# Novel Interleukins

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The effector phases of both natural and specific immunity are in large part mediated by protein hormones called cytokines. Early studies of cytokines, extending from about 1950 to 1970, largely involved the description of numerous protein factors produced by different cells that mediated particular functions in particular bioassays. An important hypothesis generated at this time was that cytokines were principally synthesized by leukocytes and primarily acted on (other) leukocytes, and thus could be called as interleukins. The golden age of cytokine research began in the 1980s. It has been characterized by the molecular cloning and expression of individual cytokine molecules and by the production of completely specific, often monoclonal, neutralizing antibodies (1). In subsequent years, many new cytokines were discovered and many previously unexpected properties of known cytokines were revealed and occured everexpanding cytokine network.

In this article we reviewed the novel interleukins.

## Interleukin-9

Interleukin-9/P40 (IL-9) is a T helper 2 (Th2) cytokine that was described as a T cell growth factor for capable of sustaining permanent antigen-independent growth of certain Th clones (2,3). IL-9, like IL-3, appears to be a relatively specific and abundant product of activated T cells. Unlike IL-2 and IL-4, P40 appeared to act on a restricted number of Th clones and failed to show any activity on cytolytic T lymphocytes (CTL) clones or on freshly isolated T cells (2,3). However, P40 receptors (P40R) were not restricted to a few unusual Th clones, they were also detected on several T cell tumors, on macrophages and on mast cell lines. The latter point is particular interest in view of the mast cell growth factor activity recently ascribed to P40 (2). In addition to T cell stimulation, several other activities have been ascribed to IL-9, including mast cell proliferation, immunoglobulin (Ig) production and neuronal differentiation (2).

The generation of erythrocytes from bone marrow or peripheral blood progenitor cells is a complex process that is supported in culture by several different hematopoietic growth factors. Erythropoietin (Epo), the primary regulator of the levels of circulating erythrocytes in vivo, is absolutely required in culture to support the final stages of erythroid development, including hemoglobinization. The growth and development of earlier erythroid progenitors, known as erythroid burst-forming units (BFU-E) can be supported by several cytokines, including IL-3, granulocyte macrophage colony-stimulating factor, IL-4. However, each of these cytokines interacts with several different hemotopoietic cell lineages, and none of them is specific in supporting erythropoiesis. However, IL-9 in combination with Epo selectively supports the prolifariton of erythroid progenitors. Thus, IL-9 is another cytokine with the potential to serve as a regulator in both lymphoid and myeloid systems (4,5).

Granzyme A and granzyme B, two members of a family of serine esterases. The exact function of these proteases is still unclear. Granzymes are thought to be involved in CTL-mediated lysis, and MRNAs for granzyme A and B have been detected by in situ hybridization in T cells at the sites of graft rejection or tissue destruction in autoimmune diabetic animals. IL-9 induces the expression of granzyme A and B in Th clones. In addition, although the expression of these proteases was until now restricted to activated T cells, it is reported in a recent study that IL-9 can similarly induce or up-regulate the expression of granzyme B in mast cell lines. IL-9 supports the expression by Th cells of a phenotype reminiscent of mast cells and further extend the functional links between these two cell types (2).

IL-9 is a strong stimulator of in vitro cell proliferation for murine thymic lymphomas and seems to be one of the most potent cytokines to protect these cells against

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dexamethasone-induced apoptosis (6). IL-9 over expression in vivo does not significantly affect normal T cell development but results in a high susceptibility to the emergence of T cell lymphomas (2).

## Interleukin-10

When activated by antigen/antigen presenting cells, Th1 clones produce IL-2, interferon @ (IFN @) and lymphotoxin, provide limited help for B cell responses and strongly activate cell mediated responrses and Th1 cells can initiate delayed type hypersensitivity (DTH). These functions of Th1 cells are particularly appropriate for destroying the infected cells during infections by intracellular pathogens. In contrast, the Th2 cytokine pattern includes IL-4, IL-5, IL-6, IL-9, IL-10 and P600 (IL-13), and Th2 cells are stimulatory for antibody responses but inhibitory for cell mediated or DTH responses. Th2 cells stimulate B cells by production of IL-4, IL-5, IL-6 and IL-10. Some of the cross-inhibitory regulators of Th1/Th2 derivation and function are known; IFN $\alpha$ is produced by Th1 cells and inhibits the proliferation of Th2 clones (7).

