Molecular mechanisms of versatile biological activity of interleukin-7

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As a result of immunological studies of the last 25 years it turned out that interleukin-7 (IL-7) is one of the most important regulatory cytokines of the immune system. It is special in many concerns. Having a strong impact on the development, proliferation and activation of immune cells it is, however, cannot be attributed to the classic cytokine-activators, like IL-2, as many types of cells require its presence at almost all stages of the development, and its spectrum of activities is impressive. The review aims to summarise the numerous data obtained on the IL-7 structure, biological activity, biological significance and features of functioning studied both in vitro and in vivo. We made the main emphasis on the IL-7 signal transduction pathways that determine the fate of T and B cells, as well as some other cells important for homeostasis of the organism. In our opinion, the analysis of literature in this field not only reveals a host of questions still unanswered, but also makes the path for perspective investigation more visible.

Keywords: cytokine, immune system, signal transduction, regulation.

Introduction. In recent years, considerable attention has been paid to studying the mechanisms of communication between different cell types important for the integrity and homeostasis of the organism. An unusually large number of signaling molecules were discovered including their receptors and intracellular messengers involved in either the activation or suppression of various genes influencing functional behavior of the cell. All these molecules form an incredibly complicated signaling network exploiting the principles of overlapping, amplification or turning off certain signaling pathways and elements. One of the most complicated signaling networks is a cytokine signaling network.

Cytokines are special signaling glycoproteins belonging to the immune system and having molecular weight less than 30 kDa. They are released into the blood and lymph mainly by T cells and act at very low concentration (10⁻¹² M).

However, in addition to T cells, cytokines are produced by broad range of cells, including immune cells like macrophages, B lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell [1]. In total, there are over 100 cytokines, that are classified according to their functions into interferons, interleukins, colony stimulating factors, chemokines and tumor necrosis factors. It is considered that the interleukins (ILs) family comprises 37 members (IL-1-37); however, currently more than 40 cytokines are designated as ILs.

This review is dedicated to a special member of the gamma-chain cytokine family – interleukin-7 (IL-7). It was discovered at Immunex Research and Development corporation in 1988 [2]. Human cDNA was first cloned in 1989 [3]. Numerous studies revealed that IL-7 is a nonredundant hematopoietic cytokine, which plays a crucial role in the development and homeostasis of many types of immune cells.
Here we try to encompass the latest data about the mechanisms of signal transduction that allow revealing an intricate network of interactions of IL-7 with other cytokine signaling systems. In spite of considerable information obtained on IL-7, still only few data on the role of interaction between IL-7 and other signaling molecules are available and need to be reviewed, as well as some other aspects of its biological effects.

**Interleukin-7 molecular structure.** Interleukin-7 is a single chain 25kD glycoprotein containing 4α helices that are internally disulfide cross-linked. Hydrophobic core of human IL-7 is formed by amino acids L16, M17, I20, L23, L24 (helix A), F55, L56, A59, L63, F66 (helix B), L79, V82, T86, L89, T93 (helix C), L128, L131, L135, I138 and W142 (helix D). As it is typical for hematopoietic cytokines, amino acid residues of side sequences are also parts of the core of the molecule. In case of IL-7 they are M27, F39, F41, F42 (loop AB) and F75 (loop BC) [4].

Human IL-7 gene is located at 8q12-q13 chromosome. The length of this gene is about 33 kb and it contains 6 exons and 5 introns. The protein product of the IL-7 gene has molecular weight of 17.4 kDa, but after N-glycosilation at three sites (Asn95, Asn116 and Asn141) it reaches 25 kDa.

IL-7 molecule contains six cysteine residues, which make three intramolecular disulphide bonds (Cys 34–Cys 129, Cys 47–Cys 141 and Cys 2–Cys 92). IL-7 molecule displays very high stability even with extreme pH variation (from 2.1 to 8.0) [5]. However, it loses its biological activity after the addition of β-mercaptoethanol, pointing to the importance of disulfide bonds [6]. Up to 6 isoforms have been described as the products of alternative splicing, and predictions of their structure have been generated. There are three additional in-frame splice variants, which lack exons either 3 or 5 or both and exon 4, respectively: IL-7delta3/4, IL-7delta4/5 and IL-7delta3/4/5. Also three out-of-frame splice variants were found: IL-7 (~56 bp exon 2), IL-7delta4 (~56 bp exon 2), and IL-7delta3/4/5 (~56 bp exon 2), which, besides the aforementioned exon deletions, miss 56 bp at the 3' end of exon 2 [7]. The biological properties of IL-7 splice variants are poorly investigated.

