

Interleukin 6 (IL-6) : The Biochemistry and Its Role on B and T Cell Development

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Abstrak

Aktivasi respon imunitas membutuhkan interaksi antara sel imunokompeten, molekul asesori dan sitokin. Dari sekian banyak sitokin, IL-6 adalah polipeptida dengan berat molekul 25 kD dan memegang peran penting pada proses imunitas. Paper ini adalah telaah pustaka singkat tentang peranan IL-6 pada sel B dan T. Bekerja sama dengan jenis sitokin lainnya, IL-6 berfungsi pada tahap akhir diferensiasi sel B yang diinduksi oleh antigen dan meningkatkan produksi antibodi. Sitokin ini mampu meningkatkan proliferasi sel thimosit dan aktivasi sel T. Dibahas pula peranan IL-6 pada imunopatogenesis AIDS.

Abstract

The induction of immune response requires the interaction among immunocompetent cells, accessory molecules and cytokines. Of these cytokines, IL-6, a 26 kD polypeptide, plays a major role on the immune response. The roles of this cytokine on the B and T cell development are reviewed briefly. In the presence of other cytokines, IL-6 acts on antigen dependent-terminal differentiation of B cells and increases significantly the antibody production. Both proliferation of thymocytes and T cell activation can be promoted by IL-6. The roles of IL-6 on the immunopathogenesis of AIDS are discussed.

Keywords : IL-6, B cells, T cells

INTRODUCTION

The immune system is an extremely impressive and complex network equipped to defend specifically against a wide variety of self and non self antigens. It is now known that cell to cell contact mediated by adhesion molecules and costimulatory signals provided by cytokines are necessary to activate the immune system.¹⁻³ Of these cytokines, interleukin 6 (IL-6), a 26 kD polypeptide, is a pleiotropic cytokine, in that it produces by a variety of cells and acts on a wide range of cells. The role of IL-6 on the immune response and tissue damage such as acute phase protein has been well recognized.⁴⁻⁷ A mechanism by which IL-6 involves in the acute phase protein occurring in the liver is beyond the scope of this article. Thus, this article is limited only to the immunoregulatory role of IL-6 on B and T cell response as well as its biochemical properties.

Biochemistry of IL-6

Historically, an attempt to purify proteins derived from the fibroblast culture resulted in a polypeptide termed interferon β .⁸ Subsequently, there were a few other proteins such as hepatocyte stimulating factor (HSF), B cell stimulatory factor-2 (BSF-2), 26 kD protein, hybridoma-plasmacytoma growth factor-2 (HPGF) and myeloid blood cell differentiation-inducing protein (MGI-2A), isolated from different sources and all shared amino acid sequence homology at both cDNA and mature form level; thus, they are termed as IL-6 (see ref. 4, for review).

The gene encoding IL-6 has been identified and located on the short arm chromosome 7p15-p21 (human) and chromosome 5 (murine).⁹⁻¹² Human cDNA of IL-6 mRNA from a T cell line¹³ or human monocytes¹⁴ was cloned. The mRNA is translated into a precursor protein containing 212 amino acids with molecular weight of 26 kD. The removal of a 28 amino

