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REVIEW ARTICLE

IL7RA genetic variants differentially affect IL-7Rα expression and alternative splicing: a role in autoimmune and infectious diseases?

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Abstract

Interleukin-7 receptor α chain (IL-7Rα) single nucleotide polymorphisms (SNPs) are associated with susceptibility to immunopathologies like autoimmune and inflammatory diseases. The current hypothesis about underlying mechanisms is based on the regulation of IL-7 availability for self-reactive T cells by influencing the generation of a soluble (s)IL-7Rα variant. This assumption was mainly predicated on the well-defined *IL7RA* SNP rs6897932, which affects alternative splicing and causes aberrant generation of the sIL-7Rα variant with potential effects on the IL-7 serum reservoir. However, more recent studies shed light on novel functions of autoimmunity risk-associated *IL7RA* SNPs and characterized the largely neglected effect of rs6897932 on membrane (m)IL-7Rα expression. These findings as well as a described role of impaired mIL-7Rα expression and *IL7RA* SNP influence on chronic infectious diseases necessitates the reevaluation of previous findings on the role of *IL7RA* SNPs in immunopathology.

Introduction

Interleukin (IL)-7 is an important cytokine for T-cell development, homeostasis, and the generation of immunological memory. Fine balanced regulation of IL-7 availability and T-cell response to IL-7 is crucial since dysregulation may contribute to development of autoimmunity and impaired immunity against chronic infections. An important role of IL-7 receptor α-chain (IL-7Rα) variants on regulation of IL-7 availability—especially for the soluble IL-7Rα—has been assumed.

Gain-of-function and loss-of-function mutations of the *IL7RA* gene either cause malignancies due to uncontrolled proliferation or abrogate development of T cells. Other *IL7RA* polymorphisms (the best-defined example is the *IL7RA* exon 6 SNP rs6897932) exert more moderate effects, e.g., on alternative splicing and expression of the soluble IL-7Rα. rs6897932 and a subset of other single nucleotide polymorphisms (SNPs) (e.g., rs1494555, rs1494558) have been shown to tag haplotypes associated with susceptibility to autoimmune diseases. Besides effects on soluble IL-7Rα expression and regulation of IL-7 availability, recent findings shed light on additional SNP-mediated mechanisms affecting other IL-7Rα variants and the membranous IL-7Rα. This review summarizes findings on *IL7RA* SNPs with moderate regulatory effects and their potential role on T-cell function. Furthermore, it is discussed how *IL7RA* SNPs may affect immune pathology of autoimmune and infectious diseases.

IL-7 availability for T cells and IL-7 receptor dependent regulation in immune homeostasis and pathology

IL-7 plays a crucial role for T-cell development and function. This is well established since both absence and aberrant strong signaling of IL-7 result in immune pathology. Abrogated IL-7 signaling leads to severe combined immunodeficiency demonstrating the crucial and nonredundant role during lymphocyte (especially T-cell) development [1]. In contrast, aberrant high IL-7 signaling causes lymphoproliferation and contributes to development of T-cell acute lymphoblastic leukemia [2, 3]. Both types of immune

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pathology in patients are caused by germline or somatic mutations, which predominantly affect the IL-7 receptor, either the private IL-7 receptor α (IL-7Rα) or the common-γ receptor chain [4]. These immune pathologies demonstrate that regulation of IL-7 responses on the level of IL-7R expression is central for balanced IL-7 functions. Several studies investigated the complex mechanisms how IL-7R expression is regulated to assure appropriate T-cell functions, and these have been reviewed elsewhere [5]. These studies were the basis for immune intervention strategies using IL-7Rα blocking antibodies, which strengthened the important role of IL-7Rα signaling in pathology of autoimmune and inflammatory diseases [6–10], as well as transplantation [11]. These promising results formed the basis for first clinical trials of anti-IL-7Rα treatment in humans [12, 13].

However, changes in IL-7 availability may also lead to immune pathology, as aberrant high IL-7 serum levels, e.g., during lymphopenia, increase the risk for T-cell mediated autoimmunity [14]. Such high IL-7 serum concentrations are mainly occurring as a consequence of immune suppressive treatment (e.g., bone marrow irradiation, anti-T-cell immune globulins or biologicals) as well in primary and secondary immune deficiencies [15, 16]. As part of recovery, IL-7 induces increased proliferation of T cells and the growing T-cell population consumes more IL-7. This feedback loop mechanism leads to normalized IL-7 levels at physiological T-cell population size. Therefore, also under lymphopenic conditions and high IL-7 levels, regulation by IL-7R expressing T cells is decisive for IL-7-mediated homeostasis [5]. There is initial evidence that certain SNPs in the *IL7RA* gene affect IL-7-dependent mechanisms during lymphopenia with clinically relevant consequences, i.e., recovery from lymphopenia in HIV/AIDS patients [17–20], or risk for development of graft-versus-host disease (GVHD) after bone marrow transplantation [21–23]. These relevant SNPs were also shown to influence susceptibility to autoimmune and inflammatory diseases [4], and, hence, attracted strong interest of the scientific community during the past two decades. Our advanced knowledge on regulation of IL-7R variants is strongly based on studies characterizing effects mediated by the *IL7RA* exon 6 SNP rs6897932.

