


Soluble IL-7R α /sCD127 in Health, Disease, and Its Potential Role as a Therapeutic Agent

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Priscila O Barros ¹
Tamara K Berthoud¹
Nawaf Aloufi²
Jonathan B Angel³

¹Chronic Disease Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada; ²Department of Biochemistry, Microbiology and Immunology, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada; ³Division of Infectious Diseases, Department of Medicine, University of Ottawa and the Ottawa Hospital, Ottawa, Ontario, Canada

Abstract: Soluble cytokine receptors can influence immune responses by modulating the biological functions of their respective ligands. These effects can be either agonistic or antagonistic and a number of soluble cytokine receptors have been shown to play critical roles in both maintenance of health and disease pathogenesis. Soluble IL-7Ra (sCD127) is one such example. With its impact on the IL-7/CD127 pathway, which is fundamental for the development and homeostasis of T cells, the role of sCD127 in health and disease has been extensively studied in recent years. Within this review, the role of sCD127 in maintaining host immune function is presented. Next, by addressing genetic factors affecting sCD127 expression and the associated levels of sCD127 production, the roles of sCD127 in auto-immune disease, infections and cancer are described. Finally, advances in the field of soluble cytokine therapy and the potential for sCD127 as a biomarker and therapeutic agent are discussed.

Keywords: sCD127, IL7RA, sIL-7R α , IL-7, soluble cytokine receptor, rs6897932 SNP

Introduction

It was not until 1985 with the discovery of the soluble IL-2 receptor (sIL-2R) that it was recognized that cytokine receptors could exist as soluble entities.¹ Over the following years, many other cytokine receptors have been cloned, resulting in the identification of cytokine receptor forms lacking the transmembrane domain, and it became clear that soluble cytokine receptors were a widespread phenomenon. Since then, it has become apparent that soluble cytokine receptors can play a valuable role in regulating the immune response, affecting the balance between their ligands and the membrane-bound receptors. It is therefore not unexpected that alterations in the expression of soluble cytokine receptors may result in human disease.

Soluble cytokine receptors usually arise from the extracellular portion of the membrane-bound protein. These proteins can be generated by proteolytic cleavage of the membrane-bound receptor, a mechanism termed ectodomain shedding, or by alternative mRNA splicing, which gives rise to a form of the receptor lacking the transmembrane domain. The role of alternative mRNA splicing in the generation of soluble receptors has been demonstrated in various studies where the presence of cDNA encoding the respective receptors, lacking the transmembrane domains, was detected. Soluble versions of IL-9R α , IL-4R α , IL-5R α and IL-7R α were shown to be generated in this manner.^{2–5} Interestingly, some soluble cytokine receptors, such as the IL-1RII^{6,7} and soluble IL-6R (sIL-6R)^{8,9} can be formed by both ectodomain shedding and alternative mRNA splicing. A third mechanism involved with the

Correspondence: Jonathan B Angel
The Ottawa Hospital, 501 Smyth Road,
Room G-8, Ottawa, ON, K1H 8L6,
Canada
Tel +1 (613) 737-8442
Fax +1 (613) 739-6866
Email jangel@ohri.ca

generation of soluble cytokine receptors is the release of exosomes containing the protein. Since exosomes carry molecules expressed on the membrane of the cell from which they originated, the cytokine receptors expressed on these vesicles are usually present in the full-length form, as observed with TNFR1, IL-6R, and IL-15R α .^{10–12}

Due to their ability to modulate the effects of their cytokine ligands, either in an agonistic or antagonistic fashion, soluble cytokine receptors can mediate a variety of immunological functions. For example, the soluble IL-1R2 can bind to both IL-1 α and IL-1 β and act as a decoy receptor to inhibit IL-1 signaling.^{13,14} Another intriguing example is found in the IL-6/IL-6R pathway, generally associated with pro-inflammatory responses. Indeed, IL-6 signaling through sIL-6R was shown to induce a pro-inflammatory response, however, the membrane-bound counterpart (mIL-6R) has been associated with anti-inflammatory and protective effects. This happens due to different signaling pathways that are triggered by the different forms of the receptor, as the soluble form induces trans-signaling pathway, whereas the membrane-bound form is involved with the classic signaling pathway.¹⁵

Ectodomain shedding by proteases has recently been shown to be important in the regulation of the immune system. For instance, the cytokine receptor sheddase, tumor necrosis factor- α converting enzyme (TACE), was originally identified as a proteolytic enzyme capable of cleaving the TNF family receptors.¹⁶ More recently, TACE was renamed ADAM17^{17,18} and is one of the most well studied among these proteases whose cytokine receptor substrates include IL-6R, IL-1R α , IL-15R α , TNF-RI and TNF-RII.¹⁹ Further, ADAM17 can mediate cleavage of IL-6R and, therefore, be involved in the pathogenic effects mediated by the sIL-6R. Indeed, the production of sIL-6R was shown to be responsible for the involvement of IL-6 in the generation of pathogenic Th17 cells and their deleterious effects in the context of autoimmunity.^{20,21}

The importance of the IL-7/CD127 in T cells function and biology is well established, and the presence of soluble IL-7R α (sIL-7R α , also known as sCD127) in the plasma has been described.^{22–24} A number of studies have demonstrated the impact of this soluble cytokine receptor both in health and in disease and will be reviewed here.

