

## **Control of IL-2 gene transcription**

Transcription of IL-2 is one of the key elements in preventing the signaled T-cell from lapsing into anergy and is controlled by multiple receptors for transcrip-

tional factors in the promoter region (figure 9.5). The key enzyme MAP kinase phosphorylates the Jun protooncogene, which then binds as a binary complex with Fos to the **AP-1** site, deletion of which abrogates 90% of IL-2 enhancer activity.

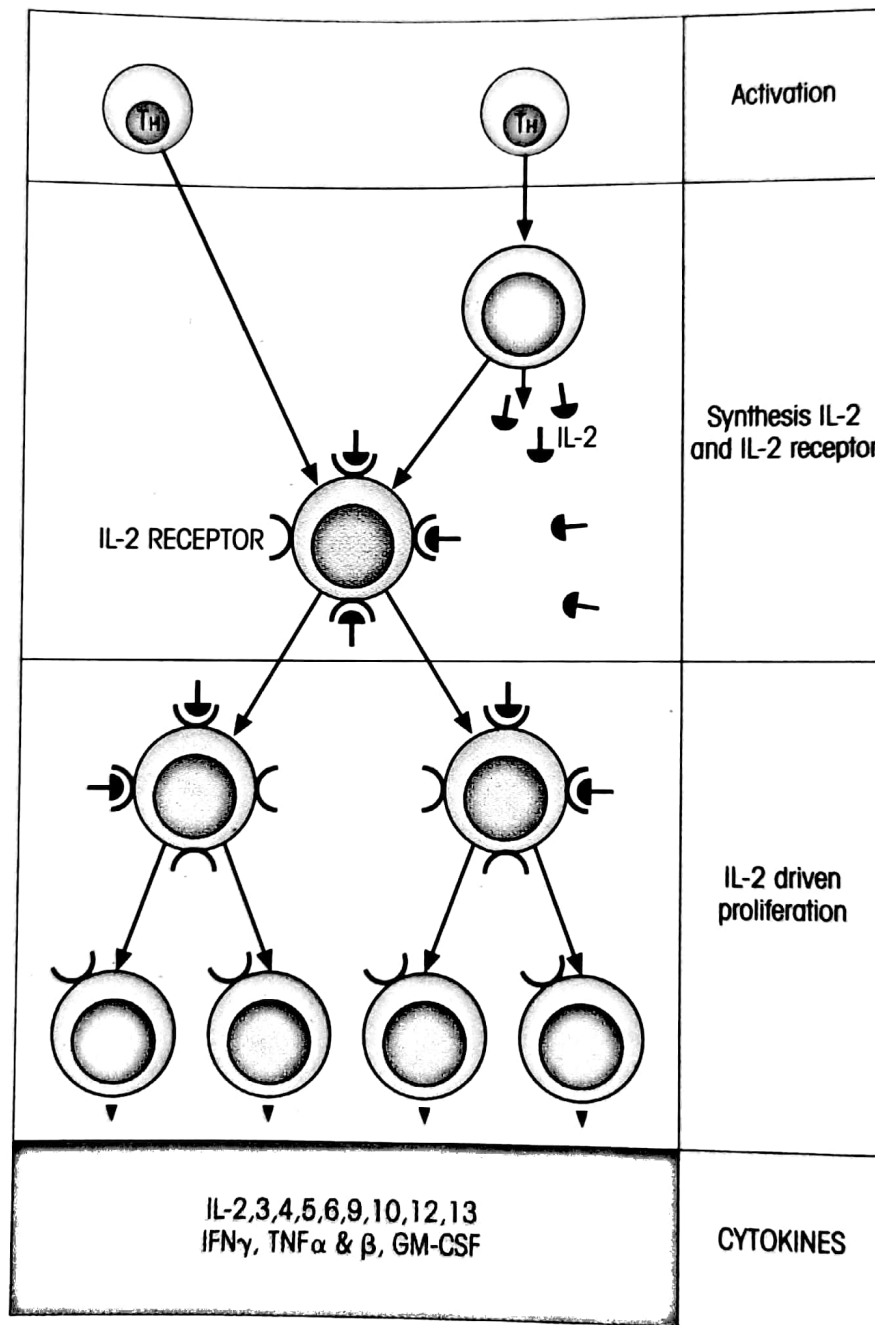
Under the influence of calcineurin, the cytoplasmic component of the *nuclear factor of activated T-cells* (**NFAT<sub>C</sub>**) becomes activated and translocates to the nucleus where it forms a binary complex with **NFAT<sub>N</sub>**, its partner which is constitutively expressed in the nucleus. The NFAT complex binds to two different IL-2 regulatory sites (figure 9.5). Note here that the calcineurin effect is blocked by the anti-T-cell drugs cyclosporin and FK506 (see chapter 17). PKC brings about the liberation of another transcriptional factor **NFκB** from its inhibitor **IκB**. In addition, the ubiquitous transcriptional factor **Oct-1** interacts with specific octamer binding sequence motifs.

We have concentrated on IL-2 transcription as an early and central consequence of T-cell activation but finally, many genes become activated leading to T-cell proliferation and the synthesis of several other cytokines and their receptors (see chapter 10).