The autoimmunity-associated SNP rs6897932 affects alternative splicing and expression of the soluble IL-7Rα variant

The membrane-associated IL-7R forms as a heterodimer composed of the IL-7Rα and the common-γ receptor chain [24, 25]. The IL-7Rα chain binds IL-7 specifically, and recruitment of the common γ-chain receptor increases affinity and catalyzes signaling [26]. Like for other cytokines and hormone receptors, a soluble (s)IL-7R variant is generated [27]. Although few studies identified shedding of mIL-7Rα as the underlying mechanism [28, 29], it is now largely accepted that alternative mRNA splicing is the dominant mechanism for sIL-7Rα generation. Secreted sIL-7Rα monomers result from exclusion of the *IL7RA* exon 6, coding for the transmembrane domain of the IL-7Rα chain [30]. This causes a shift in the reading frame and generates a new stop codon early in the exon 8 [27, 31, 32]. A truncated IL-7Rα chain lacking transmembrane and intracellular domains is translated leading to sIL-7Rα secretion [33]. The sIL-7Rα received sudden utmost interest when Gregory et al. reported association of a nonsynonymous SNP variant (i.e., rs6897932C > T; Thr → Ile) within the exon 6 of the *IL7RA* gene with susceptibility to multiple sclerosis [34]. They found that the protective allele (i.e., rs6897932T) interfered with *IL7RA* exon 6 splicing [34], and lower sIL-7Rα serum levels were found in carriers of the protective *IL7RA* allele [35–37]. Since then, several studies demonstrated the relevance of rs6897932T for protection against autoimmune and inflammatory diseases [4, 38–46]. In addition, Galarza-Munoz et al. found epistatic regulation of the rs6897932 SNP by a *DDX39B* allele (associated with multiple sclerosis susceptibility) that markedly strengthened the effect of alternative *IL7RA* splicing [47]. These studies suggested a functional role of the sIL-7Rα and—as shown for other soluble hormone and cytokine receptors—interference with IL-7 availability and consumption was assumed. In accordance, inhibition of IL-7 signaling by a sIL-7R-Fc chimera in vitro has been found [48, 49]. Lundstrom et al. provided a model for sIL-7Rα-mediated IL-7 regulation in vivo, showing that sIL-7Rα (at a specific concentration ratio relative to IL-7) may increase bioactivity of IL-7 by stabilizing the IL-7 reservoir [35]. The sIL-7Rα binds IL-7 with moderate affinity [k_D = 6 nM], but interference with high-affinity mIL-7R complex/IL-7 can be assumed because of high molar excess of sIL-7Rα in the serum (i.e., about 10^3 times more than IL-7) [35]. A role of the sIL-7Rα in ensuring IL-7 availability would strengthen the thesis that links high sIL-7Rα serum concentrations with increased risk for generation of IL-7-dependent self-reactive T cells in autoimmunity [50, 51]. In accordance, lower IL-7 concentrations were found in autoimmune disease patients carrying the protective rs6897932T genotype that causes decreased sIL-7Rα serum levels [35, 52, 53].

Previous studies strongly focused on rs6897932T-mediated effects on the sIL-7Rα and this can be explained by the fact that expected alternative splicing effects of rs6897932 SNPs on mIL-7Rα expression of T cells were not detected [48] (own unpublished data). There is now

increasing evidence that the SNP-associated mechanisms affecting IL-7 levels are more complex and that sIL-7Rα-independent mechanisms of IL-7 regulation are involved.