Biology of IL-7 and Its Receptor

IL-7 is a crucial cytokine for T cells homeostasis, as it plays a non-redundant role in the generation, development,

survival, and function of T cells in humans.^{25–28} This cytokine is primarily produced by non-haematopoietic stromal cells in the bone marrow and thymus.²⁹ Additionally, in humans, the production of IL-7 has been shown to occur in numerous non-lymphoid sites, such as intestinal epithelium,^{30,31} hepatic tissue,^{32,33} endothelial cells,³⁴ keratinocytes,³⁴ and neuronal progenitor cells in the brain.³⁴ With regard to its production by immune cells, low amounts have been detected from DCs.^{35–38}

IL-7 induces its response via signaling through its receptor, IL-7R, a heterodimer composed of two chains, an alpha chain, IL-7R α (also known as CD127), and the common cytokine receptor γ chain (γ c, also known as CD132). CD132 is shared with other cytokine receptors (ie IL-2, IL-4, IL-9, IL-15, IL-21) and expressed by most hematopoietic cells,^{39–41} whereas CD127 is also expressed on the surface of hematopoietic cells, but almost exclusively by the lymphoid lineage cells, throughout different stages of differentiation.⁴² CD127 is also shared with thymic stromal-derived lymphopoietin (TSLP) as part of a complex comprised of CD127 and TSLPR (thymic stromal-derived lymphopoietin receptor).⁴³ IL-7 engagement with CD127 induces its heterodimerization with CD132, enabling the complex to induce phosphorylation of JAK1 and JAK3.⁴⁴ Activated JAKs can, in turn, phosphorylate Y449, present on the intracellular tail of CD127, inducing anchoring and subsequent phosphorylation of STAT5. Activated STAT5 translocates to the nucleus, where it activates various transcription factors.^{40,45–47} Further, phosphorylated Y449 also activates PI3K and induces another downstream signaling cascade that results in AKT activation.⁴⁸ These signaling cascades induce the increased expression of anti-apoptotic members of the Bcl-2 family, Bcl-2 and MCL1, and decreased expression of pro-apoptotic molecules, such as BAX and BIM, among other effects that culminate with the enhancement of cell survival and proliferation.⁴⁹ The importance of this pathway is illustrated by the observation that T cells (particularly naïve and memory T cells) need IL-7 to be constantly available for their survival.^{50–53}

As discussed above, IL-7 plays a pivotal role in T cells homeostasis, thus, dysregulation of IL-7-induced pathways has been linked to several immune-mediated conditions. Given its role in T cell proliferation, IL-7 is thought to be involved with abnormal immune responses associated with autoimmune diseases, such as multiple sclerosis and diabetes.^{54,55} One mechanism by which IL-7 is believed

to play a role in the pathogenesis of disease is the alteration in the expression of its own receptor CD127.

The expression of membrane-bound CD127 (mCD127) is modulated, at least in part, by the amount of available IL-7, as high concentrations of the cytokine induce a decrease in mCD127 expression, as demonstrated *in vitro*.^{22,56} Further, genetic factors may also influence the levels of expression of mCD127. In this context, it is known that CD127, encoded by the IL7RA gene, is polymorphic and different single nucleotide polymorphisms (SNPs) are involved with generation of non-synonymous amino acid substitutions, potentially presenting negative impact on the expression of this cytokine receptor.⁵⁷ Some IL7RA SNPs have been shown to impact the splicing of IL7RA transcripts, resulting in truncated proteins. Such a mechanism has been proposed as being the main mechanism responsible for the generation of the soluble form of CD127 (sCD127) as we describe further below.

Biological Functions of sCD127

The soluble form of CD127 (sCD127) was first described in 1990 by Goodwin and colleagues.³ The group performed an analysis of cDNA clones that encode mCD127. Interestingly, they found cDNA clones that encoded a truncated form of the protein lacking the transmembrane domain, corresponding to the secreted CD127 form.³ Since then, a number of studies have been performed to understand the mechanisms involved with sCD127 expression. In this regard, it has been shown that IL-7 induces up-regulation of sCD127, possibly a result of alternative splicing.^{3,58,59} Additionally, shedding of the protein from the cell membrane has been proposed to play a role.²² Given that sCD127 is capable of binding to IL-7 with a similar binding affinity as to the membrane-bound form,³ and is detected in plasma,⁶⁰ several studies have been performed to shed light on the physiological roles of this soluble cytokine receptor.

Initial studies from our group demonstrated that both plasma-derived and recombinant sCD127 significantly inhibited IL-7-mediated STAT5 and Akt phosphorylation, cell proliferation, and Bcl-2 expression in primary CD8+ T cells. These results suggest sCD127 has an antagonistic effect on IL-7 activity.²⁴ Conversely, more recent studies demonstrated that sCD127 increases IL-7 bioactivity⁶¹ and enhances both IL-7-induced proliferation and viability,⁶² suggesting sCD127 has agonistic effects on IL-7-induced activity. Differences in the methodologies of these studies might explain the apparently conflicting

findings. Specifically, in work from our group, the inclusion or exclusion of serum during critical steps of the experiments influenced the activity of sCD127.^{24,62} Given that fetal bovine serum is composed of a wide variety of proteins, lipids, and hormones, it is possible that, with the addition of serum, the interaction of any of these molecules with sCD127 might modulate the impact of sCD127 on IL-7-induced activity. More recently, preliminary results from our group demonstrate that sCD127 did not influence IL-7-mediated down regulation of mCD127 but did enhance IL-7-mediated proliferation of both CD4+ and CD8+ T cells when administered to healthy mice.⁶³ Although the mechanism is not completely understood, these data also suggest sCD127 has agonistic effects on IL-7-induced activity. **Figure 1** summarizes the mechanisms that have been considered to influence IL-7-induced effects on CD8+ T cells.

As demonstrated above, limited evidence supports a primarily agonistic role of sCD127 on IL-7-induced effects, though further studies are needed in order to clarify the impact of this soluble cytokine receptor on IL-7-mediated effects in health.

sCD127 in Disease

Given the clear importance of this soluble cytokine receptor in modulating IL-7-induced effects on T cells function, sCD127 has also been extensively studied in the context of various immune-mediated and infectious diseases, as discussed below.