IL-10 was initially characterized a cytokine produced by Th2 lymphocytes and shown to inhibit IFN$\alpha$ production by Th1 clones. Although it is known nowadays that, IL-10 is produced by a number of cell types, including $CD8^+$ T cells, mast cell lines, keratinocytes, B cells, it still appears to play a significant role in the Th2 cells (7). Several properties of IL-10 have been described including inhibition of nonimmunological cytokine production by various cell types. The expression of intercellular adhesion molecule-1 CD54 on monocytes was significantly inhibited by IL-10 (8).

In very strong Th2 responses this can lead to allergic reaction since IL-4 induces switching to IgE and IL-5 is the major growth and differentiation factor for eosinophils. Several Th2 cytokines (IL-3, IL-4, IL-9, IL-10) are stimulatory for mast cell proliferation and activation (7). But in a recent study it was demonstrated that a novel biological action of IL-10 as an inhibitor of cytokine production by stimulated mast cells (9). Besides inhibiting macrophage cytokine synthesis IL-10 has also secondary effects on macrophage function. IL-10 has positive effects on the proliferation of peripheral and particularly thymic T cells. Although IL-4 and IL-10 both inhibit synthesis of cytokines by natural killer (NK) cells, this occurs via different mechanisms, as the inhibitory effect of IL-4 is mediated directly on purified NK cells, whereas the effects, mostly stimulatory, on mouse and human B cells. On resting B cells, IL-10 induces expression of major histocompatibility complex (MHC) Class II antigens in contrast to IL-4, which also induces MHC Class II expression, IL-10 does not induce expression of CD23 indicating that IL-10 does not act via induction of IL-4. IL-10 induces differentiation of human B cells. Activated B cells secrete larger amounts of IgG, IgA and IgM, and IL-10 also induces differentiation of anti-CD40 activated B cells to morphologically resemble plasma cells. IL-10 appears to synergize with transforming growth factor $\beta$ (TGF $\beta$) in inducing human Ig Class switching to IgA. TGF$\beta$ generally inhibits the synthesis or secretion of all Ig isotypes, even of IgA by those cells that have already switched to IgA production. IL-10 inhibits the synthesis of macrophage and T cell cytokines that would otherwise contribute to an antiviral reaction. These include IFN $\alpha$, lymphotoxin and tumor necrosis factor (TNF). Thus the production of viral IL-10, which occurs in late phase of lytic infection (7).

More direct evidence for the production of IL-10 during certain immune responses has been obtained by a number of groups who have analyzed cytokine mRNA in tissue samples. IL-10 mRNA is found at higher levels in lesions of the lepramatous from of leprosy, which involves high levels of antibody production, than in the tuberculoid form, which involves more DTH-like reactions. IL-10 and other Th2 cytokines are elevated during a chronic graft versus host (GVH) reaction. In autoimmunity and transplant rejection it appears possible that the Th2 response may result in little damage or at worst, damage caused a Th1 response. Thus in this circumstance excess production of IL-10 may be beneficial. This also raises the possibility of therapeutic use of IL-10 in situations requiring inhibition of cell mediated responses (7).

## Interleukin 11

IL-11 is a novel cytokine originally cloned from the immortalized primate bone marrow derived stromal cell line PU34. Initial studies indicated that IL-11 stimulated proliferation of both the IL-6 dependent murine plasmocytoma cell line T11-65 and T cell dependent development of Ig producing B cells. In addition Musashi and coworkers have recently reported that IL-11 can augment IL-3 dependent proliferation of multipotential murine progenitors by shortening the $G_0$ period of stem cells (10-14).

Recombinant IL-11 (R IL-11) acts directly as a megakaryocyte potentiator and may play a role in regulating human megakaryocytopoiesis (14,15). IL-11 is a potent synergistic factor stem cell proliferation and expansion of progenitors in liquid culture. Thus, it appears that IL-11 may be useful growth factor in protocols involving ex vivo manipulation of stem and progenitor cells (14). IL-11 can accelerate the recovery of the peripheral blood leukocytes, mainly neutrophils and platelets in transplant mice, effects that may be clinically useful in future applications for bone marrow transplantation and chemotherapy related cytopenias (11,13,14).

