

CYTOKINES.

Interferons :

Type I interferons : induced by viral infections, and during immune responses to antigens, under the influence of activated T-cells.

IFN- α : there are 20 related varieties, major source is the macrophage.

IFN- β : one gene product, source is the cultured fibroblast.

However, many cells produce both types.

Viral infection is the most potent natural inducer of INF type I .

All INF's bind to the same surface receptor on cells and produce the same effects.

IFN type I induces an anti-viral state in the cell and its neighbours, (inhibits viral replication and cell proliferation), promotes NK cell killing action of virally infected cells, increases expression of MHC class I molecules on virally infected cells.

Type II interferons :

INF- γ : produced by naive T-cells, TH1 helper cells, and all CD8 cells, also by NK cells.

It induces an anti-viral state, (structurally not related to other INF's.).

Activates macrophages and neutrophils, respiratory burst.

Increases expression of class I and II MHC molecules and Fc receptors.

Increases NK cell activity and Cytotoxic cells, > than INF type I.

Promotes growth of TH1 and CD8 cells, suppresses TH2 cells.

Switches to IgG2a and IgG3 synthesis. Inhibits IgE production.

Interleukins :

IL-1 :

Product of activated macrophages especially by LPS. It may also be produced by endothelial and epithelial cells. It is a major inflammatory mediator in natural immunity. Acts on endothelia to promote coagulation, and to induce endothelial adhesion molecules.

Promotes acute phase protein production of TNF.

It is pyrogenic of TNF.

If produced in large quantities, it may initiate cachexia of TNF.

Does not cause septic shock.

It acts on macrophages and endothelial cells to produce more IL-1 and IL-6.

IL-2 :

Produced by activated CD4 cells.

CD8 cells produce small amounts

It is the major growth factor of T-cells, autocrine and near-by T cells (paracrine). Promotes production of INF- γ and lymphotoxin.

Stimulates growth of NK cells to LAK cells, (promotes INF- γ production). It also activates macrophages.

Promotes growth of B-cells and antibody synthesis. (no switching).
It may also induce apoptosis of T cells (when present in large amounts) which is intriguing !

IL-4 :

Produced by TH2 cells (TH1 cells produce IFN γ and IL-2), also by mast cells. Naive cells produce mainly IL-2 upon exposure to antigen, then the T-cell progeny develops according to the antigen and the cytokines present. Helminths favour TH2 proliferation.

Growth factor for TH2 cells, depresses TH1 cells.

Inhibits macrophage activation. So does IL-10. It also stimulates growth of B cells.

Required for IgE switching.

Growth factor for mast cells.

Induces VCAM-1 on endothelia (vascular cell adhesion molecule).

It enhances activity of CD8 cytolytic cells.

IL-5 :

Produced by TH2 cells and activated mast cells..

Stimulates growth and activation of eosinophils.

Increases synthesis of IgA from mature B cells.

IL-6 :

Produced by phagocytes, endothelial cells and fibroblasts, in response to microbes and other cytokines.

Induces acute phase proteins.

Growth factor for activated B cells.

IL-8 :

Produced by phagocytes.

Acts as chemokine attracting PMN.

IL-10 :

Produced by TH2 cells and macrophages, also by mast cells and B cells.

It inhibits macrophages and their cytokine production (suppression). Thus it is a regulatory factor in macrophage activation.

It may be a switching factor for IgG4.

Inhibits TH1 and NK cells, but not B cells, it stimulates B cells to produce antibodies in vitro the significance of this is not known.

IL-12 :

Produced by monocytes and dendritic cells, induced by LPS and intracellular bacteria and virus infection..

Most potent NK cell stimulator, and also T cells to produce Interferon gamma which in turn activates the macrophages.

Enhances growth and differentiation of TH1 and CD8 cells.

IL-3 (CD4 cells, works with IL-5), IL-7 (marrow stromal cells), IL-9 (Haematopoiesis), IL-11 (marrow stromal cells) : stimulate bone marrow haematopoiesis.

TNF (cachectin, TNF- α)

Produced by activated macrophages especially by LPS.

Main function in innate inflammatory response. Induces adhesion molecules on endothelia, induces endothelial cells and macrophages to secrete chemokines.

Activates neutrophils. Stimulates macrophages.

It induces apoptosis in some cell types the significance of this is not understood.

Systemic effects :

Pyrogen by acting on the hypothalamus inducing synthesis of prostaglandins, this can be blocked by aspirin..

Acute phase response : by acting on hepatocytes increasing synthesis of certain proteins.

Reduces myocardial contractility and vascular smooth muscles leading to hypotension (septic shock).

Activates coagulation system. Killed tumour cells through thrombosis of blood vessels.

Bone marrow suppression.

Chronic administration leads to cachexia, suppression of appetite and interference with fat metabolism.

Lymphotoxin (TNF- β) :

Produced by activated T-cells.

Similar to TNF, but has no systemic effects because it is produced in small amounts.

Activates neutrophils. Tumour cell activity.

Activates vascular endothelial cells (adhesion).

TGF- β (transforming growth factor) :

Produced by activated T-cells and macrophages, and many other cell types.

It has an inhibitory effect on inflammation and immune cells both T and B cells and macrophages. Thus it may signal for shutting off immune responses

Required for IgA switching (in mice).