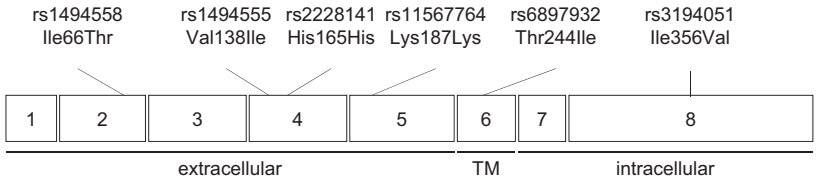
The autoimmunity risk-associated SNP rs1494558 causes lower sIL-7Rα expression

The nonsynonymous SNP (i.e., rs1494558C > T; Thr → Ile) located within the *IL7RA* exon 2 tags an autoimmunity risk-associated haplotype [34, 54]. This SNP is in strong linkage equilibrium with the rs1494555 SNP in exon 4 that has originally been identified [34]. We characterized rs1494558 effects on IL-7Rα and found decreased soluble and membranous IL-7R expression in rs1494558Ile-transfected cell lines [55]. Decreased sIL-7Rα secretion of the rs1494558Ile-tagged haplotype was confirmed in T1D patients, who had lower sIL-7Rα serum concentrations when carrying rs1494558Ile [55]. In the same study, we confirmed that also T1D patients with the rs6897932Ile haplotype had lower sIL-7Rα serum levels indicating that both autoimmunity risk- and protection-associated haplotypes are characterized by a similar pattern. Lower IL-7 serum levels of T1D patients, however, were exclusively found for the protection-associated rs6897932Ile haplotype [53]. These results, and the fact that no correlation was detected between sIL-7Rα and IL-7 serum levels from individual T1D patients [53], argue for sIL-7Rα-independent mechanisms of *IL7RA* haplotypes affecting IL-7 availability.

Differential mIL-7Rα expression is an alternative possible explanation for contrary effects mediated by rs6897932Ile and rs1494558Ile variants. To proof this assumption, we generated a cell line-based model for concomitant assessment of risk- and protection-associated variants on sIL-7Rα and mIL-7Rα expression. As expected, both variants showed similar effects on sIL-7Rα secretion, but only rs6897932Ile led to a significant increase of mIL-7Rα expression [55]. This was in accordance with the predicted effects of alternative splicing on full-length vs. shortened IL-7R mRNA expression. Jager et al. detected increased mIL-7Rα expression NK cells from multiple sclerosis patients carrying the protective haplotype tagged by rs6897932 [48]. However, no mIL-7Rα differences for T cells associated with the rs6897932-tagged haplotype were found [48] (own unpublished data). Possible explanations are the high variability of mILα-7R expression due to marked differences between T-cell subpopulations as well as described regulatory mechanisms of mIL-7Rα expression and internalization [56, 57]. These mechanisms may also restrict mIL-7Rα expression to a plateau of maximal expression potentially hiding genotype-specific effects. Initial in vitro studies to characterize genotype effects on IL-7Rα regulation of T cells, however, did not identify differences (own unpublished data). In conclusion, although previous studies suggested *IL7RA* haplotype effects on mIL-7Rα expression, the biological relevance has to be proven.

An *IL7RA* haplotype found in African populations affects alternative splicing of exon 5

The vast majority of previous studies focused on SNPs associated to autoimmune diseases and potential implications on sIL-7Rα regulation. There is, however, a significant number of additional SNPs in the *IL7RA* locus and also additional variants, besides the full length and the sIL-7Rα, have been described [31]. Based on exonic SNPs with relevance for autoimmune diseases, previous studies defined four haplotypes of the IL7RA gene in Caucasian populations (Fig. 1) [34]. Haplotype 1 is associated with increased risk to develop autoimmune diseases (tagged by the rs1494555G/rs1494558T alleles). Haplotype 3 is associated with a decreased risk to develop an autoimmune disease (tagged by the rs6897932T allele). Altogether these haplotypes comprise more than 99% of the Caucasian population (Fig. 1). Own studies in Sub-Saharan Africa showed that especially the haplotypes 1 and 3 are less frequent in this African population, whereas two additional haplotypes contribute significantly to the variability of the *IL7RA* gene locus [52]. Almost 40% of individuals from Kumasi/Ghana are haplotype 5 or 6 carriers (Fig. 1). Haplotype 6 is tagged by the rs11567764A allele and also includes the haplotype 1-tagging rs1494558T allele (Fig. 1). In a case/control study comparing tuberculosis patients with healthy contacts, we detected increased frequencies of individuals homozygous for the rs11567764A allele in the healthy contact group [52]. In addition, carriers of the rs1494558T SNP were more frequent in the contact group [52]. Contacts of tuberculosis patients are frequently infected by *Mycobacterium (M.) tuberculosis* without developing tuberculosis disease because of successful immune surveillance. Hence, higher frequencies of the rs11567764A/rs1494558T alleles suggested potential involvement in disease protection. Since the rs1494558T allele is found in two IL7RA haplotypes in Africans, it is not possible to clearly assign the relevant haplotype for differential susceptibility. However, we identified functional implications for both alleles, rs1494558T (described above) and rs11567764A [52]. rs11567764G > A is a synonymous SNP that does not affect *IL7RA* coded amino acids. Located within exon 5, however, rs11567764A was predicted to affect alternative splicing of the *IL7RA* [52]. T-cell analyses of tuberculosis patients and contacts confirmed significantly reduced expression of a IL-7Rα variant lacking exon 5–6 (Δexon_5/6) in rs11567764A carriers, whereas mRNA coding for the sIL-7Rα (i.e., Δexon_6) was not affected [52]. How differences in the expression of the Δexon_5/6 mRNA may influence T-cell



