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The biological role and potential therapeutic application of interleukin 7

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Summary

Interleukin (IL)-7 is a pleiotropic, non-redundant cytokine necessary for the development of B and T lymphocytes, in particular γδ T cell receptor-positive cell differentiation. The cytokine can function as a cofactor during myelopoiesis and the generation of cytotoxic T cells and natural killer cells, can activate monocytes/macrophages, and support the survival of mature T cells. A role for IL-7 in promoting the formation of Peyer's patch anlage has also been demonstrated. IL-7 is constitutively expressed in the thymus, bone marrow stromal cells, epithelial and dendritic cells, keratinocytes, as well as in fetal and adult liver. IL-7 acts on various cells through its receptor (IL-7R), a heterodimer consisting of an α chain (CD127) that specifically binds IL-7 and a common γ_c chain (CD132) shared by other cytokine receptors. The receptor is expressed on bone marrow progenitor cells, lymphoid T and B precursors, and mature T cells. IL-7 activity towards murine endothelial cells has been recently described. The presence of IL-7R on human endothelial cells has also been demonstrated. Several therapeutic applications of recombinant IL-7 have been proposed. These have focused on the enhancement of lymphopoiesis, promotion of stem cell engraftment, and the anti-tumor activity of the cytokine.

Key words: **interleukin 7 • interleukin-7 receptor • B cell development • T cell development • endothelium • cytokine therapy**

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INTERLEUKIN 7

Molecular structure

The murine interleukin (IL)-7 gene consists of approximately 56 kbp and is located on chromosome 3 (GenBank accession no. X07962), whereas the human gene consists of approximately 33 kbp and is located on chromosome 8q12-13 (GenBank accession no. J04156). The human gene contains 6 exons and 5 introns and has an open-reading frame of 534 bp[57, 82]. The murine IL-7 gene consists of 5 exons and its open-reading frame spans 462 bp[63]. IL-7 has been classified as a type 1 short-chain cytokine of the hematopoietin family. It is a small protein, with a molecular weight of about 17 kDa; however, because of posttranslational modifications (glycosylation), the molecular weight of the protein evaluated on sodium dodecyl sulfate (SDS) gels is about 25 kDa. The murine cytokine possesses two possible N-glycosylation sites, whereas the human protein contains three, not essential for the biological activity. Human and murine IL-7 amino-acid sequences are 60–80% homologous[30, 35, 37, 57]. Human IL-7 has 19 amino acids more than the murine protein, these inserted at positions 96–114. Both proteins also contain 6 highly conserved cysteine residues that are essential for the biological activity of the cytokine. The murine protein is relatively stable at pH 2.1–8.0 and is resistant to SDS and heat. The isoelectric point is shown to be at a pH of approx. 9.0[7]. Human and murine IL-7 transcripts are differentially spliced and polyadenylated[37, 51, 63]. As an alternative splicing of pre-mRNA has been shown to be involved in the control of gene expression, splicing-derived protein isoforms with antagonistic activity have been found. The group of Korte et al.[49] described an IL-7 alternative splice variant lacking exon 4 (IL-7δ4) in leukemic cells from children with acute lymphoblastic leukemia. The results led them to the conclusion that splicing-derived IL-7 isoforms play a potential role in modulating IL-7-mediated biological effects. Despite similarities in structure and function of murine and human IL-7, human recombinant IL-7 (rIL-7) is active on murine and human cells, whereas murine rIL-7 is not active on human cells[37].