CYTOKINE	SOURCE	EFFECTOR FUNCTION
<b>INTERLEUKINS</b>		
IL-1	Mφ, fibroblasts	Proliferation activated B- & T-cells; induction PGE <sub>2</sub> & cytokines by Mφ; induction neutrophil & T-adhesion molecules on endothelial cells; induction IL-6, IFNβ1 & GM-CSF; induction fever, acute phase proteins, bone resorption by osteoclasts
IL-2	T	Growth activated T- and B-cells; activation NK cells
IL-3	T, MC	Growth & differentiation hematopoietic precursors
IL-4	CD4 T, MC, BM stroma	Mast cell growth
IL-5	CD4 T, MC	Proliferation activated B-, T-, mast & hematopoietic precursor; induction MHC class II and FcεR on B-cells, p75 IL-2R on T-cells; isotype switch to IgG1 & IgE; Mφ APC & cytotoxic function, Mφ fusion (migration inhibition)
IL-6	CD4 T, Mφ, MC, fibroblasts	Proliferation activated B-cells; production IgM & IgA; proliferation eosinophils; expression p55 IL-2R
IL-7	BM stromal cells	Growth & differentiation B- and T-cell effectors, & hematopoietic precursors; induction acute phase proteins
IL-8	Monocytes	Proliferation pre-B, CD4- CD8- T-cells & activated mature T-cells
IL-9	T	Chemotaxis & activation neutrophils
IL-10	CD4 T, B, Mφ	Growth and proliferation T-cells
IL-11	BM stromal cells	Inhibits IFNγ secretion; inhibits mononuclear cell inflammation
IL-12	Monocytes, Mφ	Induction acute phase proteins
IL-13	T	Induction of TH1 cells
IL-16	CD8 T, CD4 (not preformed)	Inhibits mononuclear phagocyte inflammation; proliferation and differentiation B-cells Chemotaxis CD4 T-cells and eosinophils

## ACTIVATED T-CELLS PROLIFERATE IN RESPONSE TO CYTOKINES

In so far as T-cells are concerned, amplification following activation is critically dependent upon IL-2 (figure 10.7). This lymphokine is a single peptide of molecular weight 15.5 kDa which acts only on cells which express high affinity IL-2 receptors (figure 10.2). These receptors are not present on resting cells,



**Figure 10.7. Activated T-blasts expressing surface receptors for IL-2 proliferate in response to IL-2** produced by itself or by another T-cell subset. Expansion is controlled through downregulation of the IL-2 receptor by IL-2 itself. The expanded population secretes a wide variety of biologically active lymphokines of which IL-4 also enhances T-cell proliferation.

but are synthesized within a few hours after activation (figure 10.1).

Separation of an activated T-cell population into those with high and low affinity IL-2 receptors showed clearly that an adequate number of high affinity receptors were mandatory for the mitogenic action of IL-2. It is the skewed cellular distribution of these high affinity receptors which is responsible for the asynchronous division of activated T-cells on addition of IL-2. The numbers of these receptors on the cell increase under the action of antigen and of IL-2, and as antigen is cleared, so the receptor numbers decline and, with that, the responsiveness to IL-2. It should be appreciated that although IL-2 is an immunologically nonspecific T-cell growth factor, it only functions appropriately in specific responses because unstimulated T-cells do not express IL-2 receptors.

The T-cell blasts also produce an impressive array of other cytokines and the proliferative effect of IL-2 is reinforced by the action of IL-4 and, to some extent, IL-6, which react with corresponding receptors on the dividing T-cells. We must not lose sight of the importance of control mechanisms, and obvious candidates to subsume this role are transforming growth factor- $\beta$  (TGF $\beta$ ), which blocks IL-2-induced proliferation (figure 10.3b) and production of TNF $\alpha$  and  $\beta$ , and the cytokines IFN $\gamma$ , IL-4 and IL-10 which mediate the mutual antagonism of TH1 and TH2 subsets.

## **T<sub>H</sub> CELL'S CYTOKINE IN B-CELL PROLIFERATION AND DIFFERENTIATION**

CD40-CD40L-stimulated B cells start proliferation but fail to differentiate into antibody-secreting plasma unless cytokines are also present. Cytokines are soluble proteins secreted by T lymphocytes as well as other cell types in response to activating stimuli. Activated T<sub>H</sub> cells secrete cytokines.

As mentioned before, the engagement of CD40-CD40L activates B cells at one end and T<sub>H</sub> cells on the another, which starts the secretion of cytokines. Cytokines released by T<sub>H</sub> cells serve two functions:

- They augment B-cell proliferation and differentiation. Three T<sub>H</sub> cell-derived cytokines IL-2, IL-4 and IL-5 contribute to B-cell proliferation.
- They promote class switching and thus determine the type of antibodies produced, for example, IL-4.

Moreover, activated B cells enhance the expression of receptors for cytokines such as IL-2, IL-4 and IL-5 making B cells more receptive to cytokines secreted by T<sub>H</sub> cells. As a result, antigen-specific B cells respond to cytokines more than bystander B cells that have a different antigen specificity. The role of T<sub>H</sub> cells in contact-mediated and cytokine-mediated T-cell help is shown in Figure 9.10. Moreover, T<sub>H</sub> cells release cytokines in a directional manner towards the interacting B cells. This was shown by the work of C. A. Janeway. He isolated the T<sub>H</sub>-cell clone that secreted cytokine IL-4 in response to binding monoclonal antibodies to the T-cell receptor. The T<sub>H</sub> cells were adsorbed on a membrane having 3-micron pores. This membrane was suspended between two chambers in a tank. On addition of monoclonal antibodies in one chamber, T<sub>H</sub> cells bound to the membrane released IL-4 cytokines towards the chamber containing the stimulatory monoclonal antibodies.