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The Human IL-7 Receptor Gene: Deletions, Polymorphisms and Mutations

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Abstract

Most T cell subsets depend on IL-7 for survival. IL-7 binds to IL-7R α and γ_c , initiating the signaling cascade. Deletion of *IL-7R α* in humans has, for some time, been known to cause severe combined immunodeficiency. More recently, polymorphisms in *IL-7R* have been shown to be a risk factor for a number of diseases that are autoimmune or involve excess immune and inflammatory responses including multiple sclerosis, type 1 diabetes, rheumatoid arthritis, primary biliary cirrhosis, inflammatory bowel disease, atopic dermatitis, inhalation allergy, sarcoidosis and graft-versus host disease. The polymorphism that affects risk to most of these immunopathologies is T244I at the border of the extracellular domain and the transmembrane region. The same region has recently been shown to harbor gain-of-function mutations in acute lymphoblastic leukemia. These studies have suggested new therapies that target the IL-7 pathway.

Keywords

IL-7R; IL-7; T244I

1. Introduction

Interleukin-7 (IL-7) was initially discovered as a factor promoting B cell development in mice (reviewed in [1] [2]) and more recently in human B cell development [3]. IL-7 was later shown to be essential for T cell development in the thymus and for survival and proliferation of memory and naive T cells (reviewed in [4]) and T helper type 17 (Th17) cells [5]. IL-7 function is mediated by the IL-7 receptor, a membrane receptor composed of the specific IL-7R α chain and the γ_c chain shared by receptors for other cytokines (IL-2, -4, -9, -15 and -21). In this review, we will use the term “*IL-7R*” to refer to the gene encoding

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IL-7R α . The phenotypes of both *IL-7* and *IL-7R* knockout mice are dramatically lymphopenic [6,7] and defects in IL7-R cause severe immunodeficiency in humans [8] as will be discussed. TSLP is an additional ligand for IL-7R [9], and as we discuss the human impact of IL-7R variants in this review, it should be kept in mind that both the IL-7 and TSLP pathways could be involved.

2. Immunodeficiency

Severe combined immunodeficiency (SCID) is a heterogeneous group of genetic disorders caused by mutations in a number of genes involved in the development of lymphocytes. X-linked SCID is the most frequent and is caused by mutations in the gene for the γ c chain [10]. The phenotype of γ c-deficient SCID is characterized by absence of T and NK cells and a normal number of B lymphocytes [11,12]. Although γ c is shared by other cytokine receptors, the T cell deficiency is largely attributable to the loss of IL-7R signaling whereas the NK deficiency is attributable to loss of IL-15R signaling. About 10% of SCID patients showed specific mutations in *IL7RA* gene, resulting in autosomal recessive SCID with a specific T-B+NK+ phenotype [8,12-19]. It was later shown that development of B cells in adult humans probably depends on IL-7, whereas neonatal B cell development does not [3]. The SCID patients are newborns because they do not survive to adulthood without bone marrow transplantation. Therefore this would explain why they have B cells, whose neonatal development is IL-7-independent, but if they could they survive to adulthood, it is predicted that B cells would be absent, reflecting their IL-7 dependent development.

Omenn syndrome (OS) is a genetic disease characterized by severe combined immunodeficiency and autoimmune responses. Patients develop erythroderma, lymphadenopathy and recurrent infections. OS was initially thought to be induced only by non-null or “leaky” mutations in *RAG1*, *RAG2* genes inducing a block in T and B cell development (reviewed in [20]); subsequent studies demonstrated that non-null mutations in several genes, *IL7R* among them, can also cause an OS clinical phenotype. In one patient, a mutation was identified in exon 3 of *IL-7R* resulting in a cysteine to tyrosine substitution (C118Y) [21] which presumably weakens receptor signaling. Generally, these leaky mutations in OS permit development of extremely pathogenic autoreactive T cells and there may be several mechanisms of tolerance failure in these cases. One mechanism involves lack of regulatory T cells. A second mechanism involves failure to induce central tolerance because some T cell signaling is required for thymic epithelial cells to develop correctly, and they in turn are required to induce tolerance in developing T cells.

3. Autoimmunity

The IL-7 pathway is essential to immune system development and maintenance in physiological conditions. However, genetic variations in *IL-7R* are implicated in several severe autoimmune disorders (summarized in Table 1). There is a common genetic basis for several of these as will be discussed.

