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PROSPECT SYMPOSIUM

Cytokines: Molecular Keys to Homeostasis, Development, and Pathophysiology

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Abstract Identification and definition of the role and diversity of action of cytokines, the regulatory proteins including lymphokines, monokines, interleukins, interferons, and a variety of other growth factors produced by virtually every nucleated cell into the body and having pleiotropic regulatory effects on hematopoietic and many other cell types [Thompson, 1991], are in the forefront of biomedical research. The explosive development of cytokine research is reflected by the inclusion of "cytokine," first introduced as a term in 1974 to recognize that lymphokines could be produced by other than lymphoid cells in 4,267 biomedical articles published by the end of 1992. From the initial reference to cytokines in 1974 to inclusion in 45 articles in 1985, the doubling of citations each succeeding year, together with 45% of all the citations since 1974 occurring in 1992 alone, attests to the continued rapid expansion of this area of biological research. The important roles of cytokines in many physiological processes and pathophysiological conditions, although largely descriptive in nature, were recognized during the early development of this field of investigation [Balkwill and Burke, 1989; Cohen et al., 1974]. Current and future directions, as highlighted by the series of Prospect articles featuring areas as diverse as embryologic, extracellular matrix, bone, hematologic, and neurologic development and function as well as in the organism's response to foreign organisms in this issue of the Journal, are focused on broadening our understanding of the positive and negative influence of cytokines in normal and abnormal differentiation and development and on the molecular pathways underlying cytokine action. The broad areas of cellular biochemistry represented by the Prospects, moreover, emphasize the synthesis and convergence of cytokine research towards an understanding of the critical controls in development and homeostasis.

Key words: cytokine, lymphokine, interferon

For the developmental biologist, dissection of the mechanisms of autonomous developmental behavior is of great interest and growth factors, including EGF, PDGF, insulin-like, and TGF-β, have naturally received the most attention, writes Eileen D. Adamson in her Prospect, "Activities of Growth Factors in Preimplantation Embryos" [this issue]. The number of cytokines has blossomed with adoption of the RT-PCR technique to embryos during the past few years and Adamson provides a synthesis of rapidly evolving descriptions of autocrine and paracrine cytokines in the growth and differentiation of embryos. The positive and negative influence of cytokines are also important in the later stages of the pre- or peri-implantation embryo as the embryo meets the challenge of the mother's immune system. Problems of potential redundancy, autocrine versus paracrine action, and converging or overlapping signal pathways keep individual cytokine roles speculative at present and, as Adamson stresses, each of the components that appear to have a role in preimplantation development will have to be tested by gene ablation and cross-breeding studies. Clues to specific roles of cytokines also come from other molecular and biochemical approaches seeking to unravel the pleiotropic action of cytokines. Expression of matrix metalloproteinases (collagenases, stromelysins, and gelatinases) capable of degrading extracellular matrix and basement membrane components is greatly modulated by cytokines and growth factors as described by Alain Mauviel in his Prospect, "Cytokine Regulation of Metalloproteinase Gene Expression" [this issue]. Mauviel proposes that cytokines are important in matrix remodeling during normal physiologic processes such as embryonic development with cytokine overexpression initiating or contributing to pathological conditions such as cartilage degradation or to tumor progression or metastasis. In another area of growth and development Gregory R. Mundy in his Prospect, "Role of Cytokines in Bone Resorption," [this issue]

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discusses evidence that it has always appeared likely that primary control of bone resorption is mediated by local factors generated in the microenvironment of each bone remodeling packet. Mundy points out that there is considerable overlap among cytokines stimulating osteoclastic bone resorption and among cytokines which are involved in normal hematologic and lymphoid cell differentiation, e.g., M-CSF and GM-CSF, although the mechanisms controlling the release of the cytokines and pathways of their action are still unknown.