	Haplotype ID	rs1494558	rs1494555	rs2228141	rs11567764	rs6897932	rs3194051	Frequencies EU	AFR
EU/AFR	1	T	G	C	G	C	A	29.7	6.7
	2	C	A	C	G	C	G	28.2	34.6
	3	C	A	C	G	T	A	27.1	6.6
	4	C	A	T	G	C	A	14.4	12.8
AFR	5	C	A	C	G	C	A	<0.1	21.7
	6	T	A	C	A	C	A	<0.1	16.9

Fig. 1 IL-7Rα exon composition, cellular localization, and exonic SNPs are schematically shown. Respective amino acid exchanges are indicated. The table summarizes deduced haplotypes of exonic SNPs and indicates frequencies for Caucansian and African populations. Ile: isoleucine; Thr: threonine; Val: valine; His: histamine; Lys: lysine; TM: transmembrane; ID: identifier; EU: Caucasian population; AFR: African population.

function remains elusive. Since proper folding and secretion of this variant is unlikely, also indirect effects on, e.g., other alternatively spliced IL-7R variants would be possible. We assume that such differences can be of relevance for T-cell function against infection. In accordance with this assumption, aberrant low sIL-7Rα serum levels and low mIL-7Rα expression accompanied by impaired antimycobacterial functions were found in acute tuberculosis patients [58]. Future studies may address a potential role of the novel haplotypes in other infectious and autoimmune diseases in African populations.

IL7RA SNPs effects on immune pathology of autoimmune and GVHD entities

IL7RA SNP effects have been described for several diseases, and strongest evidence came from studies on multiple sclerosis [34, 43, 44, 46, 59–66]. Also, for other diseases with autoimmune pathology (i.e., type 1 diabetes [39, 42, 67, 68], systemic lupus erythematosus [45]) as well as inflammatory diseases (atopic dermatitis [41], sarcoidosis [40], arthritis [38]), an influence of *IL7RA* SNPs on disease susceptibility was shown. Predominantly, the rs6897932T-tagged haplotype was associated with disease susceptibility, but also other SNPs were identified [69, 70]. Functionally, IL-7 availability and promoting effects on the generation/expansion of self-reactive T cells [35, 71] as well as potentially inhibitory effects of IL-7 on regulatory T cells are assumed to be causative [72]. In addition, IL-7 effects early during T-cell development may be affected by other *IL7RA* SNPs. Broux et al. found that the frequency of recent thymic emigrants (RTEs) was affected in MS patients carrying the *IL7RA* haplotype 2 (termed "haplotype 4" in this paper, tagged by the rs11567685C allele that is in strong linkage disequilibrium with rs3194051G) [69]. RTEs of these MS patients were characterized by moderately increased IL-7Rα expression levels. Additional studies are needed to elucidate the underlying mechanisms and to identify the causative SNP.

Lymphopenia-induced autoimmunity strengthened the central role of IL-7 in disease pathogenesis [14]. Interestingly, lymphopenia induced by bone marrow irradiation and subsequent transplantation of hematopoietic stem cells was shown to be affected by the *IL7RA* rs6897932T allele as well [21–23]. Here, T-cell mediated GVHD is a frequent and harmful side effect correlating with high IL-7 serum concentration [73]. Donor cell *IL7RA* haplotypes were described to be associated with treatment related mortality of GVHD, whereas recipient haplotypes were not influential [22, 23]. rs6897932T donor T cells were more often associated with acute as well as chronic GVHD [22, 23]. These studies suggested that high serum IL-7/sIL-7Rα ratios in patients carrying the $sIL\text{-}7R_{low}$ rs6897932T-tagged haplotype are causative for T-cell induced GVHD. However, one may also assume rs6897932-mediated effects on mIL-7Rα expression of donor hematopoietic stem cells, which contribute to development of GvHD. Further evidence for a role of the *IL7RA* in lymphopenia-induced autoimmunity comes from patients with new onset diabetes after transplantation (NODAT). Two IL7RA alleles (i.e., rs1494558T, rs2172749C) were associated with increased risk to develop NODAT [74].