Genetic Factors Affecting sCD127 Expression and Their Influence on Disease

Genetic polymorphism of the IL7RA gene, a number of which influence sCD127 expression, has been associated with predisposition to various immune-mediated diseases, including multiple sclerosis (MS), type I diabetes, and graft versus host disease.^{64–67} A SNP in the CD127 gene, rs6897932, is associated with increased levels of sCD127 in individuals carrying the C allele when compared to the T allele of this gene. This non-synonymous SNP has this functional impact, as it leads to skipping of CD127 exon 6 during gene transcription, and has been associated with various conditions, as discussed here and shown in **Table 1**.⁶⁸ Further, beyond its impact on sCD127 expression, two studies reported that rs6897932-C allele was also associated with lower expression of

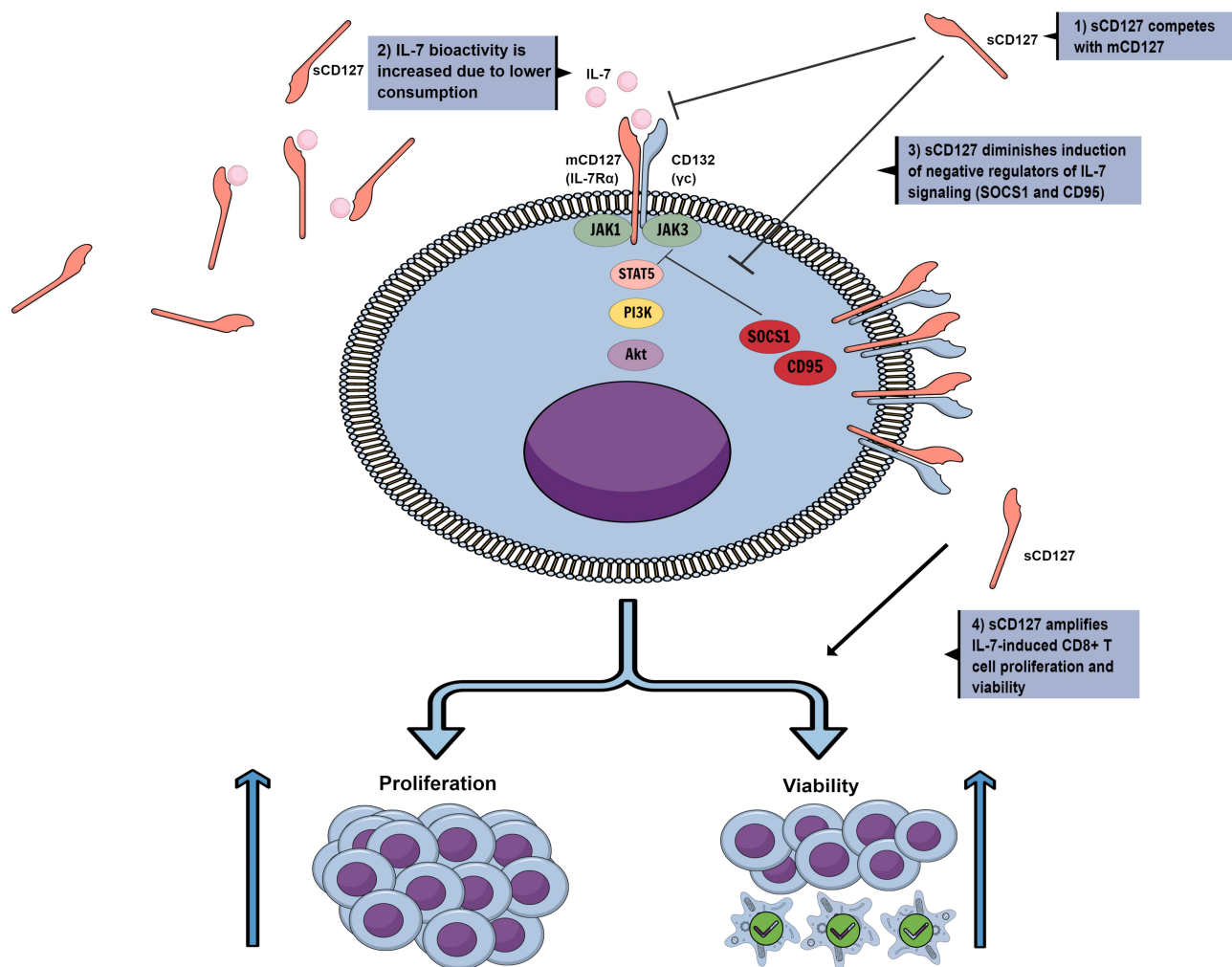


Figure 1 Possible mechanisms through which sCD127 influences IL-7-induced effects on CD8+ T cells. Most evidence suggest sCD127 has an agonistic effect on IL-7-induced activity on CD8+ T cells. sCD127 was shown to influence IL-7-induced effect through: (1) competition with mCD127 for binding to IL-7 molecules; (2) while engaged to IL-7, inducing lower consumption of the cytokine, thus, increasing its bioactivity, (3) inhibition of the activity of negative regulators of IL-7/CD127 pathway (eg, SOCS, CD95), and (4) amplification of IL-7-induced CD8+ T cell proliferation and viability.

mCD127.^{68,69} To our knowledge, there are no other published reports of an association between rs6897932 SNP and alteration in mCD127 expression.

Another SNP that has been implicated in influencing sCD127 expression is the rs2523506 SNP in the DDX39B gene.⁷⁰ DDX39B is a protein involved in pre-mRNA splicing and nuclear export of mRNAs.^{71–74} Galarza-Muñoz and colleagues have proposed that the DDX39B protein promotes the inclusion of exon 6, thus limiting sCD127 expression. The rs2523506 SNP risk allele A is, in fact, associated with the reduced expression of DDX39B, and higher levels of sCD127. Interestingly, this study also demonstrated a robust epistatic interaction between rs2523506 in DDX39B and rs6897932 in IL7RA, as an elevated risk of MS was only observed in carriers of at least one copy of the risk alleles at both loci. These results suggest these alleles can work in

concert to increase skipping of IL7R exon 6, thereby inducing higher levels of sCD127.⁷⁰ To date, there are no published reports of an association between rs2523506 and alterations in mCD127 expression.