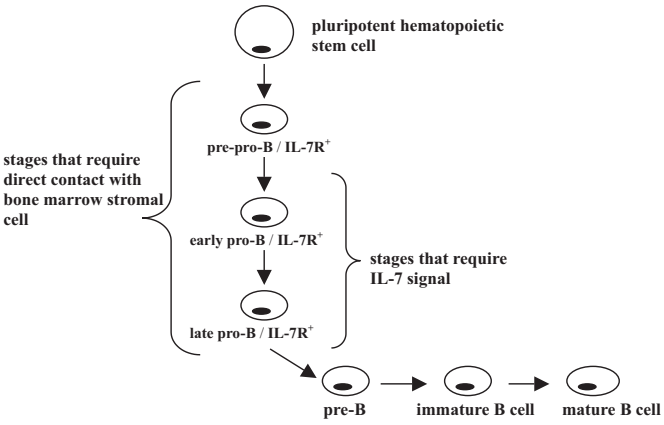

Figure 1. The role of IL-7 in the development of B lymphocytes. The earliest definable stage in B cell development, the pre-pro-B cell, expresses IL-7R, but its differentiation is independent of IL-7. The differentiation of early and late pro-B cells requires a signal from soluble IL-7 produced by the stromal cell. The last IL-7--responsive stage is the early pre-B cell.

Biological function

IL-7 is a pleiotropic cytokine that is currently the only known non-redundant cytokine absolutely necessary for B and T lymphocyte development in mice and for that of T lymphocytes in humans[10, 69, 70, 72] (Fig. 1 and 2). IL-7 was first discovered as a growth factor for murine pro-B cells[63]. Later its anti-apoptotic effect on

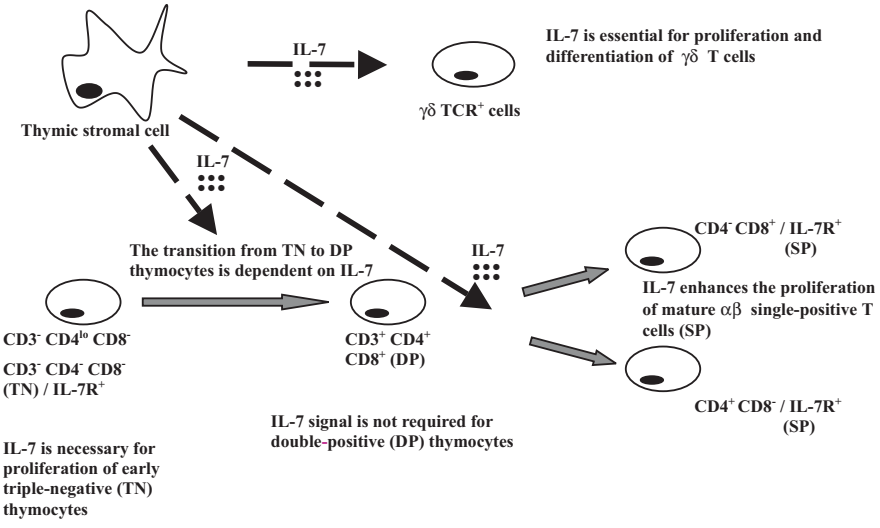

Figure 2. The role of IL-7 in the development of αβ and γδ T lymphocytes. The cytokine acts a growth factor for early (triple-negative) thymocytes, and the transition from triple-negative to double-positive thymocytes is dependent on IL-7. Double-positive T cells respond poorly to IL-7, but mature αβ T lymphocytes (single-positive) enhance their proliferation in the presence of this cytokine. IL-7 is absolutely essential for the proliferation and differentiation of γδ T lymphocytes.

mature B cells and a growth factor activity for T cell precursors: αβ and T cell receptor-positive (TCR) cells were described[2, 43]. IL-7 presence appeared to be absolutely required for TCRγδ cell differentiation[60, 40]. Murine B lymphocyte development is entirely dependent on IL-7 presence[72] (Fig. 1), and IL-7 is also required for V(D)J recombination, at least in some of the loci[41]. Dobbeling[24] showed that IL-7 represses V(D)J recombination by a glucocorticoid-sensitive pathway, but Corcoran et al.[19] demonstrated that V recombination following D-J joining is regulated by the α chain of the receptor for IL-7. Ligands of the IL-7 receptor (IL-7R) deliver an extrinsic signal that targets V segment recombination in the heavy-chain locus by altering the accessibility of DNA substrates to the recombinase. Other studies have shown that IL-7 is necessary for the rearrangement and expression of TCRγ genes in both the fetal and adult thymus. Adult thymocytes also required IL-7 for survival. In contrast, thymic IL-7 was not required for the survival or proliferation of peripheral TCRγδ cells, although it prolonged the life-span of individual TCRγδ cells[54]. IL-7 also induced V(D)J rearrangement of the murine TCRβ gene during fetal development[61].