3.1 Multiple sclerosis

Multiple sclerosis (MS) is a chronic disease characterized by inflammation of the central nervous system and progressive demyelination leading to axonal and neuronal degeneration. In a mouse model of MS, experimental allergic encephalomyelitis (EAE), the IL-7 pathway was first implicated in studies showing that IL-7 induced expansion of pathogenic myelin-specific T cells [22]. This was extended to human T cells from MS patients which were shown to increase reactivity to myelin following in vitro culture with IL-7 [23]. Subsequent studies have verified that the IL-7 pathway exacerbates EAE and shown its role in promoting development of pathogenic Th17 cells [5,24,25].

Several studies showed the first evidence of genetic association between susceptibility to MS and polymorphisms in the *IL-7R* gene [26-28]. More precise identification of a specific polymorphism in *IL-7R* was shown in many subsequent studies in different populations to increase the risk for MS. This association of *IL-7R* is second only to MHC polymorphisms in affecting risk for MS [29-38]. Other factors, such as environment or different genome variants, must also influence MS since some studies did not confirm an association [39,40]. The same allele is associated with higher risk in the autoimmune diseases type I diabetes (T1D) [41,42], rheumatoid arthritis (RA) [43], the autoinflammatory disease sarcoidosis [44], and the allergic diseases such as atopic dermatitis (AD) [45] and inhalation allergy [46] as will be discussed.

The high risk allele for MS, T1D, RA, sarcoidosis, AD and inhalation allergy encodes T244, whereas the low risk allele encodes I244. This residue is located in the 6th exon of the extracellular domain at the border of the transmembrane region. The high risk T allele was shown to exhibit an increased frequency of skipping the 6th exon during transcription, resulting in a transcript lacking the transmembrane region, and creating a soluble IL-7R [30,47]. The hypothesis formulated by the authors of these studies is that soluble IL-7R acts as a competitor of surface IL-7R and therefore lowers the availability of IL-7 to T cells in patients with the high risk allele. According to this hypothesis, administering IL-7 could benefit MS patients as well as patients with the other autoimmune diseases. However, this hypothesis is inconsistent with many animal studies that demonstrate the opposite: more IL-7 signaling increases disease severity in EAE [5, 22,24].

An alternative hypothesis would be that the functional significance of the 244T/I polymorphism in IL-7R is related to signaling strength, not to exon skipping. It has recently been shown that precisely this region of IL-7R (Figure 1) can greatly influence signaling [48,49]. It was determined that insertions immediately before or after residue 244 are gain-of-function mutations that create oncogenes driving T cell acute lymphoblastic leukemia. Threonine is a polar amino acid whereas isoleucine is hydrophobic, so they may affect the signaling function of IL-7R. It is therefore plausible that T244 signals more strongly than I244, and this promotes activation of autoimmune T cells in MS and other autoimmune diseases. This hypothesis would be consistent with data from animal models, whereas the exon skipping hypothesis is not consistent. If correct, this hypothesis has the opposite implication for therapy for MS and other autoimmune diseases: administering IL-7 could greatly exacerbate disease, whereas antagonists of the IL-7R pathway may have therapeutic efficacy.

Although polymorphisms in *IL-7R* are consistently associated with MS among different population studies, it is interesting to note that an *IL7* genetic association is less consistent. A study on a cohort on Sweden patients did not identify any *IL7* SNP related to MS [31], while a recent study on samples from US and UK revealed several SNPs associated with MS and among them, two SNPs that were not significant for the Swedish patients [50]. We will discuss the implications of *IL-7R* versus *IL-7* genetic effects in the Conclusions section.

In MS patients, the amount of IL-7R tends to be higher than normal on some T cell subsets [51]. Curiously, in MS patients with a different protective (non 244) polymorphism in the promoter region, an elevated IL-7R expression was observed [36]. Although this seems surprising (elevated IL-7R is expected to stimulate more autoimmunity) it was also associated with more Tregs and recent thymic emigrants [36], compared to other genotypes in MS patients which have relatively depressed representation of these subpopulations [36,52,53]. It has also been reported that alternative splicing patterns of *IL7* and *IL7RA* mRNAs differ between MS patient and healthy donors, splicing which could potentially affect the IL-7 pathway [54].