Multiple Sclerosis (MS) and Other Demyelinating Autoimmune Disorders of the Central Nervous System (CNS)

MS is a potentially disabling disease of the CNS and the leading cause of non-traumatic neurological disability among young adults.⁷⁵ This CNS autoimmune disorder is characterized by immune attack to the myelin sheath of neurons by auto-reactive T cells, leading to demyelination.⁷⁶ By means of large, international genome wide association studies (GWAS), various genetic factors associated with the susceptibility to MS have been identified. Both HLA alleles,

Table 1 Immune-Mediated Disorders Associated with rs6897932, the Risk Alleles, Known Functional Effects, and Disease-Specific Impact

Condition	Risk Allele	Known Functional Impacts	Disease-Specific Impact	Refs
Multiple sclerosis (MS)	C (particularly in Caucasians)	Higher sCD127 expression	Greater susceptibility to disease and more rapid disease progression	[64,68,81–83,87,88,90,91,100,104–106]
Systemic lupus erythematosus (SLE)	C	Higher serum levels of sCD127 in SLE patients which correlate with anti-C1q antibodies levels and SLEDAI score (marker of kidney disease activity)	Increased susceptibility to disease	[118,147,148]
Asthma	C		Increased susceptibility to disease	[114]
Type 1 diabetes (T1D)	C	Homozygous patients for the risk allele (CC) have higher circulating sCD127 levels compared to CT or TT	TT genotype associated with protective effect in T1D patients with early age at disease onset	[65,115,119]
Rheumatoid arthritis (RA)	Limited data, but likely T	Higher serum sCD127 levels than in healthy controls	TT genotype was associated with risk for the disease sCD127 levels were elevated in patients who were refractory to disease-modifying anti-rheumatic drugs therapy and treated with TNF α inhibitor, and this predicted poor response to anti-TNF α therapy	[117,149]
Graft versus host disease (GVHD)	T, in donors		T allele in donors associated with higher risk of acute GVHD, increased relapse of leukemia, and higher transplant-related mortality in recipients	[120–122]
Breast cancer	T		Increased susceptibility to aggressive breast tumor subtype in patients homozygous for risk allele (TT). TT genotype also associated with lower disease stages.	[123]
HIV	C in Caucasians T in non-Caucasians	TT genotype associated with lower plasma sCD127 levels T allele associated with lower plasma sCD127 levels both in Caucasian and African cohorts	T carriers: Faster recovery of CD4+ T cells in Caucasians. Higher mortality rates in a cohort from Zimbabwe.	[127,129–132]
HCV	T		T allele: More rapid progression of liver fibrosis	[135]
HIV/HCV coinfection	C		Higher risk of developing severe liver disease and higher likelihood of severe necroinflammatory activity	[136]

and some non-HLA polymorphisms have also been shown to be involved, including those related to CD127 expression.^{77–80}

Polymorphisms in cytokine receptor genes have been associated with MS⁷⁷ and one of the first identified was that of CD127.^{64,68,81} As mentioned above, in 2007, Gregory et al identified an SNP in the CD127 gene, rs6897932, where the C allele was associated with a significant risk for MS in a population of European descent and true for all clinical subtypes of MS (relapsing-remitting MS, secondary progressive MS, progressive-relapsing MS, primary progressive MS). Additionally, this study showed that the rs6897932 C allele also has a functional impact on gene expression, resulting in an increase in sCD127 levels. Thus, individuals carrying the C allele of rs6897932 express higher amounts of sCD127, when compared with the individuals with the T allele. This alteration would impact the ratio of sCD127/mCD127 expression, potentially affecting the IL-7/CD127 pathway, and therefore influencing T cells homeostasis.⁶⁸

Since then, major studies have corroborated the findings that the rs6897932 C allele is associated with a higher susceptibility to MS in cohorts of Caucasian individuals.^{81–83} However, a number of other studies with individuals from Europe are not completely in line with the original study by Gregory et al. No association between this SNP and an elevated risk for MS in individuals of European cohorts was reported by Broux et al, Rubio et al and Stankovic et al.^{84–86} Moreover, O’Doherty et al observed this association in only one of two different MS cohorts.⁸⁷ Similarly, Weber et al demonstrated an association between MS and the rs6897932 C allele in their French cohort, whereas it was not observed in their German cohort, however, a positive trend was observed in this population.⁸⁸ Further, Kreft and colleagues were not able to detect higher levels of sCD127 in MS patients, observing lower concentrations of this soluble receptor, when compared to healthy controls. When stratifying the results according to rs6897932 allele, however, higher sCD127 levels correlated with rs6897932-C risk allele carriage in both MS and healthy controls.⁸⁹

With regard to non-Caucasians, two studies performed with Japanese and Korean cohorts also demonstrated an association between rs6897932 SNP and the susceptibility to MS,^{90,91} whereas results from Iranian and Indian cohorts are not completely consistent with these findings.^{92–95} Despite having found an association between rs6897932 SNP and MS susceptibility, along with higher expression of sCD127 mRNA in an Iranian MS cohort, Sayad et al

observed a higher frequency of the T allele in the MS patients, rather than the C allele, when compared to a control group.⁹² An association between the rs6897932 SNP and MS risk, also characterized by a higher frequency of the T allele in the MS patients was observed in three additional studies, with Iranian and Indian cohorts.^{93–95} Interestingly, a number of other studies performed with Iranian, Jordanian, and Chinese Han cohorts did not find any association between the rs6897932 SNP and the MS risk.^{96–98}

With the conflicting observations outlined above, a number of meta-analyses have been performed in an attempt to clarify the impact of the CD127 rs6897932 C allele in the susceptibility to MS. In this sense, in 2014, Kim and colleagues reported that the SNP rs6897932 was associated with a higher risk for the development of MS in both Caucasians and Asians, potentially being a greater risk factor for individuals of Asian descent.⁹⁰ In 2016, Tavakolpour et al concluded that there was not enough evidence to determine if SNP is indeed linked to a higher risk of MS, while Wu et al believe that this SNP is linked to a higher risk in Europeans, but not in Asians.^{99,100} Finally, very recently, Sahami-Fard and colleagues published an updated meta-analysis of the role of this SNP in MS susceptibility. Similarly, they concluded that the rs6897932 SNP might be a risk factor for MS in Europe but not in the Middle East.¹⁰¹