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13. Sawchenko PE, Swanson LW. The distribution and cells of origin of some afferent projections to the paraventricular and supraoptic nuclei of the rat (abstract). *Soc Neurosci* 1981; 7:325.
14. Ferguson AV, Day TA, Renaud LP. Subfornical organ efferents influence the excitability of neurohypophyseal and tuberoinfundibular paraventricular nucleus in the rat. *Neuroendocrinology* 1984; 39:423-8.
15. Swanson LW. An autoradiographic study of the efferent connections of the preoptic region in the rat. *J Comp Neurol* 1976; 167:227-56.
16. Tanaka J, Kaba H, Saito H, Seto K. Lateral hypothalamic area stimulation excites neurons in the subfornical organ with efferent projections to the hypothalamic paraventricular nucleus in the rat. *Brain res* 1986; 379:200-3.
17. Lind RW. Bi-directional, chemically specified neural connections between the subfornical organ and midbrain raphe system. *Brain Res* 1986; 384:250-61.
18. Simpson JB, Routtenberg A. Subfornical organ lesions reduce intravenous angiotensin-induced drinking. *Brain Res* 1975; 88:154-61.
19. Eng R, Miselis RR. Polydipsia and abolition of angiotensin-induced drinking after transections of subfornical organ efferent projections in the rat. *Brain Res.* 1981; 225:200-6.
20. Lind RW, Johnson AK. Subfornical organ-median preoptic connections and drinking and pressor responses to angiotensin-II. *J of Neuroscience* 1982; 2 (8);1043-51.
21. Mangiapane ML, Simpson JB. Pharmacologic independence of subfornical organ receptors mediating drinking. *Brain Res* 1979; 178:507-17.
22. Padmowijoyo D. *An investigation of the subfornical organ as a receptor for histamine, acetylcholine or angiotensin-II in mediating drinking behaviour* (A Master thesis). Bangkok : Mahidol University, 1976.
23. Simpson JB, Routtenberg A. Subfornical organ : acetylcholine application elicits drinking. *Brain Res* 1974; 69:157-64.
24. Lind RW, Swanson LW, Ganten D. Angiotensin-II-immunoreactive pathways in the central nervous system of the rat: evidence for a projection from the subfornical organ to the paraventricular nucleus of the hypothalamus. *Clin and Exper - Theory and Practice.* 1984; A6 (10 & 11):1915-20.
25. McKinley MJ, Denton DA and Weisinger RS. Sensors for antidiuresis and thirst-osmoreceptors of CFS sodium detectors? *Brain Res* 1978; 141:89-103.
26. Paxinos G, Watson C. *The rat brain, in stereotaxic coordinates.* San Diego, New York, London, Toronto : Academic Press Harcourt Brace Jovanovich Publishers, 1986.
27. Heimer L, Robards MJ. *Neuroanatomical-tract Tracing Methods.* New York, London : Plenum Press, 1981.
28. Ferguson AV, Renaud LP. Hypothalamic paraventricular nucleus lesions decrease pressor responses to subfornical organ stimulation. *Brain Res* 1984; 305:361-4.
29. Ferguson AV, Day TA, Renaud LP. Subfornical organ efferents influence the excitability of neurohypophyseal and tuberoinfundibular paraventricular nucleus neurons in the rat. *Neuroendocrinology* 1984; 39:423-8.
30. Ferguson AV, Day TA, Renaud LP. Subfornical organ stimulation excites paraventricular neurons projecting to dorsal medulla. *Am J Physiol* 1984; 247:R1088-R1092.
31. Renaud LP, Ferguson AV, Day TA, Bourque CW, Sgro S. Electrophysiology of the subfornical organ and its hypothalamic connections an In-Vivo Study in the rat. *Brain Res Bull* 1985; 15:83-6.
32. Ferguson AV, Kasting NW. Electrical stimulation in subfornical organ increase plasma vasopressin concentrations in the conscious rat. *Am J Physiol* 1986; 251:R425-R428.
33. Sgro S, Ferguson AV, Renaud LP. Subfornical organ-supraoptic nucleus connections: an electrophysiologic study in the rat. *Brain Res* 1984; 303:7-13.
34. Yamashita H, Osaka T, Kannan H. Effect of electrical stimulation of the paraventricular nucleus on neurons in the subfornical organ of cats. *Brain Res* 1984; 323:176-80.
35. Weindl A, Sofroniew MV. Neurohormones and circumventricular organs. In: Knigge KM, Scott DE, Weindl A editors. *Brain-endocrine interaction III. Neuroal hormones and reproduction.* Bassel : Karger, 1978; 117-37.

acid signal sequence yields a secreted 184 amino acid protein.¹³ The cDNA for murine IL-6 was also cloned from a T cell line and it showed that murine IL-6 contains 211 amino acids including a 24 residue signal peptide.¹⁵ Both human and murine IL-6 only share homology of 65% at cDNA and 42% at protein level.^{15,16} The amino acid sequence of IL-6 is displayed in Fig 1.

IL-6 receptor has also been identified and cDNA for IL-6R from COS7 cells was cloned.¹⁷ The IL-6R contains 468 amino acids including a 19 amino acid signal peptide with a presumed trans membran domain of 28 amino acids, a cytoplasmic domain of 82 amino acids and an extracellular portion of 339 amino acids. The domain of IL-6R reveals a close similarity with that of immunoglobulin; thus, IL-6R is included in the immunoglobulin super family.⁷ IL-6R is expressed in a wide variety of cells such as activated B cells, resting T cells, plasma cell line, histiocytes cell line and glioblastoma cell line.¹⁸ Interestingly, the cytoplasmic domain of IL-6R does not act as a signal transducer. In this respect, a surface protein receptor (gp130) closely associated with IL-6R is capable of transducing the growth signal; thus, following interaction of IL-6 with its receptor, the IL-6R is intimate with gp130 and signal transduction occurs^{19,20} (see Fig. 2).