Subsequent studies have shown that IL-11 plays roles other physiological processes such as adipogenesis, neuronal differentiation, osteoclastic activities. Thus,

IL-11 represents another multipotent cytokine in the ever-expanding cytokine network (12).

## Interleukin-12

IL-12 is a heterodimeric cytokine produced by macrophages, mitogen stimulated or EBV infected B lymphocytes, keratinocytes and probably dendritic cells, with important immunoregulatory functions in vitro and in vivo. It directly stimulates activated NK and T cells to produce high levels of IFN $\alpha$, enhances their cytolytic activity and promotes maturation of Th1 cells as well as IL-2 activated B cells (16-18). The recent finding that IL-12 directs the development of a Th1 type immune response from naive T cells demonstrates the critical role of IL-12 regulating the immune response. IL-12 is a potent co-stimulus of B cell differentiation and that the signals conveyed by IL-12 seem to be qualitatively distinct from the differentiative signals delivered by other cytokines such as IL-2. The characteristics of IL-12 function described above strongly suggests its potential usefulness in cancer therapy. IL-12 exerts potent antitumor effects following systemic or local administration. IL-12 can induce a curative immune response, even in the face of an aggressive micrometastazing tumor (17,19,20). R IL-12 inhibits IgE synthesis by IL-4 stimulated lymphocytes from healthy persons and influences the development of Th subset selection involved in Ig isotype selection and may be therapeutically beneficial in the treatment of allergic diseases in which allergic specific T cells characteristically produce enhanced quantities of IL-4 and IL-10 (21). In some murine infectious disease models, IL-12 was shown to be produced endogenously in response to infection and the exogeneous administration of IL-12 to mice with either infectious diseases or tumors has resulted in significant therapeutic effects. IL-12 has considerable potential for the treatment of variety of human disorders if used the appropriate conditions (22).

## Interleukin-13

IL-13 is a relatively novel cytokine produced by activated T cells. IL-13 inhibits the production of proinflammatory cytokines and chemokines by activated monocytes (23), induces B cell proliferation and differentiation including IgE production and the expression of certain adhesion molecules on endothelial cells. All these biological properties of IL-13 are shared with IL-4, but in contrast to IL-4, IL-13 does not act on T cell (24-26). The monocyte glycosylphosphotidylinostiol (GPI)-linked protein CD14 serves as the receptor for lipopolysaccharide (LPS), and regulate monocyte-lymphocyte interactions. IL-13 inhibits CD14 expression on human monocytes. Down regulation of CD14, the LPS receptor may play a major role in the anti-inflammatory effects of IL-13. IL-13 is a monocyte chemoattractant. Human IL-13 is capatle of attracting rabbit peripheral blood monocytes at those concentrations active on human monocytes. On the other hand, no neutrophil migration is induced by IL-13 (26-28).

IL-4 and IL-13 can induce osteoblast chemotaxis. They could take part in the recruitment of osteoblasts and thereby be important in the cytokine regulation of bone resorption and healing (29). Anti-tumor effects of IL-13 in vivo most probably results from pleiotropic effects including recruitment of nonspecific cells and improved stimulation of immune-specific anti-tumor effectors (30).

## Interleukin-14 (High molecular weight-B cell growth factor)

Normal human B cell growth has been shown to be dependent on cellular activation by antigen or mitogen followed by the stimulatory action of the T cell lymphokine, B cell growth factor (BCGF). Human BCGF has been reported to be heterogenous with both low (14 to 16 kd) and high (50 kd) molecular weight forms described (31). The molecular basis of neoplastic B cell growth is complex and poorly understood. Cytokines have been postulated to contribute neoplastic cell growth, and many in vitro studies have confirmed this prediction. In a study it is reported that neoplastic B cells contain this prediction. In a study it is reported that neoplastic B cells contain a high molecular weight BCGF molecule in their cytoplasm that is secreted in most cases (32,33). Ford and coworkers (34) have recently shown that the production of IL-14 by aggressive intermediate (diffuse large cell) lymphomas of the B cell type non-Hodgkin's lymphoma (NHL) in four patients with lymphomatous effusions. In this study, IL-14 was detected in the effusion fluids by Western-Blots and IL-14 mRNA was constitutively expressed in the freshly isolated lymphoma cells that also expressed the receptor for IL-14 (IL-14R) (34). These results suggest that IL-14 may be an autocrine growth factor of these lymphomas in vivo, although other factors could also be involved with growth regulation. Because exogeneous IL-14 also stimulated NHL-B cell proliferation in vitro, use of IL-14 may be paracrine, as well as autocrine (34).