**Sites and regulation of production.** Production of IL-7 has been detected in multiple stromal tissues, including the thymus and bone marrow [8, 9]. Within the thymus, the predominant cell responsible for IL-7 production appears to be a major histocompatibility complex (MHC) class II+ epithelial cell that likely represents a cortical epithelial cell [10]. The additional sites of IL-7 production include intestinal epithelium, keratinocytes, fetal liver, adult liver, dendritic cells and follicular dendritic cells [11–17]. Thus, IL-7 is essentially a tissue-derived cytokine, with the primary sources in stromal and epithelial cells of various locations, whereas bone marrow-derived dendritic cells appear to be relatively minor sources of IL-7.

**Biological effects of IL-7.** Originally, IL-7 was described as a pre-B cell growth factor (lymphopoietin-1) found in the supernatant of the bone marrow-derived stromal cells [18]. However, the studies soon followed demonstrated that *in vitro* IL-7 was also important for mature T cell and thymocyte growth. Subsequently, *in vivo* studies have shown that IL-7 plays an important role in the T cell development [19], mature T cell homeostasis [20] and the development of so called lymphoid tissue inducer cells (LTi cells) [21], playing a key role in the development of lymph nodes and Peyer's patches [22]. IL-7 is also important for dendritic cells (DCs) [23] and natural killer cells (NK cells) [24]. Deficiencies in IL-7 or any component of IL-7R in mice result in severely impaired B and T lymphopoiesis [25].

**Interleukin-7 receptor (IL-7R).** IL-7 mediates its effects via engagement of specific receptor, IL-7R – a heterodimer comprised of IL-7Rα (also known as CD127) and the common cytokine receptor γ-chain (γc, also known as CD132), and mediates anti-apoptotic and co-stimulatory proliferative signals. As summarized in Fig. 1, IL-7-mediated signaling participates in the T cell receptor (TCR) gene rearrangement through DNA demethylation and histone acetylation during the T cell development in the thymus. IL-7-mediated signaling initiates downstream signaling pathways through Janus kinase 1 (Jak1), Jak3 and phosphatidylinositol-3-kinase (PI3K), resulting in phosphorylation and activation of signal transducer and activator of transcription 5 (STAT5).

This results in changes in the expression of B cell lymphoma 2 (Bcl-2) family members, such as increased expression of the anti-apoptotic molecules Bcl-2 and Mcl1 (myeloid cell leukaemia sequence 1) and decreased expression of the pro-apoptotic molecules BAX...
(Bcl-2-associated X protein), BIM (Bcl-2-interacting mediator of cell death) and BAD (Bcl-2 antagonist of cell death). IL-7-mediated signaling in T cells also leads to decreased levels of the cyclin-dependent kinase inhibitor p27 (also known as p27Kip1), increased levels of CDC25A (cell division cycle 25 homologue A) and changes in the expression of TCR modulators such as Casitas B-lineage lymphoma B (CBL-B). The results of IL-7-mediated signaling are increased T cell survival, increased proliferation, augmented TCR signals and, for recent thymic emigrants, TCR-independent proliferation. In contrast to other members of the γc cytokine receptor family, which are upregulated upon T cell activation and/or cytokine signaling, IL-7Rα is expressed mostly by resting T cells and is downregulated following IL-7-mediated signaling and/or T cell activation [26, 27].

The molecular weight of IL-7R protein is about 121 kDa. Both IL-7Rα and γc have a pair of conserved extracellular cysteine residues and an extracellular Trp-Ser-X-Trp-Ser motif and lack the intrinsic tyrosine kinase activity and two partially conserved regions in the membrane-proximal part of their intracellular domains. The γc chain augments IL-7 binding to IL-7Rα chain. The IL-7Rα protein exists in two isoforms: membrane-bound and soluble forms. The membrane-bound isoform is also found on the cell surface in association with IL-2Rγc [28]. Binding assays have demonstrated the presence of two IL-7 receptor affinities: a high ($K_d \sim 10^{-10}$ M) and a low ($K_d \sim 10^{-4}$ M) affinity. It has been also demonstrated that IL-7 can induce signal transduction events in cells that do not express IL-7R because of its capacity to engage other surface receptors such as Flt3 and c-kit [29].

