IMMUNOLOGY

Pre-Master – Biochemistry Department
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Introduction

The main function of our immune system is to protect us from infection in its various forms, and one of the greatest discoveries in medicine, immunization, was put into use and saved millions of lives one and half century before there were any real scientific understanding of the mechanism involved. But the immune system is a coin with two sides. For a few people, when the coin spins, it falls into the unfavorable side, and then instead of functioning purely as a protective mechanism, immune reactions harmful to the host are produced.

Because immune reaction can involve any system of the body, immunology has spread its roots into most branches of medicine. In addition of dealing with harmful conditions resulting from activity of the immune system, clinicians are now more involved than ever in dealing with patients who have diminished immune function.

Clearly therefore, an understanding of immunology leads to a wider appreciation of the role of the immune system in health and disease conditions such as tumors and hopefully in the future to improved management through immune therapy.

Cytokines

The term cytokines, which include **lymphokines**, **monokines**, **interleukines** and **interferons**, is collectively employed to designate a heterogeneous group of proteins which are produced by a wide variety of cells, lymphoid and non-lymphoid, and that induce similar, distinct, synergistic or even contradictory signals. This heterogeneous group of proteins has a number of common characteristics as follow:

- Cytokines are of low molecular weight (<80 kDa).
- Unlike endocrine hormones, they are produced transiently and locally.
- Having very short half lives.
- They are produced in very small quantities but are extremely potent, generally acting at femtomolar concentrations (10^{-15} M).
- They interact with high affinity cell surface receptors specific for each cytokine or cytokine group.

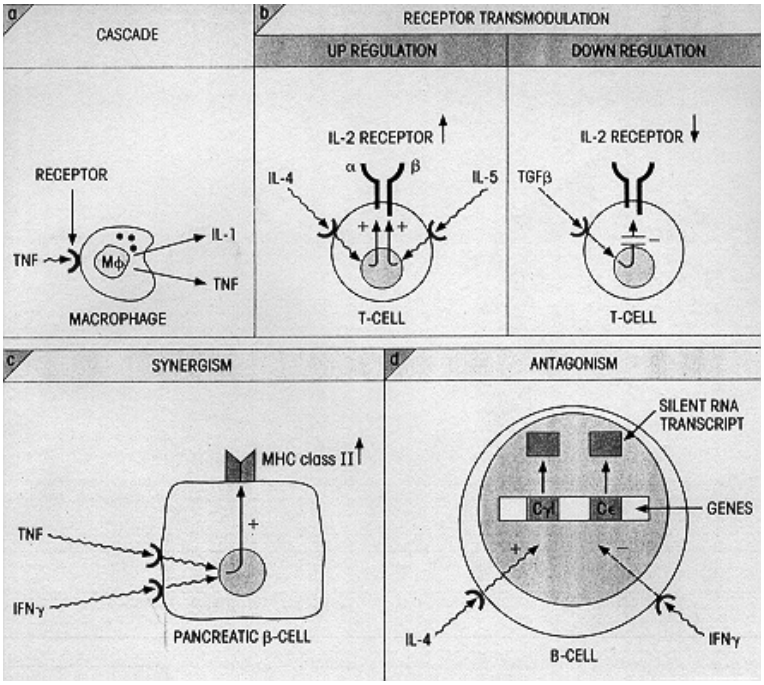

Figure 1: Network interactions of cytokines.

Cytokines regulate the amplitude and duration of the immune inflammatory responses. They must therefore be produced in a transient manner tightly regulated by the presence of foreign material. In general, they are **pleiotropic**, i.e. with multiple effects on growth and differentiation of a variety of cell types and there is considerable overlapping and redundancy between them, partially accounted for by the induction of synthesis of common proteins. Interaction between different cytokines may occur through a **cascade** in which one cytokine induces the production of another, through transmodulation of the receptor for another cytokine and through **synergism** or **antagonism** of two cytokines acting on the same cell as shown on Figure 1.

Different T cell subsets make different lymphokines

In the mouse, long term T helper (Th) clones can be divided into two types with distinct cytokine secretion as shown in Table 1. This make biological sense in that Th1 cells producing lymphokines like IFN-γ would be especially effective against intracellular infections with viruses and organisms which grow in macrophages, whereas Th2 cells are very good helpers for B cells and would seem to be adapted for defense against parasites.

Table 1: Some cytokine patterns of mouse T cell clones.

	Th1	Th2
Cytokines	IFN-γ	IL-4
	IL-2	IL-5
	TNF-β	IL-6

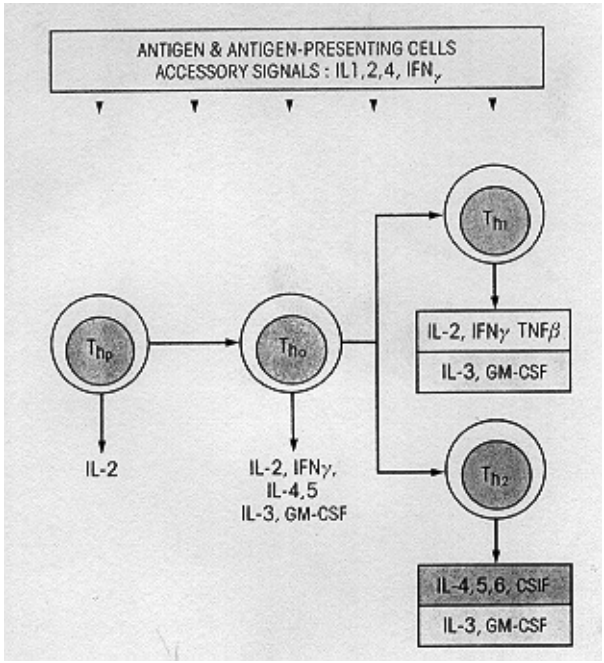

Figure 2: Possible T-helper phenotypes and their interrelationships.