The biological activities of IL-6

IL-6 can be produced from different sources such as fibroblast, mononuclear cells, endothelial cells, macrophages, keratinocytes and T-cell line, as well as certain tumor cells (such as T24 bladder carcinoma).²¹ This growing list of IL-6-producing cells suggests that IL-6 is secreted by both normal and neoplastic cells.

1. The effects of IL-6 on B cells

B cell differentiation into plasma cells can be divided into 3 major steps, viz., activation, proliferation and differentiation. In this respect, B cell activation may be proceeded by two pathways, i. e., antigen-dependent and antigen independent activation.²² Briefly, free antigens can be recognized and captured by surface immunoglobulin attached on B cells. Subsequently, the cells with their receptors (TCRs) recognize antigens plus MHC molecules and provide different cytokines which in turn help B cells to further proliferate and differentiate.²³ Antigen independent activation of B cells is mediated by T cell- derived lymphokines such as IL-4 and will not be further discussed.

It is now known that B cell activation is under control of the cytokine network. IL-4 and IL-5 play a

major role on B cells activation and proliferation.²² On the other hand, the role of IL-6 on B cells is somewhat different. In humans, antibody production in *S. aureus* Cowan I-stimulated B cell and a transformed B cell line culture is induced when IL-6 is added.¹³ Additional IL-6 at concentration up to 10 ng/ml in pokeweed mitogen (PWM) stimulated mononuclear cells induces high titer IgG, IgM and IgA antibody production.²⁵ It seems therefore that IL-6 only acts on activated B cells undergoing terminal differentiation (see Fig. 3).

It should however be noted that the biological functions of IL-6 on B cell activation require the presence of other cytokines. This is based upon the fact that only in the presence of IL-1, TNF- and TNF- β , IL-6 supports the long term growth of B cells lines *in vitro*.²⁷ Cocktail of IL-1 β and TNF- α only induces IL-6 production but fails to stimulate antibody production of human bone marrow B cells.²⁸ The antibodies of IL-1 β and TNF- α -stimulated BM cells were secreted if IL-6 was added, suggesting that the former cytokines provoke the secreted IL-6 which in turn stimulates the antibody production.²⁸

IL-6 as a factor for B cell terminal differentiation is also supported by the fact that Peyer's patch (PP) cell culture produces high rate IgA antibody when IL-6 is added.²⁹ In this study, the effect of IL-6 was much greater than that of IL-5. Further more, it also revealed that IL-6 did not induce B cell proliferation, but it did increase the number of IgA-secreting B cells. Moreover, in the IgA system where IL-5 is a potent differentiation factor,^{24,30,31} the effect of cocktail IL-5 and IL-6 on IgA production is far superior than that of IL-5 or IL-6 alone.³² In humans, additional IL-6 stimulates appendix-derived B cells to produce high rate of IgA.³³ These results suggest therefore that in the mucosal immune system, IL-6 is a potent costimulator for terminal differentiation of IgA-committed B cells and acts synergically with IL-5.

2. The effects of IL-6 on T cells

Thymocyte differentiation leading to maturation of T cells has long been an enigma. A complex interaction among components of the thymic microenvironment directs the selection of T cells in which T cells recognizing the self antigens will be neglected. Of these components, cytokines produced by both thymocytes and other thymic cells provide a bidirectional communication in controlling T cell selection and maturation.³⁴ Along with other cytokines, the ability of IL-6 to induce thymocyte proliferation has been documented. In the presence of lectins, IL-6 stimulates the proliferation of both human and murine thymocytes.^{35,36} Further analysis of phenotypic thymocytes revealed that IL-6 does not generate immature cell

MNSFSTSAFG	PVAFSLGLLL	VLPAAFPAPV	PPGEDSKDVA	APHRQPLTSS	50
ERIDKQIRYI	LDGISALRKE	TCNKSNCES	SKEALAENNL	NLPKMAEKDG	100
CFQSGFNEET	CLVKIITGLL	EFEVYLEYLQ	NRFESSEEQA	RAVQMSTKVL	150
IQFLQKKAKN	LDAITTPDPT	TNASLLTKLQ	AQNQWLQDMT	THLILRSFKE	200
FLQSSLRALR	QM				

Figure 1. Amino acid sequence of IL-6. Numbers seen represent the position of the residue. Redrawn from ref. 1.