IL-7Rα is a transmembrane heterotypic cytokine receptor belonging to the cytokine receptor homology class I (CRH1) family and to the γc family. γc functions as the activating receptor for IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21 [30]. Full-length human IL-7Rα consists of a 219-residue extracellular domain (ECD), a 25-residue transmembrane domain (TMD), and a 195-residue intracellular domain (ICD) [31]. IL-7 signaling was initially thought to function via the classical stepwise cytokine-induced receptor heterodimerization way [32]. By this mechanism, IL-7 interacts with the IL-7Rα ECD, forming a 1:1 assembly, which subsequently recruits γc, producing the signaling complex. However, the classical paradigm was questioned when IL-7Rα homodimers and IL-7Rα–γc heterodimers were demonstrated on T cells in the absence of IL-7. Neither the preassembly of IL-7Rα homodimers nor IL-7Rα–γc heterodimers induced signaling [33].

**IL-7R ligand binding.** IL-7Rα homodimer consists of two IL-7Rα molecules packed against each other with pseudotwofold symmetry (Fig. 2). This structure explains why homodimerization of IL-7Rα does not activate either IL-7 or TSLP signaling pathways. The average distance between the C-terminal domains of the α/β receptors and γc is 27 Å. Similar distance between the C-terminal domains of IL-7Rα and γc in an activating complex was predicted. However, the distance between the C-terminal domains of the homodimeric IL-7Rα structure is 110 Å. It means that the Jak1 molecules bound to the IL-7Rα ICDs are not able to activate each other because of the distance between them. The investigations demonstrated a stronger binding affinity between the full-length IL-7Rα and γc than between the IL-7Rα in a ho-
modimer on T cells at 37 °C [33]. The following studies showed that there is a stronger binding affinity for heterodimerization of the IL-7Rα–γc ECDs than for homodimerization of the IL-7Rα ECDs (Kd of 3.1 μM vs > 610 μM at 25 °C) [34].

As it has been already stated, the IL-7Rα homodimer keeps the Jak1 molecules bound to the ICDs separated by 110 Å. Likewise, the IL-7Rα–γc heterodimer would keep Jak1 and Jak3 separated by a large distance preventing activation. When IL-7 binds both IL-7Rα and γc, the receptors undergo 90° rotation away from the cell surface, bringing the two C termini of IL-7Rα and γc at a distance less than 30 Å and activating signal transduction [34].

The spontaneously formed 1:1 heterodimers of IL-7R and γc (1:1 stoichiometry) at the surface of living human CD4+ T cells in the absence of IL-7 also were described. IL-7Rα is abundant on the resting human CD4+ T cells (108 pmol/m²), but γc is present at low concentrations (12 pmol/m²) and thus restricts the heterodimer formation (10 pmol/m²) [35]. The heterodimer has a dissociation constant Kd of 19 pmol/m² which is greater than the γc chain concentration. This explains why 80% of γc are found in the bound state in cultures of living cells [36, 37]. The affinity of IL-7Rα to γc is 17-fold greater than to itself, meaning that formation of the heterodimer is largely favored and does not limit γc binding. Both heterodimers and homodimers coexist in resting cells [34].

The receptor complex compartmentalizes after IL-7 binding. Interestingly, about 70% of the proteins recruited upon IL-7 binding belong to the the cytoskeleton or are associated with lipid rafts. IL-7 binding drives receptor complex into lipid rafts. By the other probable mechanism lipid rafts are formed around the receptor. The IL-7–IL-7R complex consequently recruits proteins for the construction of the signaling complex. These recruited proteins are FERM proteins (ezrin, radixin, moesin) that anchor the rafted receptor complex to the cytoskeleton to prevent its diffusion. As far as the lipid rafts are rich in cholesterol and sphingomyelin, the membrane thickness is increased. This helps to hold the long transmembrane domain straight, which in turn keeps the juxtaposition of the cytoplasmic domains. The lateral diffusion of lipids and embedded proteins is reduced by the network of hydrogen bonds between cholesterol and sphingomyelin and this prolongs IL-7–IL-7R association, what is essential for the signaling [38]. The cytoskeleton provides a scaffold for movement of signaling proteins involving complicated machineries to dispatch signaling molecules to their targets.