A growing body of evidence indicates that ethnicity might impact clinical manifestations of MS, possibly leading to different phenotypes of the disease.^{102,103} Interestingly, despite not demonstrating an association with susceptibility to develop MS, some groups have observed that rs6897932 SNP is associated with greater disease severity. Kulakova and colleagues observed that, in their Russian cohort, MS patients that carried the T allele showed favorable manifestations of the autoimmune disorder (optic neuritis or sensory disturbances), whereas carriers of the C allele presented with manifestations that are associated with worse prognosis (eg, motor disorders, brain stem disorders, impaired coordination).¹⁰⁴ Furthermore, some studies have reported that the rs6897932 SNP was associated with a progressive course of MS, indicating that this SNP may be a determinant of the disease course.^{105,106}

Taken together, although MS is a complex and multifactorial disease, with various genetic and environmental factors involved, the balance of evidence suggests that the rs6897932 SNP is involved in its pathogenesis, either being associated with a higher susceptibility to MS or a determinant of the disease severity. The exact impact of

each allele is, however, yet to be defined, particularly in non-Caucasian populations.

In addition to MS, the impact of the rs6897932 SNP has also been studied in a less common inflammatory demyelinating disease, known as Neuromyelitis Optica (NMO). NMO is a CNS autoimmune disease characterized by recurrent immune attacks to the spinal cord and optic nerve.¹⁰⁷ For decades, NMO was considered as a severe subtype of MS, however, due to its different immunopathology, NMO and MS are now considered distinct entities. With regard to the influence of ethnicity, NMO is more frequently observed in non-Caucasian populations and non-Caucasian patients with NMO tend to have a more severe disease course than Caucasian individuals, particularly in the early phase of the disease.^{108–111}

NMO has also been linked to alterations in the IL-7/CD127 pathway, with diminished expression of sCD127 and mCD127,¹¹² however, evidence of a relationship between the rs6897932 SNP and NMO risk is limited and only available in few Asian and one Israeli cohort. Two studies have found an association between this SNP and NMO risk in Korean cohorts.^{90,96} Interestingly, Zhuang and colleagues observed an association of the rs6897932 SNP with NMO and not MS, whereas Kim et al demonstrated an association between this SNP and both NMO and MS. The association with NMO was observed especially in the group that was seropositive for aquaporin-4 (AQP4)-IgG, an antibody for AQP4, the most common water channel in the CNS, the detection of which is associated with a poorer prognosis.⁹⁶ Conversely, three studies with Southern Han Chinese, Japanese and Israeli cohorts could not find an association between rs6897932 SNP and NMO risk.^{91,112,113} In summary, given the limited sample sizes and small number of studies performed in NMO, there is not enough evidence to confirm the role of the rs6897932 SNP in this disorder.

Other Autoimmune and Immune-Mediated Conditions

Beyond its association with CNS autoimmunity, numerous studies have suggested that the rs6897932 SNP might be involved with other autoimmune disorders and immune-mediated conditions. These include asthma,¹¹⁴ type 1 diabetes,¹¹⁵ sarcoidosis,¹¹⁶ rheumatoid arthritis,¹¹⁷ and systemic lupus erythematosus (SLE).¹¹⁸

In this context, Wang and colleagues reported that the rs6897932 C allele might be a susceptibility allele to SLE, as demonstrated in their Chinese cohort.¹¹⁸ With regard to

asthma, an association of the rs6897932 C allele and increased risk of disease was demonstrated in an Indian cohort.¹¹⁴ Similarly, in a cohort with Type 1 Diabetes, Todd et al have observed an association between rs6897932 SNP and this autoimmune disorder.⁶⁵ Subsequently, Santiago and colleagues have confirmed this association. Additionally, when the patients were stratified by age, they showed that rs6897932 T allele might be protective, particularly in patients with early age at disease onset.¹¹⁵ Also in line with these studies and what has been observed in most studies in MS, it was demonstrated that T1D patients homozygous for the C risk allele had higher circulating levels of sCD127 when compared to heterozygotes (CT) and patients without the risk allele (TT).¹¹⁹ One study of patients with sarcoidosis, a chronic granulomatous inflammatory condition of unknown etiology that most frequently affects the lungs, reported an association between the rs10213865 SNP, one other polymorphism in the IL7RA gene, and the disease. Despite rs10213865 SNP not being associated with a functional impact on CD127, a complete linkage disequilibrium between the rs10213865 SNP and the rs6897932 SNP was observed. These data suggest an association between IL7RA and the risk for sarcoidosis, however, a study evaluating the possible link between rs6897932 and sarcoidosis is still lacking.¹¹⁶ The rs6897932 SNP has also been shown to have a weak association with risk for rheumatoid arthritis (RA). Interestingly, the genotype that was associated with RA risk was TT,¹¹⁷ distinct from what is seen with MS. In graft versus host disease (GVHD), a common complication following allogeneic hematopoietic stem cell transplant (HSCT),¹²⁰ donor carriage of the rs6897932 T allele was associated with lower levels of circulating sCD127 in the donors and a higher risk of acute GVHD in recipients. The patients whose donors carried the T allele also had a higher transplant-related mortality.¹²¹ Interestingly, Shamim and colleagues observed an association between rs6897932 T carriership in the donors and increased relapse of leukemia in patients that had gone through HSCT, however, in contrast with the findings previously mentioned, a trend towards reduced risk for GVHD was observed.¹²² Intriguingly, an association between the carriership of this SNP in the patients themselves and the risk for developing GVHD was not observed in any of these studies.