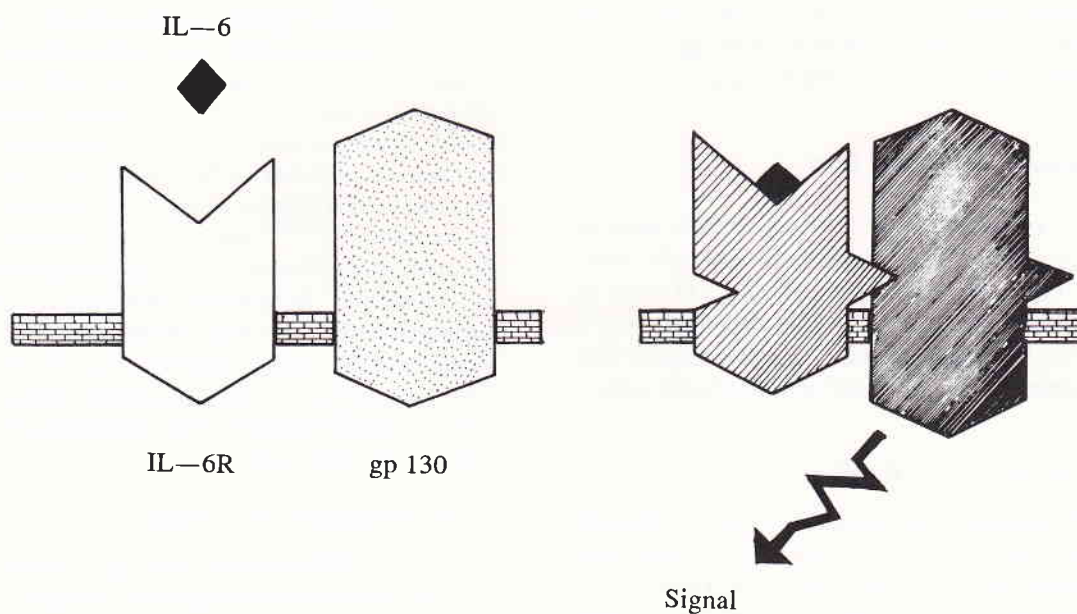


Figure 2. Signal transduction induced by the binding of IL-6 and IL-6R. The binding between ligand and receptor activates the gp130 molecule and the signal occurs. Redrawn from ref. 7.

