molar excess of IL-18 in the circulation. With high affinity of IL-18BP for IL-18, levels of free IL-18 to engage the IL-18R $\alpha$  are low. The default condition in health is that most if not all the IL-18 is bound to IL-18BP.

Primary HLH and MAS are a life-threatening conditions due to a "cytokine storm" characterized by high levels of free IL-18, soluble CD25, IFN $\gamma$  and TNF $\alpha$ , generalized cytopenia with marked inflammatory lesions in the liver, and hemophagocytosis in the bone marrow. In animal models of the disease, IFN $\gamma$  plays a central pathogenic role [6]. In humans, unusually high concentrations of IL-18 have been reported [7]; however, an imbalance between IL-18 and IL-18BP results in an excess of free IL-18 [7]. Although levels of free IL-18 in the circulation are below 1 ng/mL, in inflammatory diseases such as severe sepsis, in the active phase of MAS as well as in systemic juvenile idiopathic arthritis and adult onset Still's disease, free IL-18 is usually in the range of 5–7 ng/mL. IL-18 concentrations significantly correlate with clinical status and the biologic markers of MAS such as anemia, hypertriglyceridemia, and hyperferritinemia and also with markers of Th1 lymphocyte or macrophage activation [8].

Recently, children with a mutation in NLRC4 experience a life-threatening hyperinflammation state that is MAS, mostly manifested by intractable colitis. Free IL-18 is markedly elevated (10 ng/mL) in these patients and treatment with IL-18BP provides resolution of the inflammatory state, confirming the important role of IL-18 in this disease and the pathogenesis of MAS [9]. It is intriguing to view the excessively high circulating free IL-18 concentrations in MAS and the well-known stimulatory effects of IL-18 on NK cytotoxicity and IFN $\gamma$  production. Membrane IL-18 may account for a significant effect of IL-18 on NK cells [10]. Since IL-18 stimulates CD25 expression on NK cells and induces autophagy, there is IL-2-induced NK cell proliferation as shown in El-Darawish's report [2]. That report therefore makes an important contribution to IL-18 and IFN $\gamma$ -mediated disease. Thus, neutralization of IL-18 with IL-18BP is likely to be effective in congenital HLH

syndromes and acquired MAS as well as to prevent progression to MAS in systemic juvenile idiopathic arthritis and adult onset Still's disease. Although these diseases relate to IFN $\gamma$  and NK cells, neutralization of IL-18 may be effective in heart and renal failure, diseases that have minor if any role for IFN $\gamma$ .

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**Independent of IFN $\gamma$  induction**Th2 responses

heart failure  
 neutrophil activation  
 metabolic syndrome  
 myocardial infarction  
 acute kidney injury  
 TL2 ligand induced arthritis  
 NLRC4 mutation colitis  
 neurodegeneration  
 seizures

**Related to IFN $\gamma$  induction**Th1 responses

NK cell activation  
 psoriasis  
 macrophage activation syndrome  
 Crohn's Disease  
 EAE (multiple sclerosis)  
 type 1 diabetes  
 rheumatoid arthritis  
 Wegener's Disease  
 Hemophagocytic-  
 Lymphohistiocytosis syndromes

**Figure 1.**

The role of IL-18 in disease related and unrelated to IFN $\gamma$ . These data are derived from a review of IL-18 and IL-18BP [3].