The general picture emerging from these studies is that the rs6897932 SNP probably plays a role in these various immune-mediated conditions, most likely due to its impact in IL-7/CD127 pathway, as a result of the shift in the

relative expression of mCD127 and sCD127. In most cases, the T allele was shown to be protective, however, for some diseases, the T allele was associated with greater risk of disease. This is most likely due to the distinct immunopathological mechanisms involved with the various diseases that have been studied. Further evaluation of the possible association of this SNP with some disorders for which data is scarce (eg, sarcoidosis and asthma) is needed. Additionally, more research needs to be done in cohorts of different ethnic backgrounds, especially in conditions where ethnicity was shown to impact immunopathological aspects of the disease, like MS and NMO.

Cancer

The association between various cancers and the rs6897932 SNP has also been evaluated. Recently, with regard to breast cancer, patients homozygous for the rs6897932-T allele were shown to have an increased susceptibility for a subtype of a particularly aggressive breast tumor.¹²³ Interestingly, despite being associated with the risk for this aggressive subtype, TT patients tended to have lower disease stages. This phenomenon is possibly due to enhanced IL-7R signaling that, through STAT5 activation, might induce a decrease in stem and mesenchymal cell markers in the tumor cells (eg, CD44), lower levels of which have been shown to be associated with better prognosis.^{123,124} Conversely, one study evaluated the relationship between rs6897932 and lymphoma (Hodgkin lymphoma and B cell lymphoma) and no significant difference was found in the distribution of the individual alleles or genotype frequencies between the controls and patients group.¹²⁵

Infectious Diseases

Impairments in the IL-7/CD127 pathway have also been described in the context of different infectious diseases, and so, the impact on sCD127 expression and its association with genetic background have also been investigated. The potential relevance of the rs6897932 SNP in the context of infectious diseases and most frequently in the setting of HIV disease has been evaluated. HIV-1 infection, the cause of acquired immunodeficiency syndrome (AIDS), remains a great threat to the global public health. The introduction of HAART (highly active antiretroviral therapy), a cocktail of multiple drugs targeting different steps of the viral life cycle, has transformed HIV infection into a manageable chronic disease, dramatically reducing its morbidity and mortality. Despite the clear beneficial effects of HAART in HIV+ individuals, a degree of immune dysfunction persists, including altered expression

of mCD127 and sCD127. Interestingly, a factor that might affect the impact of HAART on the altered expression of both mCD127 and sCD127 is how soon after infection treatment is initiated. In this regard, T cells derived from late presenting HIV+ individuals (CD4 counts <200 cells/ul before HAART) were shown to express lower mCD127 levels and higher sCD127 in the plasma when compared with both non-late presenters and healthy controls. Both mCD127 expression and sCD127 levels normalized after several months of HAART.¹²⁶ Additionally, late presenting HIV+ individuals with the rs6897932-T allele were shown to have faster CD4+ recovery and higher CD4+ T cell counts at the end of the follow-up.¹²⁷

As previously mentioned, alterations in the circulating levels of sCD127 in HIV+ individuals have been reported by a number of groups. Indeed, this was observed both in treated and untreated cohorts. Rose and colleagues observed lower levels of sCD127 in chronically HIV-infected individuals not receiving treatment.⁶⁰ In contrast, studies from our group and Carini et al demonstrated increased sCD127 circulating levels in treated and untreated HIV infection.^{22,24,128} Moreover, one group reported no significant differences in the sCD127 levels in HIV+ patients.²³ The discrepancies observed in these results are likely, at least in part, related to distinct methodologies used for the quantification of sCD127 in each of the studies. Interestingly, lower plasma levels of sCD127 have been associated with the rs6897932 TT genotype in HIV+ individuals.¹²⁹ Further, the rs6897932 SNP has been also associated with immune recovery in HIV patients. In two Caucasian cohorts, the T allele was associated with a faster rate of CD4+ T cell recovery after initiation of HAART.^{129,130}

In line with what was observed in MS, ethnic background or other factors appear to influence how the rs6897932 SNP impacts cell-mediated immune responses in the context of HIV. In a study performed with two cohorts, the rs6897932-T allele was not associated with faster recovery of CD4+ T cells in the African cohort, whereas this association was observed in the Caucasians group. In spite of these divergent results, an association was found between the rs6897932 T allele and lower sCD127 levels in both cohorts.¹³¹ With regard to disease progression, in a cohort from Zimbabwe, the rs6897932-T allele was shown to be associated with higher rates of mortality.¹³² In contrast, a study performed with two Spanish cohorts did not observe an association between this SNP and HIV disease progression.¹³³

One frequent comorbidity observed in HIV-infected individuals is co-infection with hepatitis C virus (HCV).¹³⁴ HCV

causes chronic infection in about two-thirds of those infected, being responsible for chronic liver disease, liver failure and, hepatocellular carcinoma in a significant proportion of the patients. In HCV mono-infected individuals, the rs6897932-T allele has been shown to be associated with higher risk of liver fibrosis progression.¹³⁵ With regard to HIV/HCV co-infected patients, however, María Guzmán-Fulgencio et al reported that those who were homozygous for the rs6897932-C allele were at increased risk of developing severe liver disease. They also observed that HIV/HCV coinfecting individuals who were homozygous for the C allele had a higher likelihood of pathologically graded severe necroinflammatory activity.¹³⁶ Given the limited data, it is not possible to conclude how each allele of the rs6897932 SNP impacts HCV progression, however, together, these data suggest this SNP might be a factor involved in the immunopathogenesis of HCV mono- and/or co-infection with HIV.

Role of sCD127 in Disease Pathogenesis Association Between sCD127 Levels and Disease

sCD127 levels are altered in the plasma of patients suffering from a number of immune-related conditions where impairment in the IL-7 pathway has been suggested to play a role. As such, beyond the impact of genetic factors, the levels of this soluble cytokine receptor might be independently involved with the immune dysfunction observed in the context of the various diseases.