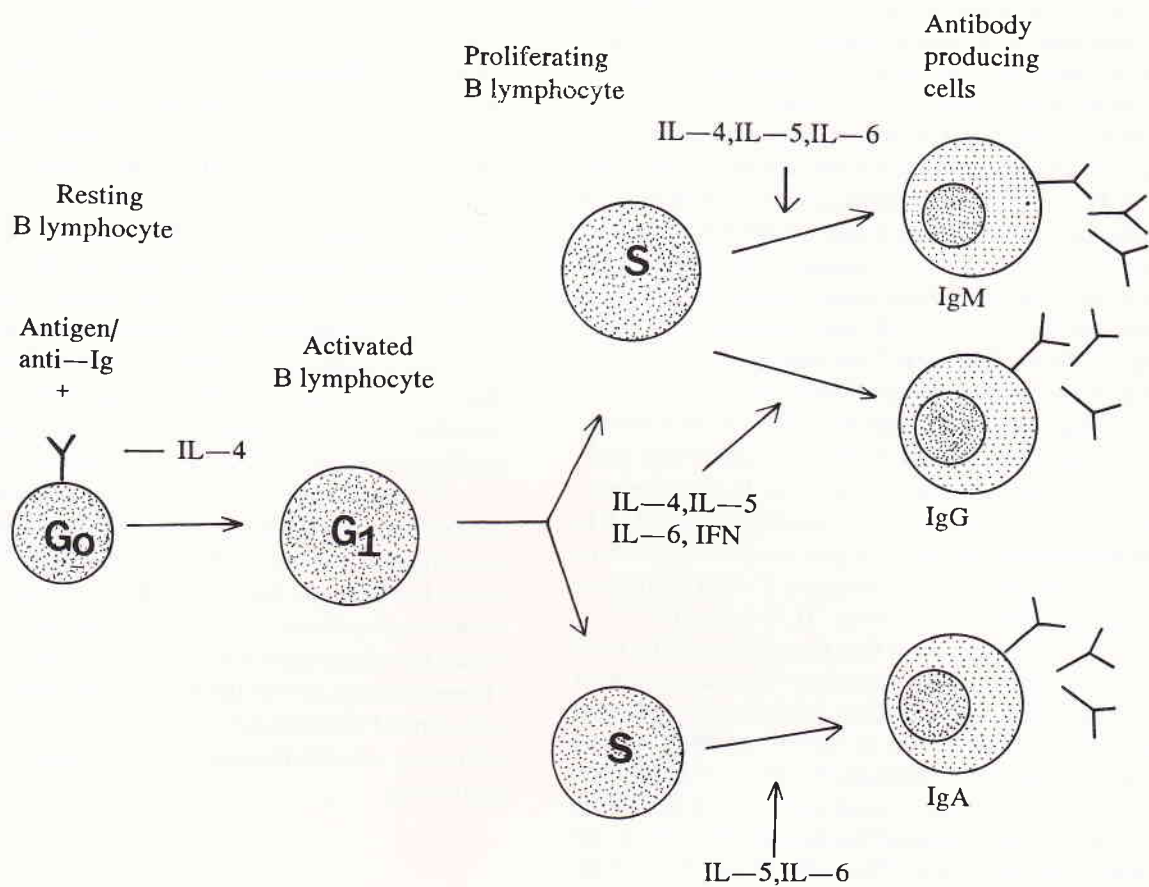


Figure 3. The role of IL-6 on the antigen-dependent B cell activation. This model shows the interaction between IL-6 and other cytokines in regulating B cell differentiation. Therefore, the immune network seen is not exclusively mediated by IL-6 rather the function of IL-6 on the target cells requires synergically other type of cytokines. Modified from ref. 26.

proliferation but it does stimulate $L3T4^+Lyt2^-$ and $L3T4^-Lyt2^+$ -mature thymocytes.^{36,37} Indeed, it recently showed that the development of immature thymocytes is in fact mediated by IL-7.³⁸ Thus, one may interpret that IL-6 acts on the thymocyte development following the action of IL-7. The role of IL-6 on the thymocytes is further evidenced that IL-1-stimulated thymocyte proliferation requires the presence of IL-6; thus, IL-1 induces IL-6 production and increases the sensitivity of thymocytes for IL-6.³⁹

The exact mechanism of T cell activation is still far from clear. However, IL-2 has been known to provide a costimulatory signal on this cell activation,⁴⁰ thus lack of IL-2 may induce T cell anergy, leading to the induction of T cell tolerance.⁴¹ Evidences have emerged that IL-6 may be a good candidate for T cell activation in IL-2-independent fashion. Ceuppens, et al., pointed out that IL-6 acts synergically with PHA

to induce strong T cell proliferation without the addition of IL-2.⁴² Likewise, thymocyte proliferation can be induced by IL-6, in IL-2 independent fashion.⁴³ It remains however to be determined what the physiological relevance of these observations are, since it appears that IL-2 and IL-2R may involve in IL-6-induced T cell proliferation.⁴ For example, IL-6 is able to restore the proliferation of ConA or Anti-TcR antibody-stimulated T cells, but this effect is blocked by anti IL-2 antibody.⁴⁴ This study also shows that purified $CD8^-$ T cells can be activated by IL-6 in the presence of ConA to secrete IL-2, suggesting that IL-6 is a second signal in primary-antigen-receptor-dependent T cell activation. IL-6 activities on T cells activation may therefore be referred as an "IL-2 inducer".^{37,45}

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It becomes apparent that the abilities of IL-6 on T cell proliferation have somehow been complicated by the fact that this cytokine inhibits delayed type hypersensitivity (DTH) in an animal model.⁴⁶ Given that DTH response is mediated by Th1 cells and suppressed by the cytokines (such as IL-4 and IL-10) of Th2 cells⁴⁷, it would appear that IL-6 of Th2 cells down regulates the function of Th1 cells. If so, should Th1 cells be suppressed by IL-6, it needs arguably another mechanism other than mentioned above. One possibility is that IL-6 does not induce CD4 cells into type 1 and type 2 cells, it rather stimulates this cell subset into Th0 type cells which secrete various cytokines.⁴⁸ Thus, no effector T cells for DTH response would be generated if IL-6 is present. Whether IL-6-mediated DTH unresponsiveness is orchestrated by this pathway remains to be investigated.