The cytokine can function as a cofactor during myelopoiesis[26, 45] and generation of cytotoxic T cells[92], natural killer (NK) cells[71, 74], and lymphokine--activated killer (LAK) cells[3]. It can also activate monocytes/macrophages[4] and support the development and survival of mature T cells (reviewed by Komschlies et al.[48]). IL-7 has also been demonstrated to promote the formation of some organs, i.e. Peyer's patch anlage[1, 90].

IL-7 is one of the cytokines that possess a lectin activity. It was demonstrated that it binds preferentially to the sialyl-Tn antigenic structure present on the surface of colon, breast, and other human adenocarcinomas[13, 17]. Bizouarne et al.[11] and Denis et al.[22] showed that IL-7 could activate murine endothelial cells to express a fucose-specific lectin molecule. The cytokine is presented on the endothelial surface upon binding to the glycosaminoglycans that are part of the cell-surface molecular complexes. One hypothesis suggests that IL-7 requires glycosaminoglycans (e.g. heparan sulfate) for efficient binding to IL-7R[13]. Therefore, the biological effects of IL-7 could be modulated by subendothelial extracellular matrix components[6, 18].

Distribution in the organism

IL-7, originally called lymphopoietin-1, was isolated and cloned for the first time as a murine B cell precursor growth factor from an established stromal cell line[63]. Human IL-7 cDNA was cloned in 1989 by Goodwin et al.[37] IL-7 is constitutively expressed in the thymus[86], bone marrow stromal cells[87], intestinal epithelial cells[85], dendritic and follicular dendritic cells (DCs)[23, 52, 80], fetal and adult liver[34, 39], and keratinocytes[59]. The presence of IL-7 was also reported in cultured *in vitro* endothelial cells from human tonsils[52, 78], intestine[64], and umbilical cord[89], and *in vivo* in dermal endothelial cells[75]. Interestingly, the expression of IL-7 protein has not been detected in normal mature B lymphocytes, although it has been reported in Epstein-Barr virus-transformed lymphocytes. The IL-7 transcript was present in normal lymphoblastoid B cell lines as well as in malignant B cells[10]. In fact, IL-7, known as a "typically" lymphopoietic cytokine, seems to be an essentially tissue-derived cytokine.

RECEPTOR FOR IL-7

Structure

IL-7 can act on various cells through its receptor, IL-7R. The receptor is a member of the hematopoietin/cytokine receptor superfamily. It is a heterodimer consisting of an α chain (CD127) that specifically binds IL-7 and a common γ_c chain (CD132), which is also a component of several other cytokine receptors, i.e. IL-2R, IL-4R, IL-9R, IL-15R, and IL-21R[8, 41, 66, 68, 91]. IL-7R α chain has a 220--amino-acid extracellular domain, a 25-amino-acid transmembrane fragment, and a 195-amino-acid cytoplasmic tail. The mature protein has an observed molecular weight of about 75 kDa, although the predicted molecular weight is 49.5 kDa; the difference is probably caused by posttranslational modification of one or more of the 6 potential N-glycosylation sites. Both the α and γ_c chains of IL-7R have a pair of conserved extracellular cysteine residues and an extracellular Trp-Ser-X-Trp-Ser motif and lack intrinsic tyrosine kinase activity[5]. The α chain of IL-7R is also a component of the receptor for thymic stromal-derived lymphopoietin, a cytokine important in the early stages of B and T cell development[73] (Fig. 3). The α chain exists in membrane-bound and soluble forms[36, 65]. The production of soluble forms of IL-7R is a result of an alternative splicing of the IL-7R gene. The gene is located on human chromosome 5p13, and mouse chromosome 15. Recent studies by Franchimont et al.[29] identified IL-7Rα as a glucocorticoid-inducible gene. The up-regulation of IL-7Rα by glucocorticoids was associated with enhanced IL--7-mediated signaling and function. For high-affinity binding of IL-7, necessary for survival or proliferation signal transduction, both the α and γ_c chains are required[53] (Fig. 3). On T cells, high- and low-affinity receptors are expressed according to the state of activation of the cell[7, 28, 67].