As previously discussed, sCD127 levels are altered in HIV infection and given the importance of CD8⁺ T cells function in virus-specific cell-mediated immune responses, the role of this cell compartment in the sCD127 expression has been evaluated. In this context, Carini and co-workers observed increased expression of sCD127 from CD8⁺ T cells isolated from HIV infected individuals.¹²⁸ As suggested by the authors, this phenomenon might be related to HIV-1 proteins inducing downregulation of mCD127.¹²⁸ Indeed, downregulation of mCD127, in both CD4⁺ and CD8⁺ T cells derived from HIV⁺ individuals is well documented.^{137–139} Accordingly, Tat protein was shown to be involved in mCD127 downregulation from the surface of CD8⁺ T cells.¹⁴⁰

In the setting of septic shock, sCD127 levels appear to be altered. Results, however, seem conflicting as sCD127 levels have been shown to be upregulated¹⁴¹ or downregulated¹⁴² when compared to healthy controls. Additionally, Delwarde et al observed lower levels of mRNA encoding total CD127, only mCD127 or only sCD127 in patients with septic shock.¹⁴³ Interestingly, when stratifying the patients group into survivors and

non-survivors, both Demaret et al and Peronnet et al showed sCD127 levels are higher in patients who survived when compared to non-survivors.^{142,144} It must be noted that the study performed by Peronnet and colleagues included a mixed ICU population and not only individuals with septic shock.¹⁴²

Impaired sensitivity to IL-7 has been demonstrated in patients with tuberculosis.¹⁴⁵ In one study, patients with tuberculosis also presented with lower sCD127 and higher IL-7 levels in the plasma when compared to healthy controls. sCD127 levels increased in response to the treatment, reaching levels that were comparable to the ones observed in the healthy controls.¹⁴⁵ Interestingly, in non-human primates, it was shown that animals that were vaccinated with rBCG had increased survival and higher CD127 mRNA levels in the lungs, with most of it encoding for sCD127.¹⁴⁶

As for autoimmune disorders, in the context of T1D, detection of autoantibodies against antigens found in secretory granules within pancreatic islet cells and that are involved in the pathogenesis of T1D was shown to be associated with higher circulating levels of CD127.¹¹⁹ Interestingly, the authors also demonstrated that sCD127 is glycosylated in patients with T1D and that glycosylated sCD127 is not as effective at inhibiting T cells expansion as is un-glycosylated sCD127.¹¹⁹ In patients with SLE, plasma levels of sCD127 were correlated with SLEDAI score (a marker of kidney disease activity) and anti-C1q antibody levels, suggesting an association between the soluble cytokine receptor and SLE disease activity.^{147,148} With regard to patients with RA who were refractory to disease-modifying anti-rheumatic drugs therapy and treated with a TNF α inhibitor, elevated sCD127 serum levels strongly predicted a poor response to the anti-TNF therapy.¹⁴⁹ Additionally, regarding primary Sjogren's syndrome, an autoimmune condition characterized by inflammation of exocrine glands, especially salivary and lacrimal glands, has been shown to be associated with elevated levels of circulating sCD127. Further, the levels of CCL25, a chemokine involved with recruiting CCR9⁺ Th cells to the salivary glands, were strongly correlated with sCD127 levels.¹⁵⁰ As it has been suggested that sCD127 enhances IL-7 activity *in vivo*,⁶¹ this correlation between sCD127 and CCL25 levels may indicate that this soluble cytokine receptor plays a role in the inflammation of the salivary glands.¹⁵⁰

Finally, with regard to Sézary Syndrome, a rare and severe variant of cutaneous T cell lymphoma, has been associated with impaired adaptive immune responses, along with IL-7/IL-7R pathway disturbances and has recently been shown to be associated with higher levels of sCD127 in the serum, along with lower levels of IL-7.¹⁵¹

sCD127 as a Potential Biomarker and Therapeutic Agent

As sCD127 levels are altered in several disorders, it is possible that sCD127 levels could be used as a biomarker, to better define the prognosis or even as a tool to evaluate disease progression or the response to the therapy. For instance, it is known that due to the heterogeneous immunopathology associated with septic shock, deciding on the optimal therapeutic approach for each case may not be straightforward.¹⁵² In this setting, plasma sCD127 levels were proposed as a possible biomarker for the identification of septic shock patients who were at higher risk of death, as the circulating levels of this soluble cytokine receptor were elevated in non-survivors within the first 4 days after the onset of the shock.¹⁴⁴ These results are in line with a study performed with ICU patients, where sCD127 levels were also higher in patients who did not survive when compared to survivors.¹⁴² Further studies should be performed to evaluate the possibility of using sCD127 plasma levels as a tool that would help determine which septic shock patients would have a higher risk of death.

As for tuberculosis, Lundtoft et al suggest sCD127 along with IL-7 levels could be used as a biomarker for diagnosis of the disease. By receiver operator curve analysis of a cohort of adult patients with tuberculosis and health controls in Ghana, accurate prediction was achieved for 73% of all donors. Given that the plasma levels of both IL-7 and sCD127 normalize following the treatment, the combined use of IL-7 and sCD127 could, thus, be used as a biomarker of a successful tuberculosis chemotherapy. Future studies in the setting of tuberculosis are clearly needed.¹⁴⁵

Concerning autoimmune disorders, in patients with MS, in an attempt to find a less expensive and more practical alternative to MRI to use for predicting clinical outcomes, Bedri and colleagues evaluated a number of soluble cytokine receptors in the plasma of MS patients treated with a variety of drugs. They observed that in patients homozygous for the r6897932-C allele, treatment with fingolimod induced a more significant increase in sCD127 levels, than in the other groups. The group also reported that different treatments have been shown to impact sCD127 levels differently, thus, sCD127 levels might be exploited as a possible biomarker of treatment outcome, as they propose.¹⁵³