**IL-7R signaling. Jak/STAT and Src activation.** As it was said, the binding of IL-7 to the IL-7R leads to dimerization of α and γc chains, which brings Jak1 and Jak3 in close proximity and allows for trans-phosphorylation, resulting in the increased kinase activity. Activated Jak kinases phosphorylate tyrosine residues of the IL-7Rα chain ICD that in turn creates docking sites for SH2 containing proteins. Jak3–/– or the γc–/– knock-out mice have similar phenotypes as well as IL-7–/– or the IL-7Rα–/– knock-out mice. Mutations in Jak3 or the γc chain in humans lead to a T-NK-B-SCID phenotype [39, 40]. Jak1–/– mice exhibit a severe reduction of T and B cells, are runt at birth, and die perinatally [41]. IL-7Rα phosphorylation is crucial for initiating down-stream signaling as it leads to the recruitment of STAT proteins to these phosphorylated residues. Phosphorylation of the STAT proteins allows them to dimerize and translocate to the nucleus where they act as transcription factors by binding to specific promoters [42]. The STAT family includes seven STAT proteins (STAT 1–4, 5a, 5b and STAT6). Only STAT1, STAT3, STAT5a and STAT5b take part in IL-7 signaling [43,44]. STAT1 does not play a direct role in lymphopoiesis but STAT3 is required, because a serious reduction in pro-B, pre-B, immature
and mature B cells, and pro-B cells was observed in STAT3\textsuperscript{−/−} mice. Additionally, these mice exhibited a decrease in proliferative responses to IL-7 [43]. STAT5 is the main STAT protein activated by IL-7 and mediates most of the responses of Jak/STAT pathway in cells, including the activation of ccdn2, ccdn3, Bcl-2, Bcl-xl, and Mcl-1 [45,46]. STAT5 is recruited to phosphorylated Tyr449 of the IL-7R\textalpha chain where it is subsequently phosphorylated by Jak and Src kinases. STAT5\textalpha and STAT5\textbeta are absolutely essential for th cell development. This was proved by using STAT5\textalpha/b double deficient mice, which have been arrested at the pre-pro-B cell stage. IL-7R\textbeta mice had similar phenotype [47]. Moreover, the constitutive activation of STAT5\textbeta in IL-7R\textsuperscript{−/−} mice significantly increased pro-B cells [48]. The use of Rag1-Cre knock-in mice for conditional mutagenesis of STAT5 in B cells led to complete inactivation of STAT5 which caused severe defects in the further development of B cells [49]. IL-7 binding also recruits Src kinases to IL-7R\textalpha including both p59fyn and p53lyn. The Src kinase inhibitors are shown to be involved in impaired proliferative responses to IL-7 [50]. The Src family kinases play redundant roles during the B cell development and their function in IL-7 signaling has yet to be fully elucidated. One potential role is to help to activate the STAT proteins, because Src kinases can directly phosphorylate the STAT proteins independently or in conjunction with the Jak proteins [51].

**PI3K/Akt and MAPK/Erk pathways.** IL-7 binding to its receptor also leads to activation of phosphatidylinositol 3-kinase (PI3K). PI3K is a heterodimeric protein built of two subunits: catalytic subunit (p110\textalpha, p110\textbeta or p110\textdelta) and regulatory subunit (p55\textalpha, p55\textbeta or p85\textalpha). P85\textalpha of PI3K is also SH2 containing protein which is recruited to phosphorylated Tyr449 of IL-7R\textalpha [52]. Mutations of Tyr499 or the p85 subunit, as well as use of the PI3K inhibitors, resulted in a loss of the IL-7-induced proliferation and impaired the B cell development [53–55]. The p110\textalpha\textsuperscript{−/−} and p110\textalpha\textsuperscript{−/−} double deficient mice were arrested at the pre-B cell stage, but showed less impaired proliferative responses to IL-7, which means that the p110\textalpha and p110\textalpha subunits play essential but redundant roles during B lymphopoiesis [56].