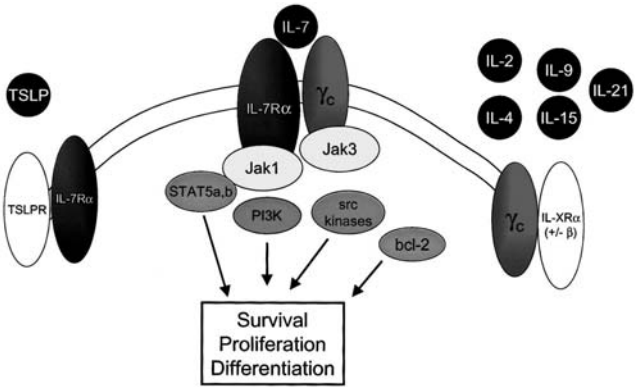

Figure 3. The schematic structure and cellular signaling of IL-7R. The receptor for IL-7 consists of a specific α chain and a common γ_c chain. IL-7Rα is also a component of the thymic stromal lymphopoietin receptor (TSLPR), whereas the γ_c chain is present in other cytokines, such as IL-2, IL-4, IL-9, IL-15, and IL-21. The Jak/STAT pathway, PI-3 kinase, or src kinases family can mediate the cellular signaling upon binding of IL-7 to IL-7R. From Fry and Mackall[30] (copyright American Society of Hematology, used with permission).

Signal transduction

The intracellular mechanisms mediating signaling from IL-7 are not fully elucidated. The signal from IL-7 could be transferred into the cell through several non-receptor tyrosine kinases that associate with the cytoplasmic tail of the receptor. This includes the Jak/STAT pathway, src family kinases ($p59^{fyn}$ in mice and $p59^{fyn}$, $p56^{lck}$, and $p53/p56^{lyn}$ in humans) and PI3 kinase. In T lymphocytes, the MAPK family (p38) is also involved[21]. The binding of IL-7 to its receptor activates Jak1 and Jak3 kinases, which are also activated by other cytokines that share the γ_c receptor subunit. Jak kinases can further activate signal transducers and transcription activators (STAT1, STAT3, and STAT5), the translocation of which to the nucleus results in the activation of DNA transcription. An aberration in Jak-mediated signal transduction has been described in the severe combined immunodeficiency syndrome (SCID). Mutation in the Jak3 kinase gene as well as in the α chain gene of IL-7R resulted in autosomal, recessive SCID, whereas mutation in the γ_c chain gene caused X-linked SCID[15, 53].

IL-7R distribution

The presence of IL-7R has been reported mainly in hematopoietic human and murine cell systems and selected myeloid cells. IL-7Rα is expressed on B and T cell lineages. The receptor is expressed on bone marrow progenitor cells, lymphoid T and B precursors, and mature T cells[40, 42, 44, 50]. The activated IL-7R is a transducer of several biological signals playing important roles in the function of the immune system. The cytokine, via its receptor, affects the maturation and/or augments the proliferation of pre-B and pre-T cells[2, 60, 84]. The expression of IL-7R was also detected on epithelial cells and neurons (reviewed by Hofmeister et al.[41]). Interestingly, it has also been suggested that IL-7 can induce signal transduction events in cells that do not express IL-7R because of the ability to engage other surface receptors, such as FLT3 and c-kit[20].