3.2 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a common autoimmune/inflammatory condition characterized by a severe chronic inflammation of joints. A role of the T244I polymorphism in *IL7RA* gene was described as a genetic predisposition to RA [43]. This may not be generalized to other populations since another study did not confirm this gene as a risk locus [55]. Many studies have examined expression of IL-7 and IL-7R in RA with somewhat different conclusions, which may be explained by the different treatments the patients were undergoing [56]. Synovial CD4⁺ T cells from RA patients express high levels of IL-7R [57], and it has been suggested that IL-7 induces production of TNF which is a well established mediator of inflammation in RA and a target of current therapy. A correlation between IL7 and TNF levels has been also demonstrated in synovial fluid from RA patients [58]. Thus, the levels of IL-7R, regulated by polymorphisms, could affect this pathway.

3.3 Diabetes

Type I diabetes mellitus (T1D), an autoimmune disease with an onset in childhood and young adults, affects about 0.05% of the population and is currently rising. T1D is caused by destruction of pancreatic β -islets by an autoimmune inflammatory process driven by infiltrating cytotoxic lymphocytes and Th1 cytokines (IFN- γ , IL-2 and TNF- α) and leading to complete loss of insulin production.

An effect of the T244I polymorphism in *IL7R* has been associated with risk for type I diabetes in a genome-wide association study (GWAS) [41] and later confirmed in a Spanish cohort of young T1D patients [42]. As previously discussed in the MS section, I244 in the 6th exon appeared to be protective. Thus, the homozygous I244 allele was present in 6% of controls, but only 1.5% in young diabetics. A caveat is that, in the Spanish cohort, the *IL7R* SNP was in linkage disequilibrium with calcyphosine like (*CAPSL*) gene and it could not be rigorously determined that it was the IL-7R allele that produced the effects [42]. It has been

suggested that endogenously elevated levels of IL-7 may induce preferential expansion of autoreactive memory T cells [59].

The most extensively explored mouse model of T1D is the non-obese diabetic (NOD), developed over 30 years ago, which spontaneously develops T1D. Although more than 30 loci have been implicated in the NOD phenotype, none thus far implicated the IL-7 pathway. It would be of interest to test whether, as in man, perturbations of the IL-7 pathway affect T1D in NOD mice.

3.4 Primary Biliary Cirrhosis

Primary biliary cirrhosis (PBC) is an autoimmune disease of the liver with a previously established association with MHC. A recent GWAS study of PBC patients in the UK [60] showed a susceptibility locus containing the *IL-7R* gene, and this was implicated as the candidate gene. Although the analyzed SNP was not directly related to T244I, the results show the more common allele imparting increased risk, and that would be consistent with T244.

4. Excess immune and inflammatory responses

IL-7 is a homeostatic cytokine controlling survival and proliferation of naïve and memory T cells. As suggested in the preceding sections, excess signaling from the IL-7R is implicated in autoimmune diseases, and as we will discuss, other pathologies attributed to excess immune and inflammatory responses.

4.1 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is caused by an abnormal immune response to intestinal bacteria, resulting in collateral damage to the host tissues (reviewed in [61,62]). An involvement for IL-7 in the pathogenesis of IBD was first suggested by mouse models [63-67] and infiltrating T cells in both mice and humans express high levels of IL-7R. Although IL-7 production has been detected in bowel tissues, systemic rather than intestinal IL-7 was found to be involved in murine colitis [68-70]. In human IBD patients, elevated IL-7 was detected in serum [71], and curiously it rose even higher in remission, thus the actual level of IL-7 was not associated with pathology [72]. Polymorphisms in *IL-7R* were recently found to affect risk for ulcerative colitis [73], one of the two major forms of IBD. Curiously, the ulcerative colitis-associated SNP in IL-7R is not at residue 244, so there may be an additional mechanism involved.

4.2 Atopic dermatitis and psoriasis

A possible IL-7 involvement in skin diseases was suggested by the initial finding that IL-7 is produced by human and murine keratinocytes [74]. Atopic dermatitis (AD) is an extremely common skin condition (over 6% of adults have at least mild AD) dominated by a Th2 response. The same IL-7R polymorphism (T244I) found to affect risk for MS, RA and T1D was also found to increase risk for AD in a cohort of German patients [45]. In patients with severe atopic dermatitis against mite allergens, skin biopsies before patch testing showed

elevated *IL7* mRNA compared to controls, and this rose further following patch application [75].