Perspective

The relevancy of IL-6 on the B and T cell development is more appreciated if the associated pathological features are discussed. IL-6 has been believed to play a role on cardiac myxoma, rheumatoid arthritis, psoriasis, lymphoma and leukemia.⁷

However, the role of this cytokine on the pathogenesis of AIDS (acquired immunodeficiency syndrome) is perhaps one of the most intriguing questions.

Recent studies showed that IL-6 is believed to be involved in the spreading of HIV (human immunodeficiency virus) infection as demonstrated by a high level of serum IL-6 and soluble IL-6 receptor and an increased number of IL-6-producing monocyte cells from HIV-infected donors.⁴⁹⁻⁵² HIV is capable to

induce the excessive production of IL-6 in human B cells, in the presence of IL-4.⁵³ These results may therefore explain partly the occurrence of B cell hyperactivation in HIV-infected patients.⁵⁴ Furthermore, a report of Schnittman, et al., revealed that thymic epithelial cells produce IL-6 which induces the HIV replication in chronically infected HIV cells.⁵⁵ These results suggested that in AIDS patients, IL-6 in the thymus may maintain and promote the HIV replication of intrathymic precursor T cells. Hence, treatment of HIV-infected patients with antiretroviral agents may only partly suppress the HIV replication, but the T cell defect still occurs due to the fact that IL-6 prevents the intrathymic development of T cells by enhancing HIV replication in the infected T cell precursor.

Whilst the role of IL-6 on the previously mentioned pathological features is still being profoundly investigated, the use of this cytokine for clinical purposes has been put forward in the animal model. Injection of recombinant IL-6 reduces the tumor growth in mice, by enhancing the activities of cytotoxic T cells.⁵⁶ These findings reveal the broad spectrum of IL-6 for the clinical immunotherapy and hence raise the possibility as an alternative for IL-2 usage in tumor regression.

CONCLUSION

It becomes apparent that IL-6 is one of the cytokines which serves as an immunoregulator. This cytokine shows to act on the antigen-dependent terminal differentiation of B cells and to enhance the antibody production. Both thymocyte proliferation and T cell activation can be up-regulated by IL-6. Thus, the pathological features associated with these abilities of IL-6 on T and B cell Development would be obvious. For example, increased serum IL-6 and HIV replication in thymus in HIV-infected patients reveal, to some degree, the influence of IL-6 on the course of AIDS.

REFERENCES

1. Arai K, Lee F, Miyajima A, Miyatake S, Arai N, Yokota T. Cytokines: coordinators of immune and inflammatory responses. *Ann Rev Biochem* 1990;59:783-836.
2. Springer TA. Adhesion receptors of the immune system. *Nature* 1990;346:425-34.
3. Patarroyo M. Leukocyte adhesion in host defence and tissue injury. *Clin Immunol Immunopathol* 1991;60:333-48.
4. Le J, Vilcek J. Interleukin 6: A multifunctional cytokine regulating immune reactions and acute phase protein response. *lab Invest* 1989;61:588-602.

