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بعض الوثائق الأصلية تالفة

بالرسالة صفحات لم ترد بالأصل

A STUDY OF INTERLEUKIN-2 RECEPTOR EXPRESSION IN INFANCY AND EARLY CHILDHOOD

الرسالة مقدمة للحصول على درجة الماجستير

Thesis

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Chapter I

INTRODUCTION

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Background

Cytokines are polypeptide products of activated lymphocytes and other cells that participate in a variety of cellular responses including those regulating the immune system.[1] They are released in response to antigens, but in contrast to the biochemical composition of antibodies, their structure is not determined by that of the stimulating antigen. Since most cytokines possess more than one biologic property; a nomenclature that employs the term "interleukin" followed by a number has been developed.[2]

Interleukin 2 (IL-2) is produced by activated T-lymphocytes. T-cells are special lineage of lymphocytes that arise from maturation of stem cells in the thymus, hence the name T-cells.[3] Progenitor cells from either the bone marrow or fetal liver enter the thymus and undergo stages of differentiation resulting in migration of mature T-lymphocytes into the blood and peripheral lymphoid tissues. Inside the thymus, the immature cells acquire surface receptors and differentiate into cluster of differentiation 4 ($CD4^+$ helper cells) or cluster of differentiation 8 ($CD8^+$ suppressor cells).[4] CD4 and CD8 T-cells represent about 70% and 25% respectively of the total T-cell population in the blood and peripheral lymphoid tissues. Minor subsets can express neither receptor or both receptors and account for the remaining 4% and 1% respectively.[5] CD4 and CD8 are membrane glycoproteins that bind to class II and class I major histocompatibility complex (MHC) antigens respectively.[6]

T-lymphocytes initiate immune responses, mediate antigen-specific effector responses and regulate the activity of other leukocytes. These regulatory effects are carried-out through the production of potent cytokines; namely the interleukins. An important one produced by activated T-lymphocytes is IL-2.[7]

Interlukin 2

IL-2 was first identified in 1975 as a growth-promoting activity for bone marrow-derived T-lymphocytes. Since then, the spectrum of its recognized biological activity has expanded significantly to include direct effects on the natural killer (NK) cells, lymphokine activated killer cells (LAK), monocytes, macrophages and oligodendrocytes.[3] The biological effects of IL-2 are mediated through the binding of this growth factor to specific receptors present on these various cellular targets, the interleukin-2 receptor (IL-2R).

IL-2 is a 15.5 glycoprotein produced by activated T-cells. Some studies suggest that activated B-cells may share in the ability to produce IL-2. The complete primary structure of IL-2 in eight mammalian species has been deduce by cloning of human, gibbon, ape, murine, bovine, rat, sheep and porcine IL-2 c-DNA. Substantial similarity is seen across these species.[9] The human IL-2 gene has been mapped to chromosome 4q band 26-28. The three dimensional structure of the human IL-2 protein remains the subject of some controversy.[10]

Independent of its effects on T-cell proliferation, IL-2 also stimulates T-cells to secrete other lymphokines as IL-4 and gamma interferon. Resting B-cells, activated by antigens, also express high affinity IL-2 receptors, yet at a 10 times lower level than T-cells. So, IL-2 may promote the growth of these B-cells as well as induce their differentiation processes and secretion of immunoglobulins. Such latter response is, for example, mediated via the induction of J-chain m-RNA, needed for the synthesis of IgM pentamers.[11]

Interleukin-2 Receptor

Important advances have been recently made in defining multicomponent structure and ligand-binding properties of the high affinity IL-2R complex. This high affinity Interleukin-2 receptor (IL-2R) has now been shown to consist of distinct IL-2 binding membrane-associated components. IL-2R is composed of 3 distinct membrane-associate subunits: a 55 KDa alpha chain (IL-2R alpha), a 75 KDa beta chain (IL-2R beta) and a 64 KDa gamma chain (IL-2R gamma). While these subunits also bind IL-2 with very low affinity, heterodimerization and heterotimerization of the subunits permit binding with intermediate and high affinity respectively.[12] Although substantial progress has been made in defining the molecular properties of IL-2 and its cellular receptor, the precise mechanism by which the ligand-receptor complex transduces growth-promoting intracellular signals remains unclear. However, several studies suggest that activation of receptor-associated tyrosine kinase(s) may be involved.

The progress in the characterization of the human high affinity IL-2R complex was facilitated by the development of a sensitive IL-2 bioassay and a receptor binding bioassay. Purified, radiolabelled IL-2 for these receptor binding assays was either isolated from IL-2 secreting cell lines or produced by recombinant DNA technology. Another major advance in the analysis of the IL-2 R was the generation of anti-receptor monoclonal antibodies. The first anti-IL-2R antibody was prepared using tumor cells from a patient with adult T-cell leukemia as the immunogen. This antibody did not bind to normal resting T-cells but did react strongly with mitogen-activated T-cells, hence the name anti-Tac (T activated). This antibody blocks the binding of IL-2 to the high affinity IL-2R and also inhibits IL-2 induced proliferation. The binding is especially to the alpha subunit. The human IL-2R alpha gene was cloned and localized to chromosome 10p band 14-15.[13-15]

* *The alpha chain of IL-2R*

The alpha chain is a 55 KDa glycoprotein from the surface of the high affinity IL-2 binding cells. Affinity columns prepared either with immobilized anti-Tac or IL-2 reacted with some p55 protein and amino-termianl amino acid sequence information derived from the purified p55 polypeptide, thus permitting the isolation of full length IL-2R alpha cDNA clones.[16-21]

* *The beta chain of IL-2R*

The beta chain is a 75 KDa glycoprotein from the surface of the high affinity IL-2 binding cells. Affinity columns prepared either with immobilized anti-Tac or IL-2 reacted with some p75 protein and amino-

termianl amino acid sequence information derived from the purified p75 polypeptide, thus permitting the isolation of full length IL-2R beta cDNA clones. IL-2R beta chain alone forms the intermediate affinity receptor. Together IL-2R alpha and beta form the high affinity receptor[22-25]

* *The gamma chain of IL-2R*

Affinity columns prepared either with immobilized anti-Tac or IL-2 reacted with some p64 protein and amino-termianl amino acid sequence information derived from the purified p64 polypeptide. The gamma chain is a 64 KDa glycoprotein from the surface of the high affinity IL-2 binding cells. Together IL-2R alpha, beta and gamma form the high affinity receptor[26-27]

Function of the IL-2/IL-2R system

The de novo synthesis and secretion of IL-2 and the expression of high affinity IL-2R represents early consequences of antigen or mitogen-induced activation of resting T-cells. The subsequent interaction of IL-2 with the high affinity receptors promotes the rapid clonal expansion of the effector T-cell population originally activated by antigen. The subsequent decline in both IL-2 synthesis and high affinity receptors display contributes to the normal termination of the T-cell immune response. In addition to its growth-promoting function, the IL-2 stimulates T-cells to produce other lymphokines, including interferon gamma and IL-4 revealing its capacity to act as a differentiation signal. While the role of IL-2 in the growth of T-cells activated via the T-cell receptor (TCR) by antigen is well established,