In psoriasis, polymorphisms in *IL7R* have not as yet been reported to affect risk, whereas overexpression of *IL-7* may be involved. Although an initial study did not identify *IL7* mRNA in skin biopsies from patients with psoriasis [76], subsequent studies showed elevated *IL-7* protein levels in serum [77-79] and in lesion skin biopsies [77]. In mice, *IL-7* overexpression in keratinocytes induced severe dermatitis [80,81].

4.3 Asthma-Rhinitis-Allergy

Asthma is a chronic inflammatory disease of the airways and *IL7R* has been identified as one of the multiple asthma susceptibility loci [82]. Moreover, susceptibility to inhalation allergy was shown to be affected by the same T244I polymorphism in exon 6 of *IL-7R* that affects risk for MS, RA, T1D and AD. A second coding polymorphism in exon 4 of the extracellular domain of *IL-7R* was also implicated in inhalation allergy [46]. Because the cytokine TSLP also acts via the *IL-7R*, and is associated with allergy, it is possible that some of these polymorphisms affect TSLP signaling rather than *IL-7*.

4.4 Sarcoidosis

Sarcoidosis is a chronic granulomatous lung disease with a massive Th1 influx in the lesions. The T244I polymorphism was shown to confer risk for sarcoidosis in a cohort of Dutch Caucasian patients [44]. The same study also showed a trend for T244I association in Lofgren's disease, another granulomatous lung disease, but the size of the patient population was insufficient to determine significance.

4.5 Graft-versus host disease

In graft-versus host disease (GVHD), a polymorphism in *IL-7R* in the donor population was linked to acute disease and mortality [83,84]. However, this did not appear to relate to the T244I exon 6 polymorphism as observed in MS, T1D, RA and AD, but rather to polymorphisms in the coding region in exons 2 and 4. The T46I polymorphism in exon 2 is on the opposite face of the binding pocket for *IL-7*. Since it is not directly involved in ligand binding, it may influence the conformation of the protein or conceivably be involved in binding TSLP; however that would not fit the steric pattern of other related receptors (Scott Walsh personal communication). The I118V polymorphism in exon 4 may affect the association with γc (Scott Walsh personal communication) or possibly the TSLPR and was also implicated in inhalation allergy [46]. Thus T46I affects GVHD and I118V affects both allergy and GVHD, but neither of these polymorphisms has been found to affect MS, RA, T1D or AD as does the exon 6 polymorphism. This difference is as yet unexplained, but may offer clues to different properties of *IL-7R*.

5. Acute Lymphoblastic Leukemia

The *IL-7* pathway has long been suspected to play a role in lymphoid cancers because of its effects of inducing survival and proliferation of normal lymphocytes. *IL-7R* was detected on both T-cell acute lymphoblastic leukemia (T-ALL) [85-89] and B-cell chronic lymphocytic

leukemia (B-CLL) [90,91] and in vitro, IL-7 induced proliferation of T- and B-ALL cells [85,88,92,93]. Although most cells from ALL patients proliferated without differentiation [86,93,94], there was a subgroup of patients whose cells matured in response to IL-7 [94]. IL-7 delayed spontaneous in vitro apoptosis in T-ALL cells, upregulating expression of anti-apoptotic Bcl-2 [95] and inducing cell cycle progression through p27^{Kip1} downregulation [96]. IL-7 stimulation of T-ALL was also reported to interfere with drug-induced apoptosis and cell cycle arrest by prednisolone [97], dexamethasone and doxorubicin [98] and rapamycin [99].

Most recently, gain of function mutations in *IL-7R* have been shown to act as oncogenes in T-ALL [48] and B-ALL [49]. These mutations are generally insertions of bases encoding a cysteine and a proline into the 6th exon of the extracellular domain at the border of the extracellular and transmembrane region, close to the T244I residue. The cysteines form divalent bonds, homodimerizing mutant IL-7Rs and the prolines are also generally required. Signaling is ligand-independent and also independent of γ_c . This is the first example of gain-of-function mutations in this receptor family and it was quite surprising that homodimerization of IL-7R could trigger signaling. Ligand normally recruits γ_c chain, bringing Jak3 into the receptor complex, activating Jak1 that is bound to the intracellular domain of IL-7R. Bivalent antibodies against the wild type IL-7R presumably homodimerize these chains but do not induce signaling. In mutant receptors, it is possible that the proline residue in the insertion induces a conformational change in IL-7R that allows adjacent Jak1s to mutually activate one another.