5. Akira S, Hirano T, Taga T, Kishimoto T. Biology of multi-functional cytokines: IL 6 and related molecules (IL 1 and TNF). *FASEB J* 1990;4:2860-7.
6. Heinrich PC, Castell JV, Andus T. Interleukin-6 and the acute phase response. *Biochem J* 1990;265:621-36.
7. Hirano T, Kishimoto T. Biological and clinical aspects of interleukin 6. *Immunol Today* 1990;11:443-9.
8. Weissenbach J, Chernajovsky Y, Zeevi M, Shulman L, et al. Two interferon mRNAs in human fibroblast: *in vitro* translation and *Escherichia coli* cloning studies. *Proc Natl Acad Sci USA* 1980;77:7152-6.
9. Sehgal PB, Zilberstein A, Ruggieri M-R, May LT, et al. Human chromosome 7 carries the beta2 interferon gene. *Proc Natl Acad Sci USA* 1986;83:5219-22.
10. Bowcock AM, Kidd JR, Lathorp M, Danashvar L, et al. The human "beta-2 interferon/hepatocyte stimulating factor/interleukin-6" gene: DNA polymorphism studies and localization to chromosome 7p21. *Genomics* 1988;3:8-16.
11. Ferguson-Smith AC, Chen YF, Nerman MS, May LT, et al. Regional localization of the "beta2-interferon/B-cell stimulatory factor 2/hepatocyte stimulating factor" gene to human chromosome 7p21-21. *Genomics* 1988;2:203-8.
12. Mock BA, Nordan RP, Justice MJ, et al. The murine IL-6 gene maps to the proximal region of chromosome 5. *J Immunol* 1989;142:1372-6.
13. Hirano T, Yasukawa K, Harada H, Taga T, et al. Complementary DNA for novel human interleukin (BSF-2) that induces B lymphocytes to produce immunoglobulin. *Nature* 1986;324:73-6.
14. Brakenhoff JPI, DeGroot ER, Evers RF, Pannekoek H, Aarden LA. Molecular cloning and expression of hybridoma growth factor in *Escherichia coli*. *J Immunol* 1987;139:4116-21.
15. Van Snick J, Cayphas S, Szikora J, Renauld J, et al. cDNA cloning of murine interleukin-HP1: homology with human interleukin 6. *Eur J Immunol* 1988;18:193-7.
16. Simpson RJ, Moritz RL, RUBira MR, Van Snick J. Murine hybridoma/plasmacytoma growth factor: complete amino acid sequence and relation to human interleukin-6. *Eur J Biochem* 1988;176:187-97.
17. Yamasaki K, Taga T, Hirata Y, Yawata H, et al. Cloning and expression of the human interleukin-6 (BSF-2/IFN beta) receptor. *Science* 1988;241:825-8.
18. Taga T, Kawanishi K, Hardy RR, Hirano T, Kishimoto T. Receptor for B cell stimulatory factor 2 (BSF-2): quantitation, specificity, distribution and regulation of the expression. *J Exp Med* 1987;166:967-81.
19. Taga T, Hibi M, Hirata Y, Yamasaki K, et al. Interleukin-6 triggers the association of its receptor with possible signal transducer, gp130. *Cell* 1989;58:573-81.
20. Saito M, Yoshida K, Hibi M, Taga T, Kishimoto T. Molecular cloning of a murine IL-6 receptor-associated signal transducer, gp130, and its regulated expression *in vivo*. *J Immunol* 1992;148:4066-71.
21. Van Snick J, Nordan RP. Interleukin 6. In: Habencicht A, editor. *Growth factors, differentiation factors and cytokines*. Berlin: Springer-Verlag, 1990;163-76.
22. Kishimoto T, Hirano T. Molecular regulation of B lymphocyte response. *Ann Rev Immunol* 1988;6:485-512.
23. Kourilsky P, Claverie J-M. MHC-antigen interaction: what does T cell receptor see?. *Adv Immunol* 1989;45:107-93.
24. Harriman GR, Strober W. The immunobiology of interleukin 5. *Year Immunol*. 1989;5:160-77.
25. Muraguchi A, Hirano T, Tang B, Matsuda T, et al. The essential role of B cell stimulatory factor-2 (BSF-2/IL-6) for the terminal differentiation of B cells. *J Exp Med* 1988;167:332-44.
26. Abbas AK. A reassessment of the mechanisms of antigen specific T-cell-dependent B cell activation. *Immunol Today* 1988;9:89-94.
27. Abken H, Fluck J, Willecke K. Four cell-secreted cytokines act synergistically to maintain long term proliferation of human B cell lines *in vitro*. *J Immunol* 1992;149:2685-794.
28. Roldan E, Rodriguez C, Navac G, Parra C, Brieva JA. Cytokine network regulating terminal maturation of human bone marrow B cells capable of spontaneous and high rate Ig secretion *in vitro*. *J Immunol* 1992;149:236-71.
29. Beagley KW, Eldridge JH, Lee F, Kiyono H, et al. Interleukins and IgA synthesis. Human and murine interleukin 6 induce high rate IgA secretion in IgA-committed B cells. *J Exp Med* 1989;169:2133-48.
30. Beagley KW, Eldridge JH, Kiyono H, Everson MP, et al. Recombinant murine IL-5 induces high rate IgA synthesis in cycling IgA-positive Peyer's patch B cells. *J Immunol* 1988;141:2035-45.
31. Schoenbeck S, McKenzie DT, Kagnoff MF. Interleukin 5 is a differentiation factor for IgA B cells. *Eur J Immunol* 1989;19:965-9.
32. Kunimoto DY, Nordan RP, Strober W. IL-6 is a potent cofactor of IL-1 IgM synthesis and of IL-5 in IgA synthesis. *J Immunol* 1989;143:2230-5.
33. Fujihashi K, McGhee JR, Lue C, Beagley KW, et al. Human appendix B cells naturally express receptors for and respond to interleukin-6 with selective IgA1 and IgA2 synthesis. *J Clin Invest* 1991;88:248-52.
34. Ritter MA, Boyd RL. Development in the thymus: it takes two to tango. *Immunol Today* 1993;14:462-9.
35. Lotz M, Jirik F, Kabouridis R, et al. B cells stimulating factor 2/interleukin 6 is a costimulant for human thymocytes and T lymphocytes. *J Exp Med* 1988;167:1253-8.
36. Uyttenhove C, Coulie PG, Van Snick JT. T cell growth and differentiation induced by interleukin-HP1/IL-6, the murine hybridoma/plasmacytoma growth factor. *J Exp Med* 1988;167:1417-27.
37. Quentmeier H, Klaucke J, Muhlradt PF, Drexler HG. Role of IL-6, IL-2, and IL-4 in the *in vitro* induction of cytotoxic T cells. *J Immunol* 1992;149:3316-20.
38. Bertagnoli M, Herrmann S. IL-7 Supports the generation of cytotoxic T lymphocytes from thymocytes. *J Immunol* 1990;145:1706-12.
39. Helle M, Boeije L, Aarden L. IL-6 is an intermediate in IL-1-induced thymocyte proliferation. *J Immunol* 1989;142:4335-8.
40. Altman A, Mustelin T, Moggshall KM. T lymphocyte activation: A biological model of signal transduction. *CRC Crit Rev Immunol* 1990;10:347-91.