The most important downstream mediator of PI3K is serine/threonine kinase Akt (PKB). Akt regulates a large number of pro- and anti-apoptotic factors. One of the important targets of Akt is the Forkhead box (FoxO) family of transcription factors (TFs) [57]. Akt phosphorylates the FoxO proteins which in turn bind 14–3–3 proteins. The phosphorylation retains them in the cytosol where they are unable to regulate the gene transcription. Akt regulates cell survival inducing Bcl-2 and Bcl-xl, and inhibiting Bad by phosphorylating it and causing it to be retained in the cytosol where it remains inactive [58].

IL-7R signaling also involves the MAPK/Erk pathway. Treatment of pre-B cells with Erk inhibitors as well as deletion of Erk1/2 in mice blocked the pro-B to pre-B cell transition and caused a decreased IL-7-induced pro-B/pre-B cell survival and proliferation. This means that Erk is an extremely important molecule in IL-7 responses [54, 57]. Activated Erk proteins translocate to the nucleus where they phosphorylate a variety of TFs including Elk and CREB, which in turn induce the expression of proliferation associated targets llf2, Mef2c, Mef2d and myc [59]. The adaptor protein Shc also may be an important mediator in MAPK/Erk pathway because the pro-B cells containing a defective Shc protein displayed an increased apoptosis level [60, 61].

**IL-7/Jak3/NFATc1 signaling pathway.** As it was mentioned, there are a variety of signaling pathways mediating the IL-7 influence on cells. These include Jak/STAT, PI3K/Akt, MAPK/Erk signaling pathways and there are a huge number of molecules involved in signal transduction. For instance, the Jak1 and Jak3/STAT5 signaling pathway leads to production of the effector molecules, such as Bcl-2, which are crucial for T and B cell progression and proliferation (Fig. 1). The IL-7–STAT5 pathway is the only critical pathway of the pre-TCR development of T cells in the thymus [62,63]. However, recently Patra et al. identified the alternative IL-7/NFATc1 pathway that cooperates with the IL-7/STAT5 during the thymocyte development [64].

IL-7 signaling was found to activate NFATc1 and facilitate its translocation to the nucleus, which was independent of STAT5 but dependent on the Tyr371 phosphorylation of Jak3. NFATc1 is a member of the NFAT family of transcription factors. NFATc1 is a lymphoid-specific factor involved in the differentiation and function of T cells. NFATc1 increases Bcl-2 expression by cooperating with STAT5, which in turn affects the survival of thymocytes [65].


**Negative regulators of IL-7 signaling.** There are multiple mechanisms of downregulation of IL-7 signaling, including phosphatases, cytokine-inducible inhibitor molecules, transcriptional suppressors and STAT degradation. They are necessary for termination of the signaling of overactive cytokines to prevent autoimmunity or tumourigenicity. SHP-1 is one of the negative regulators of cytokine signaling [66]. SHP-1 can dephosphorylate both Jak as well as activated receptor subunits, depending on the pathway activated [67]. SOCS-1 and CIS-1 have also been identified as suppressors of cytokine signaling [68]. For instance, SOCS-1 (suppressor of cytokine signaling proteins-1) can inhibit Jak-kinas due to the binding of phosphorylated tyrosine residues. The cytokine inducible src homology-2 protein (CIS) binds directly to the activated IL-7R. The protein inhibitors of activated STATs (PIAS) are proposed to inactivate STATs. Subsequently, several other members of inhibitors were found (CIS2-CIS7/ SOCS2-SOCS7) [68, 69]. Bel-6 also can bind the STAT docking site on the receptor ICD and repress the signaling. Additionally, CIS/CIS1 negatively regulates STAT5 activation [70]. Inhibition of the downstream signaling of Jak5 has been shown to abrogate constitutive STAT3 DNA binding, inhibit cell proliferation and induce apoptosis in human breast carcinoma cell lines. Moreover, the expression of dominant negative STAT3 in these cells induces growth arrest and apoptosis [71]. The degradation of STAT is another way by which the Jak-STAT pathway can be negatively regulated [72]. The accumulation of STATs in the nucleus can also be regulated at the level of nuclear import or/and export [42]. The mechanisms that control these processes are not completely understood.