IL-2

Interleukin 2 (IL-2) was originally discovered in **tissue culture** supernatants from human peripheral blood lymphocytes stimulated with T cell specific **mitogen**.

Cloning data for the mouse sequence suggested that IL-2 is initially translated as a 169 amino acid polypeptide. Mouse and human IL-2 share a 70-76% homology at the nucleotide level and 63% homology at the amino acid level.

IL-2 exerts its effects through a specific receptor system found primarily on T cells, B cells and natural killer (NK) cells. The IL-2 **receptor** is a multi-subunit system consisting of a 55 kD alpha-subunit and 70 kD beta-subunit. Whereas the beta subunit it expressed on resting T cells, the alpha subunit expression must be induced by mitogenic stimulation.

A soluble form of IL-2 receptor (sIL-2R) has also been identified, which is released by mitogen-activated or antigen-activated T cells. The soluble IL-2R has been studied as a marker for T cell involvement in a number of disease states including autoimmune disorders, malignancies, transplant rejection, and

infectious diseases. Measurement of the soluble IL-2R may serve to monitor the severity and progression of a disease, as well as the efficacy of treatment.

In addition to its traditional effects on T cell growth, IL-2 has been reported to:

- participate in the activation, tumoricidal activity, and growth of NK cells;
- B cell growth and immunoglobulin production
- interferon-gamma production
- induce IL-6 production by human monocytes

IL-4

Interleukin-4 (IL-4) was described in 1982 by William Paul and co-workers upon discovering that supernatants from PMA-stimulated EL-4 thymoma cells.

IL-4 is a pleiotropic cytokine produced by T cells, mast cells and activated human basophils that regulates a wide range of B cell responses including proliferation, expression of MHC class II antigen, and expression of IgG and IgE molecules.

IL-4 induces proliferation of T cells and mast cells, both activation and suppression of various macrophage functions.

IL-4 is a complex glycoprotein with an apparent molecular weight of 18-20 kDa.

Human and murine IL-4 share 50% homology at the amino acid level but there is no species cross-reactivity.

In contrast to IL-1, IL-6 and IL-10, which are produced by a wide variety of cell types, IL-4, like IL-2 and IFN-γ, is produced by a small number of cell types. IL-4 production is concentrated among the Th2 subset of activated T cells.

IL-4 exerts its biological activity through a specific high affinity receptor expressed by resting T cells, B cells.

IL-4 binds to a receptor that has two subunits, the 140 kDa IL-4R alpha chain, and the 75 kDa subunit. The sIL-4R has been shown to bind IL-4 with high affinity and to inhibit its biological effects.

The biological activities ascribed to IL-4 involve a wide range of cell types and include:

- induction of the differentiation of T helper cells into Th2 cells;
- upregulation of MHC Class II expression in resting B cells;
- enhancement of IgG1, IgE and sIgM production by B cells;
- regulation of circulating IgE levels associated with parasitic infections;
- inhibition of the ability of activated macrophages to kill a variety of intracellular and extracellular pathogens

As a multifunctional cytokine that augments certain T and B cell response, IL-4 is being researched for potential application as a therapeutic agent in several areas, including:

- reconstitution of cellular and humoral immune function following bone marrow transplantation;
- treatment of rheumatoid arthritis;
- counter-balancing of the Th2 over-expression observed in diseases such as allergy and possibly AIDS;
- growth inhibition of solid tumors and B cell lymphomas
- reduction in inflammatory processes through down-regulating the production of IL-1, TNF and IL-6.

IFN-γ

The interferons (IFNs) were initially described by their abilities to induce anti-viral immune response, and were subsequently divided into two groups.

Type I IFNs are induced primarily by viral or bacterial insult, and include leukocyte-derived IFN-alpha, and fibroblast-derived IFN-beta.

Interferon-gamma (IFN-γ) is the sole representative of the Type II interferons. It is apparently produced exclusively by T lymphocytes and NK cells in response to mitogenic or antigenic stimulation, and provides the first line of antiviral defense.

IFN-gamma may be distinguished from IFN-alpha and IFN-beta by its higher apparent molecular weight, sensitivity to pH, thermal stability, and differential anti-viral activity. Murine IFN-gamma is a 136 amino acid polypeptide that exhibits only about 40% homology with the human form, which may contribute to the apparent lack of species cross-reactivity.

IFN-gamma binds to a high-affinity cell-surface receptor of approximately 90 kD, which consists of a 228 residue extracellular domain, a transmembrane domain, and an intracellular domain of 200 amino acids.

Despite the crucial role played by IFN-gamma in anti-viral defense, research has focused recently upon its immunoregulatory activities, particularly in the area of T helper cell development.

Additional reported activities for IFN-gamma include: induction/augmentation of MHC class I and II antigens on macrophages, T and B cells; induction and modulation of macrophage antigens; induction of B cell proliferation, differentiation, and secretion.

IFN-gamma is also reported to provide therapeutic effect in animal models, for the treatment of rheumatoid, hepatitis B and C, and more recently, in the control of intracellular parasites including leischmaniasis and schistosomiasis.