An unexpected IL-7 activity towards murine endothelial cells has been described[11, 12, 22]. Endothelium is critical for blood circulation and homeostasis and also plays an important role in the pathogenesis of atherosclerosis, inflammation, and cancer progression. Microvascular endothelial cells recognize blood-borne circulating cells and allow them to extravasate in a tissue-specific manner (Gowans and Knight[38], reviewed by Butcher and Picker[16]). In 1993, observations by Bizouarne et al.[11] and Denis et al.[22] showed that murine endothelial cells from peripheral lymph nodes could be specifically activated by IL-7 to induce the expression of lectin adhesion molecule. Further studies carried out in the same mouse model showed a selective induction of addressin (MECA 79 antigen) expression upon IL-7 treatment[12]. These observations strongly suggested the presence of IL-7R on murine endothelial cells. Our study demonstrated that human endothelial cells possess a receptor for IL-7. Five endothelial cell lines, derived from peripheral or mesenteric lymph nodes, lung, and appendix[47], were analyzed. The presence of the α chain of the receptor (IL-7Rα) was detected in all the cell lines tested[25].

POTENTIAL MEDICAL APPLICATIONS OF IL-7

Based on the wide range of *in vitro* and *in vivo* studies of IL-7 function, several medical and clinical applications of recombinant IL-7 have been proposed. They are focused on the enhancement of lymphopoiesis, promotion of stem cell engraftment, and anti-tumor activity of the cytokine. There are also several studies describing the anti-microbial activity of this cytokine.

Lymphoid reconstitution

Since IL-7 is a cytokine that can augment the proliferation of lymphoid cells, it may serve as a factor that accelerates lymphoid regeneration in lymphopenic patients. Lymphopenia may be a result of primary or secondary T and B cell immunodeficiencies (e.g. AIDS, SCID, infectious diseases) or chemotherapy/irradiation of cancer patients. IL-7 was also effective in increasing mouse peripheral T cell repopulation after bone marrow transplantation[14]. Recent

studies indicate that IL-7 increased $CD4^+$ T cell numbers in irradiated primates after hematopoietic cell transplantation[81]. The increase in T cell numbers in monkeys occurred due to the stimulation of peripheral expansion, whereas in mouse models, IL-7 stimulated their *de novo* generation. Despite these positive effects, it should be mentioned that side effects were noted in monkeys after administration of IL-7, in particular, thrombocytopenia and a disease similar to graft-versus-host disease (GVHD)[81], and in mice GVHD deterioration[77]. Recombinant IL-7 has also been used for the treatment of simian immunodeficiency virus-infected non-human primates[31]. The cytokine induced peripheral T cell restoration in both T cell-repleted and T cell-depleted monkeys. These findings suggest that IL-7 can be considered as a promising immunorestorative agent.

The role of IL-7 in human immunodeficiency virus (HIV) infection is controversial. Interesting studies were presented by Mussini et al.[62] They investigated a group of HIV-positive patients with dramatic impairment of the immune system who were able to fully reconstitute their immune system after receiving highly active antiretroviral therapy (HAART). IL-7 plasma levels were high in these patients; moreover, a significant number of T lymphocytes ($CD4^+$ and $CD8^+$) expressed IL-7R α chain. The authors concluded that in these patients an upregulation of the IL-7/IL-7R system takes place and, therefore, the clinical use of IL-7, in association with antiretroviral therapy, should be considered. However, other effects of this cytokine should be taken into account, as it was shown that IL-7 can augment *in vitro* HIV-1 infection of both thymocytes and lymphocytes[79]. Ruiz-Mateos et al.[76] presented opposite conclusions, finding an inverse correlation between IL-7 levels and thymic volume in HIV-infected adults before HAART therapy. The authors suggested that a baseline IL-7 level might trigger thymic rebound in HIV-infected patients under HAART, although only in those patients without irreversible damage to the thymus and the peripheral lymphoid organs. In conclusion, Ruiz-Mateos et al.[76] did not recommend the use of IL-7 for immunomodulatory therapy in patients with HIV infection.

