

Is Interleukin 17, An Inducible Cytokine That Stimulates Production of Other Cytokines, Merely a Redundant Player in a Sea of Other Biomolecules?

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Hematopoiesis, the production of blood cells, is a dynamic process, the regulation of which under normal conditions must be a tightly controlled process (1–7). Abnormalities in this process no doubt lead to acceleration of malignant and non-malignant disorders. It is over the last 40 yr that these normal and abnormal processes have begun to be unravelled and better defined. This is in large part due to the development of *in vitro* and *in vivo* assays that recognize and allow quantitation of different subsets of hematopoietic stem and progenitor cells. Stem cells are defined as cells with multipotential lineage differentiation capacity and the ability to self-renew (make more cells of their own kind). The earliest stem cells would be those with the greatest self-renewal capacity and would include the long-term marrow repopulating cell. Stem cells with less self-renewal and differentiation capacity exist and were originally defined by the *in vivo* spleen colony forming cell assay in mice. Progenitor cells are considered to have less self-renewal capacity, but the earliest subsets of these can be multipotential.

We now know that hematopoiesis is regulated by an interacting network of cell–cell and cytokine–cell interactions (1–7). Hematopoietic stem and progenitor cells are influenced in their capacity to proliferate, differentiate, and possibly to self-renew, by accessory cell-derived biomolecules, most of which can be classified as cytokines. It is only in the last 15 or so years that our knowledge of cytokines and their actions has blossomed. This is due to the recombinant DNA technology revolution that has allowed the identification, cloning and expression of an increasing number of genes for cytokines and their receptors. We are at a stage where the *in vitro* actions of cytokines which were first noted in the laboratory are rapidly translated into preclinical and clinical studies to assess the efficacy of these cytokines for potential clinical benefit (8–12). The most obvious of these translational efforts have been with the colony stimulating factors such as erythropoietin, granulocyte colony stimulating factor, granulocyte-macrophage colony stimulating factor, and most recently, thrombopoietin.

There are now over 50 bioactive molecules that are known to influence stem or progenitor cell proliferation and differentiation by stimulating, suppressing or enhancing the stimulation or suppression of these cells (1–7, 13). These effects can be direct on the stem or progenitor cells them-

selves, actions which are most rigorously determined *in vitro* with an initial culture of a single isolated stem or progenitor cell (14–16), or the effects can be indirectly mediated. This latter effect involves accessory cells which can be induced by a number of stimuli, including cytokines, to produce and release a single, but more likely a group of cytokines (1–7, 17–23) which can then directly act on stem or progenitor cells or have a cascading effect on induction of the production or release of additional cytokines or other biologically active molecules.

Accessory cells can be mature morphologically recognizable blood cells, such as lymphocytes (both T and B cells), monocytes, macrophages and natural killer cells, or stromal cell elements such as fibroblasts, endothelial cells, epithelial cells, adipocytes and muscle cells (1–7, 17–23).

A listing of biologically active molecules with known direct or indirect effects on stem and progenitor cell proliferation and differentiation is shown in Table 1 (1–7, 24–30). This listing is not meant to be all-inclusive as new cytokines are still being discovered. It is in this context that the article by Fossiez et al. (31) in this issue of the *Journal of Experimental Medicine*, which describes the cloning and action of expressed human IL-17, is of interest. This study follows up on the cloning of murine IL-17 (cytotoxic T-lymphocyte-associated antigen-8, CTLA-8) (32) and complements the recent studies of Yao and colleagues regarding human IL-17 (33) and its novel receptor (34).

Murine IL-17 was identified as part of a search to detect novel molecules involved in functions of the immune system (32). This gene was found as a single copy in cells from mice, rats and humans and was mapped at a single site on mouse chromosome 1A and human chromosome 2q31. Murine IL-17 cDNA contained an opening reading frame that encoded a putative protein of 150 amino acids, which turned out to be 57% homologous to the putative protein encoded by the open reading frame (ORF) 13 gene of a T-lymphotropic virus, herpesvirus Saimiri. This suggested another virus-captured gene with possible functional activity. A number of such virus-captured genes, hypothesized to be important for the residency of viruses in mammalian systems, have been previously reported (reviewed in references 31–34), including that of IL-10, which has 70% homology with an EBV gene, BCRF1 (35). In the paper by

Fossiez et al. (31), the viral counterpart of human IL-17, ORF13, had some activities similar to that of human IL-17, much like BCRF1 and IL-10 that were shown to have some activities in common (35).