In individuals with SLE, the use of sCD127 serum levels has also been proposed to be used as a biomarker. This is the result of two studies that demonstrated sCD127 levels to be correlated to SLEDAI score, a marker of kidney disease

activity in SLE, especially in patients with lupus nephritis.^{147,148} Interestingly, Chi and collaborators also observed a correlation between sCD127 plasma levels and anti-C1q antibodies in SLE patients.¹⁴⁸ These studies suggest that screening of sCD127 plasma levels might be a useful tool to assess disease activity in SLE patients. In the context of RA, given that elevated sCD127 levels predicted poor response to anti-TNF therapy, the quantification of the soluble cytokine receptor could potentially be used as a biomarker to predict response to treatment, potentially helping avoid an ineffective therapy.¹⁴⁹

Finally, with regard to GVHD, studies have suggested that quantification of plasma levels of sCD127 in the donor might be useful to predict the risk of development of GVHD. In this sense, POIRET and colleagues have shown that low sCD127 levels were linked to higher risk of developing GVHD in any grade.¹⁵⁴ Additionally, an elevated IL-7/sCD127 ratio was shown to be a predictor of moderate to severe aGVHD.¹²¹

Given their ability to influence the effects induced by their ligands, soluble cytokine receptors have been studied in the treatment of several immune-mediated disorders characterized by the detrimental effects caused by the cytokine ligand. One interesting example, currently being studied as a possible therapy, is the administration of sgp130 in autoimmune disorders where IL-6-induced pathogenesis was identified. gp130 (CD130) is a co-receptor and part of the membrane-bound IL-6R receptor complex, which mediates signal transduction following IL-6 engagement. Interestingly, its soluble form, sgp130, has an antagonistic effect as it inhibits the trans-signaling pathway by binding to IL-6/sIL-6R complexes. Given that the trans-signaling pathway has been associated with IL-6-induced pathogenesis, whereas the classic pathway not only possesses a great deal of importance in innate immunity but also does not seem to be associated with disease pathogenesis, this strategy is expected to be safer than current therapies that also block mLIL-6R signaling (ie, tocilizumab). The use of sgp130 fused to Fc (Olamkicept) is currently in Phase II clinical trials for inflammatory bowel disease.¹⁵⁵ Moreover, since IL-6 may play an important role in the cytokine storm associated with infection by SARS-CoV2 (COVID-19), a clinical trial for the use of tocilizumab has started and the possible use of sgp130 has also been considered in this setting.^{156,157}

One other example of a soluble cytokine receptor, currently in use for treatment of rheumatoid arthritis, psoriasis, chronic plaque psoriasis, and others, is the TNFR2-Fc (Etanercept).^{158,159} Etanercept is a protein composed of two molecules of the soluble cytokine receptor TNFR2

fused to human IgG1. Through binding to TNF- α , Etanercept interferes with its interaction with membrane-bound TNF receptors, thereby acting as an effective TNF- α inhibitor.^{158,159} Indeed, this medication is the first line biologic disease-modifying antirheumatic drug for treatment of individuals with psoriasis with active dactylitis or enthesitis, despite treatment with methotrexate.^{160,161}

Since sCD127 has been shown to modulate IL-7 activity, this soluble cytokine receptor might also be a candidate for use in treatment of a number of conditions in which IL-7 is implicated in the pathophysiology. In a murine model of lung cancer, administration of IL-7/IL-7R α -Fc resulted in higher levels of inflammation in the tumor environment, enhancing APC activity and, consequently, T cell activity, when compared to IL-7 alone. Further, this treatment was able to induce an anti-tumor environment, attributed to higher levels of IFN- γ , CXCL-9 and CXCL-10. The treatment also resulted in tumor size reduction, along with enhanced survival.¹⁶²

Administration of sCD127, in a mouse model of MS (ie, experimental autoimmune encephalomyelitis (EAE)), induces an increase in the bioactivity of IL-7. This was associated with the exacerbation of disease as characterized by greater symptoms of EAE in the animals that were injected with both IL-7 and sCD127 when compared to animals receiving IL-7 alone. The sCD127-induced increase in IL-7 bioactivity in these experiments may be due to limiting the consumption of IL-7, but also because sCD127 impairs the induction of negative regulators of IL-7 signaling (SOCS-1 and CD95), facilitating inducing IL-7-mediated homeostatic expansion.⁶¹ Given that exacerbation of EAE was observed in this study, the administration of this soluble cytokine receptor must be considered carefully in future studies in order to avoid the possibility of triggering autoimmunity.⁶¹ Lastly, preliminary results by our group demonstrate that, following T-cell depletion in healthy mice, administration of sCD127, along with IL-7, induces a more rapid reconstitution of T cells, particularly in the CD8+ T cell compartment.⁶³ These data suggest administration of sCD127, in combination with IL-7, could potentially be useful in the treatment of lymphopenia in situations, such as following chemo or radiation therapy.

Concluding Statement

Given the abundance of evidence, it is clear that sCD127 plays an important role in modulating IL-7-dependent activities, both in health and in disease. Several studies suggest a role for sCD127 in the immunopathogenesis of a variety of conditions, as is the case with other soluble cytokine receptors. Future

studies should better elucidate the impact of rs6897932 SNP in different ethnicities, especially in conditions where ethnic background was shown to impact clinical outcomes. The possible role of sCD127 as a biomarker, as supported by studies in septic shock, SLE and GVHD, could prove to be useful in guiding prognosis and be an important tool used to optimize individual therapeutic approaches. As for the potential use of sCD127 in therapy, this possibility should be better studied, with appropriate caution, given the association between sCD127 and autoimmunity. Collectively, limited but accumulating data suggest sCD127 plays an important role in modulating the IL-7/CD127 pathway, likely in an agonistic fashion. Due to the heterogeneity of the disorders discussed here, this activity of sCD127 likely has different implications. Ultimately sCD127 might prove to be a useful tool for the therapy in settings where there is a need to restore or enhance IL-7 activity or a potential biomarker to better guide clinical decision-making.

Disclosure

The authors report no conflicts of interest in this work.

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