41. Schwartz RH. A cell culture model for T lymphocyte clonal anergy. *Science* 1990;248:1349-56.
42. Ceuppens JL, Baroja ML, Lorre K, Van Damme J, Billiau A. Human T cell activation with phytohemagglutinin. The function of IL-6 as an accessory signal. *J Immunol* 1988;141:3868-74.
43. Le J, Fredrickson G, Reis LFL, Diamantstein T, et al. Interleukin 2-dependent and interleukin 2-independent pathways of regulation of thymocyte function by interleukin 6. *Proc natl Acad Sci USA* 1988;85:8643-7.
44. Garman RD, Jacobs KA, Clark SC, Raulet DH. B-cell stimulatory factor 2 (β 2 interferon) functions as a second signal for interleukin 2 production by mature murine T cells. *Proc Natl Acad Sci USA* 1987;76:29-33.
45. Houssiau F, Van Snick J. IL6 and the T-cell response. *Res Immunol* 1992;143:740-3.
46. Mihara M, Ikuta M, Koishihara Y, Ohsugi Y. Interleukin 6 inhibits delayed-type hypersensitivity and the development of adjuvant arthritis. *Eur J Immunol* 1991;21:2327-31.
47. Street NE, Mosman TR. Functional diversity of T lymphocytes due to secretion of different cytokine patterns. *FASEB J* 1991;5:171-8.
48. Croft M, Swain SL. B cell response to helper cell subsets. II. Both stage of T cell differentiation and the cytokines secreted determine the extent and nature of helper activity. *J Immunol* 1991;147:3679-89.
49. Birx DL, Redfield RR, Tencer K, Fowler A, et al. induction of interleukin 6 during immunodeficiency virus infection. *Blood* 1990;76:2303-10.
50. Breen EC, Rezai AR, Nakajima K, Beall GN, et al. Infection with HIV is associated with elevated IL-6 levels and production. *J Immunol* 1990;144:480-8.
51. Twigg HL, Iwamoto GK, Soloman DA. Role of cytokine in alveolar macrophage accessory cell function in HIV-infected individuals. *J Immunol* 1992;149:1462-9.
52. Honda M, Yamamoto S, Cheng M, Yasukawa K, et al. Human soluble IL-6 receptor: its detection and enhanced release by HIV infection. *J Immunol* 1992;148:2175-80.
53. Boue F, Wallon C, Gourjard C, Barre-Sinoussi F, et al. HIV induces IL-6 production by human B lymphocytes. *J Immunol* 1992;148:3761-7.
54. Rosenberg ZF, Fauci AS. Immunopathogenic mechanisms of HIV infection: cytokine induction of HIV. *Immunol Today* 1990;11:176-80.
55. Schnittman S, Singer KH, Greenhouse JJ, Stanley SK, et al. Thymic microenvironment induces HIV expression. Physiologic secretion of IL-6 by thymic epithelial cells up-regulates virus expression in chronically infected cells. *J Immunol* 1992;147:2553-8.
56. Mule JJ, Custer MC, Travis WD, Rosenberg SA. Cellular mechanisms of the antitumor activity of recombinant IL06 in mice. *J Immunol* 1992;148:2622-9.