Of particular interest is the rather restricted set of cells that produce IL-17 (31–34). This contrasts with the ubiquitous nature of cells expressing the IL-17 receptor gene (34) although whether all cells expressing the IL-17 receptor will respond to IL-17 is not yet known. Moreover, whether the ubiquitous expression of the murine IL-17 receptor gene will also be seen in the human system will need to be evaluated. Of the large number of cell types evaluated for expression of IL-17, it is the T-lymphocytes that appear to be the major source of IL-17 (31, 33); the IL-17 gene under normal conditions needs to be induced for production of IL-17. In particular, it is the activated memory CD4⁺ T cell subset that has been implicated as an IL-17 producer (31). Whether different stimuli will be able to activate IL-17 production in other cells, and whether IL-17 itself has a role in IL-17 production remains to be determined. A number of cytokines, at first thought to be very restricted in production were later found to be more broadly produced. The exact intracellular molecular mechanisms of IL-17 production have also to be worked out. How much effort is made in this direction may reflect how relevant IL-17 is found to be in the regulation of the immune and hematopoietic systems, and whether or not IL-17 can be used in a clinical sense for treatment of certain disorders.

Upon the discovery of any new biologically active cytokine, high hopes are usually engendered that the cytokine will be of importance to a functional system and that the cytokine, or perhaps a soluble form of the cytokine receptor, may be clinically useful. Whether this turns out to be the case or not will require time and effort. That IL-17 has some interesting characteristics is clear. Human IL-17 and its virus “trapped” counterpart ORF13 have the capacity to induce the production of other cytokines from stromal cell elements, such as fibroblasts, endothelial cells and epithelial cells (31, 33). Thus, it has been determined that IL-17 can induce the release of IL-6, IL-8, G-CSF, and PGE₂, and can also enhance the surface expression of the intracellular adhesion molecule-1 (ICAM-1) (31, 33). Interestingly these induced molecules have different activities. IL-6 has been implicated in a number of activities including growth of hematopoietic stem and progenitor cells and their expansion *ex vivo* (36–38). IL-8 has been shown to have myelosuppressive activity *in vitro* and *in vivo* for stem and immature subsets of myeloid progenitors (7, 26, 39, 40). G-CSF has early and later acting effects on stimulation and acceleration of hematopoiesis, especially of the neutrophil lineage (1–7). Prostaglandin E has demonstrated enhancing activity for erythropoiesis and suppressing activity for lymphopoiesis and myelopoiesis, most specifically for monocytopenia (1–7). Thus, through the induction of production of a number of cytokines, a single cytokine can have a broad set of not entirely predictable effects that can be seen as a summation of all events, some of which have the potential of counterbalancing each other.

I can remember a time in the 1970s when scientists considered a molecule to be relevant physiologically only when a very specific function could be demonstrated for that molecule. It was considered that a molecule with many end functions could not be of significance to cell regulation. It is abundantly clear now that all cytokines are relatively pleiotropic in action. So where does this place IL-17 in the overall setting of those cytokines listed in Table 1? Many of those biomolecules listed have, as at least one of their functional capacities, the ability to induce the release of other cytokines from accessory cells, be these stromal or hemato-

Table 1. *Biomolecules with Known Direct or Indirect Actions on Hematopoietic Stem and Progenitor Cells*

Interleukins (IL)
IL-1 to IL-17
Colony Stimulating Factors (CSF)
Granulocyte (G)-Macrophage (M)-CSF
G-CSF
M-CSF
Eosinophil (Eos)-CSF (=IL-5)
Multi-CSF (=IL-3)
Erythropoietin (Epo)
Thrombopoietin (TPO)
Tumor Necrosis Factor (TNF)- α , β
Interferons (IFN)- α , β , γ
Transforming Growth Factor (TGF)- β
Activin
Inhibin
H-Ferritin
Lactoferrin
Prostaglandin (PG)E ₁ , E ₂
Vascular Endothelial Cell Growth Factor (VEGF)
Macrophage Stimulating Protein (MSP)
Chemokines
Macrophage Inflammatory Protein (MIP)-1 α
MIP-1 β
MIP-2 α (=GRO- β)
MIP-2 β (=GRO- γ)
GRO- α
IL-8
Platelet Factor (PF)-4
γ -Interferon Inducible Protein 10 (IP-10)
Monocyte Chemotactic Peptide (MCP)-1 (=MCAF)
MIP-Related Protein (MRP)-1
MRP-2
ENA-78
Steel Factor
Flt3-ligand