**IL-7Rα regulation.** One of the most important mechanisms of regulation of IL-7 signaling is the regulation of the amount of its receptor alpha chain (IL-7Rα) present on the surface of the IL-7 dependent cells, as far as the level of IL-7Rα directly correlates with the cell sensitivity to IL-7. The consumption of IL-7 is strictly controlled by IL-7-induced downregulation of IL-7Rα, because of the limiting amount of available IL-7. This downregulation allows maximizing the total number of the cells which can receive proliferative and survival signals of IL-7 [73]. In the absence of IL-7 signaling, IL-7Rα expression on the cell surface is regulated by ephrin molecules (Efns). The deletion of ephrin genes in T cells, particularly Efnb1 and Efnb2, leads to a decreased peripheral naive T cell compartment size. These Efns stabilize IL-7Rα expression on T cells interacting directly with IL-7Rα [74]. In Efnb1/Efnb2 double deficient T cells upon IL-7 stimulation it was observed a stronger downregulation of IL-7Rα, as well as a decreased STAT5 phosphorylation level. Upon IL-7 stimulation, IL-7Rα expression on the cell surface is downregulated. Although IL-7Rα regulation occurs at the transcriptional level by multiple mechanisms, it is also regulated at the post-translational level. IL-7Rα does not persist stably at the cell surface in the absence of IL-7, but is rather constantly endocytosed via the clathrin-coated pits and recycled back to the plasma membrane [75]. In the absence of IL-7, only a fraction of IL-7Rα is degraded through the proteasomal and lysosomal pathway, with the rest recycled back to the plasma membrane. Upon IL-7 stimulation, the degradation/recycling ratio is inverted in favor of degradation, leading to a decreased surface expression of IL-7Rα [75]. Such an increased degradation is dependent on the Jak-3 activity and it concerns only IL-7Rα, but not the γc, as it was shown by the studies with the human lymphoma T cell line [75, 76].

**Soluble IL-7R.** Additionally to relatively well described membrane-bound cytokine receptors there are soluble forms of many of them. The functions of soluble receptors are definitely less understood but they are known to play an essential role in cytokine biology [77]. Soluble IL-7Rα (sIL-7Rα) circulates at high concentration (nmol/mL) compared to IL-7 in healthy humans (pmol/mL) [78]. Besides, the biologic effects of sIL7Rα remain unclear. The biochemical studies showed that sIL7Rα is derived from alternative splicing and comprises an isoform lacking exon 6 (Δ6IL-7Rα) and having a unique 26-aa sequence [31]. Soluble IL-7Rα was reported to block IL-7 signaling. In these studies it was used the IL-7Rα-Fc fusion protein, consisting of the ECD of IL7Rα and human Fc-fragment, which has a lower affinity to IL-7 than native sIL7Rα. However, the coadministration of the same molecule, IL7Rα-Fc, with IL-7 enhanced antitumor effects compared with the administration of IL-7 alone in the immunotherapy model of lung cancer in mice [79]. Complexing IL-7 to anti-IL-7 mAb also enhanced the potency of IL-7 in
mucine models [80, 81]. The next studies have shown that the competition between IL-7R and sIL-7Rα serves to make IL-7 available for all cells according to their needs. This is possible because sIL-7Rα binds IL-7 with nanomolar affinity, whereas IL-7R binds it with picomolar affinity. That is why sIL-7Rα diminishes the availability of free IL-7 and modestly compete with cell-associated IL7R. This results in decreased early signaling, as evidenced by diminished STAT5 phosphorylation, but also leads to IL-7 consumption, leading in turn to overall more enhanced IL-7 effects in the cells which have limited amounts of IL-7. The coadministration of sIL7Rα plus IL-7 increased the half-life of IL-7 in vivo, increased IL-7-mediated homeostatic peripheral expansion of lymphocytes during lymphopenia, and worsened the severity of experimental autoimmune encephalitis compared with that in mice receiving IL-7 alone. However, the administration of sIL-7Rα alone in the same model had no effect [82]. Thus, the experimental data suggest that sIL-7Rα plays the role of a carrier protein, and that the binding of IL-7 to it potentiates the biological activity of IL-7.

Conclusions. The review aims to summarize numerous data on the cytokine IL-7 structure, biological activity, biological significance and features of functioning studied both in vitro and in vivo. We have made the main emphasis on the IL-7 potential and conditions to govern the activity of the appropriate signal transduction pathways that determine the fate of T and B cells, as well as LTI cells, NK cells and DCs, which are extremely essential for the development of immunological reactions of the organism. In our opinion, the literature analysis in this field reveals a host of questions remained unanswered so far, and also makes the path for perspective investigation more visible.

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