The antisense studies involving the IL-14 gene, may be of significant interest in regard to the pathogenesis of NHL-B cases. They used IL-14 PT-ASO (Antisense phosphorothioate oligonucleotide) that were designed for efficient uptake. Specific inhibition of in vitro NHL-B cell growth by IL-14 ASO may indicate downregulation of the IL-14 gene, possibly through inhibition of mRNA translation. These studies show that IL-14 may play a significant role in the rapid proliferation of aggresive NHL-B. Interrupting this pathway could be useful goal therapy for patients resistant to conventional chemotherapy (34).

## Interleukin-15

IL-15 is a novel cytokine with biological functions similar to those of IL-2 but with no significant sequence homology. It mediates its functions through the β and α chains of the IL-2 receptor and its own unique @ chain (35). IL-15 induces T cell proliferation, enhances NK cell cytotoxicity and antibody-dependent cell mediated cytotoxicity, upregulates production of NK cell-derived cotokines, including IFN α, granulocyte/macrorphage colony-stimulating factor and TNF-α and can costimulate proliferation and differentiation of B cells activated with anti-IgM (36-38).

IL-15 can be detected at mRNA level in several normal human tissues including placenta, kidney and skeletal muscle (39). This cytokine may be a novel anabolic agent to increase skeletal muscle mass. Production by epithelial and fibroblast cell lines and peripheral blood monocytes has been shown but, unlike IL-2, IL-15 is not produced by activated T cells (36,37). IL-15 is also a potent T-lymphocyte chemoattractant. Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the presence of activated T lymphocytes, macrophages and synoviocytes in the synovial membrane. The mechanisms of T-cell activation in RA are currently unclear. The identification of significant levels of a macrophage derived cytokine capable of T-cell chemoattraction, activation and maturation in RA synovial fluid contributing to RA pathogenesis (37).

In vitro studies have shown induction of CTL and lymphokine activated killer (LAK) cell activity in peripheral blood mononuclear cells (PBMCs) from normal donors by IL-15 against known tumor targets The results of the study performed to investigate the role of IL-15 in generating LAK activity from melanoma patient lympocytes suggested LAK activity could be generated from melanoma patient PBMCs in the presence of IL-15 to lyse autologous tumor cells in a non-MHC-restricted manner. This new cytokine may play an important role in antitumor immunity with a possible use for cancer immunotherapy (35).

## Interleukin-16

IL-16 (formerly known as lymphocyte chemoattractant factor) is a lymphocyte chemoattractant factor of T cell origin with selective activity for $CD4^+$ T cells. In addition to its chemotactic activity. IL-16 is a competence growth fctor for CD4@+ T cells (40-42).

At sites of inflammation, mononuclear cells are in close contact with aggregated platelets. Although the physiologic role of this association is not celar, this proximity suggests that platelet derived mediators may play a role in chemoattraction of T lympocytes. In the current study it was investigated that serotonin receptor bearing lymphocyte modulation of T cell migration. Serotonin-stimulated human blood mononuclear cells secrete lymphocyte chemoattractant activity with selective activity for $CD4^+$ T cells. This chemoattractant activity was observed within two hours of exposure to serotonin and was blocked by serotonin type 2 receptor antagonists. Serotonin induced secretion of IL-16 from $CD8^+$, not $CD4^+$, T cells which did not require denovo protein synthesis. These studies describe a potential mechanism by which platelet derived serotonin in humans, might regulate the recruitment of $CD4^+$ T cells early in the course of inflammatory responses. In another study it was demonstrated that IL-16 is released following subsegmental allergen chalenge of atopic asthmatic subjects but not from normal individuals. A possible seenario in asthma is that antigen induces release of mast cell-derived platelet activating factor, which stimulates the release of serotonin. The presence of serotonin along with histamine would then induce the release of IL-16 from previously recruited of resident $CD8^+$ T cells. IL-16, in addition to other lymphocyte chemoattractans would then initiate the recruitment of $CD4^+$ cells thought to orchestrate much of the chronic inflammatory process (42).

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