Information on these molecules can be found in references 1–7, 24–30.

poietic cells. Will IL-17 be found to be merely a redundant cytokine floating, after induction of its production, in a "sea" of other redundant cytokines? The full range of cytokine-induction capacities of individual cytokines is not known and perhaps someday some ambitious investigator will have the energy to do a comparative analysis of which cytokines induce the production/release of what cytokines from which cells. Some of this can already be gleaned from the literature, but it would be best for variables to be controlled within a laboratory using the same cytokines and cell preparations. This would give us some insight into the overlapping and non-overlapping inductive capacities of individual cytokines. Redundancy in action itself does not mean the biomolecule is not important. Redundancy is probably the means by which the body protects itself against insults that may disturb the production or action of one or more cytokines or cytokine receptors. Many cytokines can be currently classified in this redundant, but necessary category for "safety fall backs."

Sometimes, what a cytokine cannot do is as informative to its overall place in an interacting network as to what the cytokine can do. Steel factor (SLF) and Flt3-ligand (L) are both produced by stromal cells (30, 41) and are ligands for tyrosine kinase receptors. SLF and Flt3-L are very potent co-stimulating cytokines for early hematopoietic cells (29, 30). Whether or not SLF and Flt3-L fall into the category of IL-17-inducible proteins would be valuable information. Since cytokines can act synergistically to induce production/release of cytokines (17-20, 31), the effects of multiple cytokines would also have to be taken into consideration. This makes comparative categorizing of the cytokine inductive capacities of different cytokines an even more daunting task. Out of necessity, these studies will have to be done in vitro using highly purified cell populations and their subsets. In the paper by Fossiez et al. (31), TNF- α and IFN- γ were found to have additive effects on the IL-17-induced secretion of IL-6; while neither IL-17 nor TNF- α induced release of GM-CSF, the combination of IL-17 plus TNF- α was effective in this event. Induction of pro-

duction of cytokines by IL-17, alone and in combination with other cytokines, can be through transcriptional, post-transcriptional or the combination of transcriptional and posttranscriptional effects, and it is highly possible that the mechanisms of cytokine production will not be similar in all cases. The observation by Yao et al. (34) that murine IL-17 stimulates activity of the transcriptional factor NF- κ B, which is known to regulate a number of gene products involved in cell activation and growth control (reviewed in reference 34), offers the possibility that some of the cytokine induction effects of IL-17 may be mediated by a common intracellular event. It has been noted that both glycosylated and non-glycosylated forms of the homodimeric IL-17 molecule are secreted (31, 33). It would be of interest to know if the activities of IL-17 relate to the glycosylated state.

How these in vitro activities relate to the in vivo situation is more difficult to evaluate. One method to evaluate this is to administer IL-17 to mice. Results of such studies could set the stage for clinical evaluation of this molecule. Also, whether a portion of the IL-17 molecule or a small peptide with sequence homology to IL-17 will be shown to have similar activities may be of interest. Peptides that induce the release of cytokines are available (42, 43). A molecule or peptide that induces the release of a number of other cytokines may be of value clinically, as long as the combined effects of the induced molecules don't cancel each other out (43).

Is the function of IL-17 only to induce the production of other cytokines? Efforts in this area may be clarified through the use of mice in which the genes for IL-17 and/or the IL-17 receptor are "knocked-out." Whether these "knock-outs" will be embryonic lethal, or result in functional abnormalities could shed light on whether IL-17 is merely another molecule with redundant activities, or if functions of IL-17 not yet recognized are in the offering. The ubiquitous expression of the IL-17 receptor gene (34) suggest the possibility of other functions for IL-17. Moreover, abnormalities could suggest a role for IL-17 in human disease progression.

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