Anti-tumor activity of IL-7

There are several reports from both murine and human studies describing the anti-tumor activity of IL-7. In melanoma-bearing mice, maximal anti-tumor effect was reached after treatment with IL-7 in combination with local hyperthermia. Restoration of NK cell activity as well as increases in IL-1α, IL-6, tumor necrosis factor α, and interferon (IFN)-γ levels were accompanied by a prolongation of survival time[88]. The anti-tumor effect was also observed in patients with metastatic melanoma. The application of exogenous IL-7 augmented LAK cell proliferation and activity[55]. There are many other studies describing the effect of systemic administration of IL-7 in antitumor treatment (see Fry and Mackall[30] for a review). Concluding, it seems that IL-7 is a molecule that can augment anti-tumor immunity.

Several investigators have used gene transfer techniques to increase local production of IL-7 in tumor cells or within the tumor microenvironment. IL-7 gene transfer enhances the immune response to tumor cells and can support tumor regression. Finke et al.[27] applied adenovirus-enhanced CD3 receptor-mediated IL-7 gene transfer in SCID mouse bearing human lymphoma. An episomally replicating plasmid containing human IL-7 cDNA under the control of a cytomegalovirus promoter was used for transfecting cytokine-induced killer (CIK) cells. Transfected CIK cells demonstrated a significantly higher cytotoxic activity against various tumor cell lines (e.g. renal cell carcinoma, malignant melanoma, and colon carcinoma) compared with non-transfected cells. A report by Miller et al.[58] described the intratumoral administration of IL-7 gene-modified DCs. In two different murine lung cancer models, IL-7-transduced DCs (DC-AdIL-7) were administered intratumorally, resulting in complete tumor regression. Compared with other intratumoral therapies, including rIL-7, AdIL-7 vector alone, unmodified DCs, IL-7-transduced fibroblasts, or DCs pulsed with tumor lysates, the DC-AdIL-7 therapy was much more effective in augmenting immunogenicity and achieving anti-tumor response. Another group described the application of lentiviral vectors for IL-7 gene transfer into resting primary T lymphocytes[83]. An interesting study by Bello-Fernandez et al.[9] describes the use of a bicistronic retroviral vector containing the IL-7 cytokine gene and the surface immunoselectable low-affinity nerve growth factor receptor gene. The vector was used for the transduction of DC-like cells obtained from patients with acute myelogenous leukemia. It was shown that IL-7-modified leukemic cells induce stronger T cell stimulation and that cytokine-transduced DC-like cells can effectively prime and generate cytotoxic T lymphocytes against autologous leukemic blasts.

Anti-microbial activity of IL-7

Another potentially useful application of IL-7 is connected with its anti-microbial activity. It has been shown that in mice infected with a polycythemia-inducing strain of Friend virus complex, administration of IL-7 can prolong survival time and reduce

viral load. The result is connected with NK cell activation and IL-6 and IFN-γ level restoration[56]. The observations by Kasper et al.[46] on mice infected with *Toxoplasma gondii* indicate that exogenous administration of human rIL-7 is effective in stimulating the immune response to the infection, mainly by increasing IFN-γ production and augmenting the $CD8^+$ T cell-mediated cytotoxic T lymphocyte response. However, the studies carried out on BALB/c mice genetically susceptible to infection with *Leishmania major* revealed that IL-7 treatment at the beginning of the infection significantly accelerated death of the animals. The disease-aggravating activity of IL-7 is thought to be primarily due to augmentation of B cell lymphopoiesis and an increase in T helper type 2 immunity[33]. These results are in contrast to the previously reported finding that *in vitro* IL-7 treatment of murine macrophages (originating both from BALB/c and resistant C57BL/6 mice) infected with *Leishmania major* leads to a reduction in the percentage of infected cells[32].

CONCLUSIONS

IL-7 has a broader range of activity than previously believed and may play an important role not only in lymphocyte development and activation, but also in the inflammatory immune response. The potential clinical usefulness of IL-7 in lymphoid reconstitution, infectious diseases treatment, and anti-tumor therapy is promising. However, there are still areas in the field of IL-7 biology that remain to be elucidated, for example IL-7 signal transduction and/or the regulation of the expression of the cytokine as well as its receptor.

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