A potential role of *IL7RA* SNPs and IL-7 sensitivity in chronic infectious diseases

In contrast to the aforementioned immune pathologies, a role of *IL7RA* SNPs in infectious diseases remains enigmatic. Strongest evidence for a role of IL-7 in infections have been provided from studies on HIV/AIDS. Here, IL-7 may play a

dual role being important for immune reconstitution after CD4$^+$ T-cell depletion [75–78] and to sustain effector/memory T-cell functions during antiviral host defense. Early studies demonstrated IL-7-promoted antigen-specific effector T-cell functions including enhanced antiviral cytotoxicity [28, 79]. Impaired IL-7 response of antiviral cytotoxic T-cell response and lower IL-7Rα expression have been described for HIV/AIDS patients [80–86]. Interestingly, gene association studies demonstrated improved immune recovery in treated HIV/AIDS patients carrying the rs6897932-tagged haplotype [17–20], whereas contrary results of haplotype effects for disease progression and mortality of HIV-infected individuals were found [87, 88]. Previously we identified rs6897932 SNP effects for tuberculosis patients, where the rs6897932T allele contributed to differential sIL-7Rα serum levels found during acute disease [58]. Frequencies of rs6897932T allele carriers, however, were not different between tuberculosis patients and healthy contacts [58]. Tuberculosis patients were characterized by increased IL-7 and lower sIL-7Rα serum levels. As for HIV/AIDS patients, impaired mIL-7Rα expression likely affected IL-7 consumption of tuberculosis patients [58]. Increased IL-7 serum concentrations were also found in patients with cystic fibrosis who are highly susceptible for repeated and chronic infections [89]. Although we did not find a correlation with specific infectious agents, we demonstrated clinical relevance since IL-7 serum levels increased during disease course and correlated with decreased lung function of cystic fibrosis patients [89]. Functional T-cell assays could not be performed as part of this study and, hence, it remains elusive if impaired IL-7 consumption was causative as we assume for *M. tuberculosis* infection.

Future approaches for elucidation of IL-7/IL-7R functions and the role of *IL7RA* SNPs

Previous studies strongly focused on the sIL-7Rα-mediated function for IL-7-availability. This was comprehensible given the significant effect of the rs6897932 SNP on sIL-7Rα expression and IL-7 serum levels. Novel findings for the role of the rs1494558 SNP in IL-7Rα expression and potential effects of the rs6897932 SNP on mIL-7Rα expression should broaden the focus of future studies to elucidate differential effects of disease associated polymorphisms. Lymphopenia-induced autoimmunity and GVHD can be promising models to demonstrate the biological significance of *IL7RA* SNPs.

In addition to its role in IL-7 response, *IL7RA* SNPs may also affect signaling of thymic stromal lymphopoetin (TSLP). The TSLP receptor and IL-7Rα form the heterodimeric receptor for TSLP, which is an important factor in allergic diseases [90].

To the best of our knowledge, there are no reports of *IL7RA* SNP effects on TSLP signaling. Although the TSLP receptor is only weakly expressed on T cells [91], other immune cell populations that express TSLP receptor and IL-7Rα concomitantly (e.g., monocytes after activation [92]) may be affected by *IL7RA* haplotype differences. In this regard, Al-Mossawi et al. could recently show that expected rs6897932 SNP effects on differential mIL-7Rα and sIL-7Rα expression are seen for lipopolysaccharide- or TNFα-activated monocytes [93]. These important observations should broaden our view on the role of IL-7/mIL-7Rα beyond lymphoid cell populations and consider potential effects of *IL7RA* SNPs on TSLP signaling.

Future studies should also investigate potential effects of *IL7RA* SNPs in chronic infectious diseases and impaired T-cell sensitivity to IL-7. This may affect T-cell exhaustion and memory generation with potential relevance for recurrence of chronic infections. Finally, novel *IL7RA* SNPs and differences between populations (e.g., between Caucasians and Africans) should be investigated in more detail. How novel *IL7RA* SNPs affect immune pathology may improve our general understanding of disease mechanisms.

Conclusions

IL7RA genetic variants affect the fine balanced regulation of IL-7 availability and dependent T-cell functions with potential effects on autoimmune and infectious disease pathologies. The influence of sIL-7Rα on IL-7 serum level is an important factor but not the only relevant mechanism. Novel functions of *IL7RA* SNPs rs11567764, rs1494558, and rs6897932 may contribute to our understanding of underlying mechanisms, especially the role of membranous IL-7R expression in immune pathology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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