Cytokines represent one of the most important elements in the communication among different cell types and reciprocal cytokine interaction between phagocytic cells and lymphocytes, particularly natural killer (NK), T, and B lymphocytes, is of central importance in the regulation of both the innate and the immune resistance, the theme of Giorgio Trinchieri et al. in their Prospect, "Cytokine Crosstalk Between Phagocytic Cells and Lymphocytes: Relevance for Differentiation/Activation of Phagocytic Cells and Regulation of Adaptive Immunity" [this issue]. In yet another area of cytokine physiological communication, hormone secretion from the pituitary, cytokines are now recognized to play an important role in modulating the neuroendocrine system, the interest of Linda C. Payne et al. in their Prospect, "Hypothalamic Releasing Hormone Mediates The Effects of IL-1 on Sleep," [this issue] they clarify recent evidence linking IL-1 to growth hormone releasing hormone and to corticotropin releasing hormone in regards to their effects on sleep. Caleb E. Finch et al. in their Prospect, "TGF-β1 is an Organizer of Responses to Neurodegeneration," [this issue] further define cytokine neurophysiological/pathological interactions. Reviewing evidence from TGFβ1 interactions with neural elements and hormones, they suggest that TGFβ peptides have organizing roles in responses to neurodegeneration and brain injury, including immunomodulation, neuroantiproliferation, and neuroprotection and promote synaptic reorganization by effects on neural adhesion molecules and on the extracellular matrix.

The previously recognized importance of cytokines in bacterial infection have in recent years been extended to viral and parasitic diseases providing insights into physiology and pathophysiology, as well as potential new avenues for therapeutic intervention. In an additional example of cytokine regulation of differentiation, Steven L. Reiner and Richard M. Locksley in their Prospect, "Cytokines in the Differentiation of Th1/Th2 $CD4^+$ Subsets in Leishmaniasis," [this issue] describe the usefulness of experimental murine leishmania to study Th1/Th2 lymphocyte development and the protective role of Th1 ($CD4^+$ helper lymphocyte clones producing IFN-γ, lymphotoxin, and IL-2 and mediating delayed type hypersensitivity) in comparison with the non-protective role of Th2 ($CD4^+$ T helper lymphocyte clones producing IL-4, -5, -6, and -10 and helping B lymphocyte function) lymphocytes in the development of murine leishmaniasis and its application to human homeostasis and resistance to infection. They propose that understanding the basis of the presumed cytokine dependent "switch" (Th1 to Th2 lymphocytes) is critical not only for the development of effective vaccines against Leishmania, but for the understanding of the most fundamental of decisions made by the developing $CD4^+$ effector populations against antigens as a general homeostatic response. In another recent unrelated yet supportive study, François Erard et al. [1993] have described an IL-4 dependent switching mechanism where CD8 cytolytic T cell responses can be turned into IL-4, -5, and -10 cytokine producing responses, i.e., the cells under the direct influence of IL-4 have "switched" to become $CD8^-CD4^-$ lymphocytes that make Th2 type cytokines and help B cells.

New developments in cytokine virus interactions differing from the classically recognized ability of interferons to prevent virus infection are occurring at both the virus and the cellular levels. At the virus level, William S.M. Wold in his Prospect, "Adenovirus Genes That Modulate the Sensitivity of Virus-Infected Cells to Lysis by TNF," [this issue] discusses novel adenovirus proteins that counter the antiviral effect of TNF and their potential for study of TNF signal transduction. In recent years a number of other examples of virus genes or gene products that block cytokine or related immunologic action have been recognized and are providing important clues to understanding pathways of cytokine action [Gooding, 1992; Barinaga, 1992]. Cytokines can also affect virus gene expression. In his Prospect, "Cytokine Involvement in Viral Permissiveness and the Progression of HIV Disease," [this issue] Salvatore T. Butera relates, using HIV-1 as an example, ways that cytokines can influence not only virus expression but also virus host range and virus receptor expression.

Recent studies in other laboratories show that cytokines, e.g., TGF-β, IFN-γ, and leukoregulin, can specifically down-regulate expression of the early E6 and E7 genes of human papillomavirus [Woodworth et al., 1992] and that leukoregulin can enhance the antiviral action of acyclovir in cells acute infected with herpessimplex virus [Hooks et al., 1991]. Cytokine interactions in bacterial, viral, and parasitic infections offer unique opportunities to study cytokine signal transduction and modulation of gene expression that may be helpful in further delineating the control of cytokine expression and pathways of molecular action.

The series of cytokine Prospect articles in this issue of the *Journal of Cellular Biochemistry* illustrates our increasing understanding of the pleiotropic actions of cytokines in the positive and negative regulation of cellular development, function, and homeostasis. Although many of the observations are by their early nature descriptive, the continuing development of increasingly sensitive and introspective analytic methods such as RT-PCR, transgenic and knockout animals, and delineation of cytokine virus interactions provide powerful new approaches to dissect and define the molecular pathways and actions of cytokines. The field is new and the prospects are bright that we will continue to define and understand these molecular keys controlling the many stages of biological growth and development.

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