6. Conclusions

Deficiency of the IL-7 receptor pathway has been known for some time to cause the dramatic phenotype of SCID. More recent studies show the effects of more subtle perturbations in *IL-7R*. Given the potent effects of the IL-7 pathway in lymphocytes, it is perhaps not surprising that genetic variations in *IL-7R* could contribute to immunopathologic diseases. We have discussed the effects of polymorphisms in autoimmunity and in excess immune/inflammatory disorders, and of mutations driving leukemia.

Polymorphisms in *IL-7R*, in addition to affecting autoimmunity, could also influence susceptibility to infectious diseases although this remains to be demonstrated. It has been suggested that IL-7R is one of the few cytokine receptors to show “balancing selection”, a term that describes an advantage for a population to preserve multiple alleles [100]. The extreme example of an immune locus showing balancing selection is MHC whose diversity must accommodate many old and emerging pathogens. In the case of IL-7R, a more vigorously responding receptor may offer greater protection from, as that study argues, helminth parasites, but with added risk of autoimmunity. What T cell subsets receive strengthened IL-7R signals that benefit the host in infection and which ones promote autoimmunity? Is the IL-7R effect on survival, proliferation, tolerance, T cell receptor signaling, or localization of the relevant T cells? There are many speculations on these questions but no clear answers yet.

It is curious that, in contrast to the *IL-7R* locus, the *IL-7* locus has shown little association with human disease. *IL-7* deficiency has created no examples of SCID and there is little polymorphism association with disease. Yet the mouse knockouts of *IL-7* and *IL-7R* are very similar phenotypes. One explanation is that TSLP, the other ligand for *IL-7R*, has more redundant activities with *IL-7* in man than mouse. Another possibility is that rather modest changes in *IL-7R* level or activity have a greater impact than changes in *IL-7*, which may be mainly controlled by consumption [1].

The genetic association of *IL-7R* with diseases suggests new therapeutic approaches directed to *IL-7R* and its downstream signaling components. For example, inhibitors of Janus kinases are in clinical trials for rheumatoid arthritis. These inhibitors may be effective in the other disorders we have discussed such as MS, T1D, RA, sarcoidosis, AD, inhalation allergy, primary biliary cirrhosis, GVHD and ALL.

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Abbreviations

IL-7 interleukin-7

IL-7R	interleukin-7 receptor
Th17	T helper type 17
TSLP	thymic stromal lymphopoietin
SCID	Severe combined immunodeficiency
MS	multiple sclerosis
EAE	experimental allergic encephalomyelitis
T1D	type I diabetes
RA	rheumatoid arthritis
AD	atopic dermatitis
SNP	single-nucleotide polymorphism
Tregs	regulatory T cells
GWAS	genome-wide association study
IBD	inflammatory bowel disease
GVHD	graft-versus host disease
T-ALL	T-cell acute lymphoblastic leukemia
B-ALL	B-cell acute lymphoblastic leukemia
B-CLL	B-cell chronic lymphocytic leukemia

Highlights

- Polymorphisms in IL-7R have recently been linked to a number of immunopathologies.
- Immunopathologies include multiple sclerosis, type 1 diabetes and rheumatoid arthritis.
- They also include inflammatory bowel disease, inhalation allergy and others.
- We propose a new mechanism for the IL-7R polymorphism effect in immunopathology.
- Gain-of-function mutations in IL-7R occur in acute lymphoblastic leukemia.

Figure 1.

Exon 6 of IL-7Ra: The T244I MS susceptibility polymorphism is located in a hotspot of activating insertions in T-ALL.

Table 1**Disease risk associated with polymorphisms in *IL-7R***

Disease	<i>IL-7R</i> Polymorphism	References
Multiple Sclerosis	T244I (exon 6)	29, 30, 31
Type 1 Diabetes	T244I (exon 6)	41, 42
Rheumatoid Arthritis	T244I (exon 6)	43
Sarcoidosis	T244I (exon 6)	44
Atopic Dermatitis	T244I (exon 6) and T46I (exon 2)	45
Inhalation Allergy	T244I (exon 6) and I118V (exon 4)	46
Omenn Syndrome	C118Y (exon3)	21
Graft-versus Host Disease	T46I (exon 2) and I118V (exon 4)	83, 84
Primary Biliary Cirrhosis	(possible T244I)	60
Inflammatory Bowel Disease	(non 244)	73