The advent of soluble common gamma chain rocks the T cell world: A novel therapeutic target for autoimmune diseases

Byunghyuk Lee, Changwan Hong

Department of Anatomy, Pusan National University School of Medicine, Yangsan, 626-870, South Korea

Correspondence: Changwan Hong
E-mail: chong@pusan.ac.kr
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The common gamma chain (γc) is the central signaling unit for the γc cytokine receptor family. γc cytokine signaling is mainly regulated by cytokine-specific receptor alpha chain expression levels but not γc expression levels. Here we will highlight that a soluble form of γc (sγc) expression, which is generated by alternative splicing, impairs naïve T cell survival and promotes inflammation in a manner of inhibiting IL-7 and IL-2 signaling, representatively. Furthermore, sγc expression is significantly enhanced upon T cell activation. sγc enhances in vitro and in vivo Th17 differentiation through dampening of IL-2 signal, and sγc-overexpressing mice are consequently more susceptible to EAE. Therefore, sγc is a novel immunoregulator that control T cell biology by regulation of γc cytokine signaling.

Keywords: Soluble common gamma chain; Th17; IL-2, IL-7; Cytokine; Autoimmune disease


Introduction

Cytokines of the γc family, which include IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21, play critical roles in the development and differentiation of T lineage cells. γc cytokine receptors, which are aptly named as such because of their common requirement of the IL-2 receptor γ-chain (γc), require γc for ligand binding and also for initiation of downstream signaling [1]. γc is important because it associates with Janus kinase 3 (JAK3) that transactivates other JAK molecules within a γc receptor complex [2, 3]. JAK activation, on the other hand, is essential for recruitment and phosphorylation of STAT proteins and PI-3 kinases which is a common pathway of all γc cytokines [4]. Interestingly, while γc is essential for γc cytokine signaling, γc itself does not show any specificity for a particular cytokine and γc alone cannot bind free ligands [5]. Consequently, expression of cytokine specific receptor subunits, such as IL-7 receptor α-chain (IL-7Rα) for IL-7 or IL-2Rβ for IL-2, is deemed critical to confer ligand specificity and to initiate γc receptor signaling. Moreover, the extent of γc cytokine responses is also thought to be regulated by cytokine specific receptor subunits, and notably not by the γc receptor [1]. IL-7 stimulation, for example, effectively terminates IL-7 signaling by
downregulating expression of IL-7Rα but without affecting γc expression [6]. IL-2 stimulation, on the other hand, amplifies IL-2 signaling as it upregulates expression of its proprietary receptors, IL-2Rα and IL-2Rβ[7, 8]. Increased IL-2 signaling however does not involve increased IL-2γ (γc) expression [1]. Therefore, γc is critical for productive γc cytokine signaling but has been considered irrelevant for regulation of IL-2 signaling in particular and γc cytokine signaling in general. In fact, γc levels are presumed to be developmentally unchanged and to be sustained during T cell activation and differentiation [1]. Thus, expression of cytokine specific subunits and not that of γc has been proposed as an alternative rheostat of γc cytokine signaling. Collectively, γc expression is classically regarded as being constitutive and as not being involved in controlling γc cytokine signaling [1]. However, we found that activated murine T cells produced soluble form of γc by alternative splicing and they negatively regulated γc cytokine signaling. Here, we will discuss about a novel function of γc as a immunomodulator capable of controlling γc cytokine signaling and T cell differentiation.

Generation of γc

The extent and magnitude of cytokine signaling must be tightly controlled since excessive cytokine signaling can lead to inflammation, autoimmunity, and cancer while diminished cytokine signaling can result in immune deficiency and lymphopenia. Consequently, the immune system employs various ways to precisely tune both the strength and duration of cytokine signaling in individual cells. One of the mechanisms that control cytokine signaling is the generation of soluble cytokine receptors, which are present as immunomodulatory molecules in body fluid of human and mice. Soluble cytokine receptors has two major functions: inhibitors of their membrane-bound counterparts by competing for ligand to prevent signaling or inducers of relevant cytokine responsiveness by serving as binding proteins to stabilize ligand or trans-signaling of cytokine-binding soluble cytokine receptor complex. The molecular mechanisms that generate soluble cytokine receptors include proteolytic cleavage of transmembrane receptors catalyzed by membrane proteases, alternative splicing of mRNA transcripts, and transcription of distinct genes that encode soluble cytokine receptors [9].

A murine soluble γc was present in sera of mice and identified as a negative and selective regulator of cytokine responses [10]. However, what mechanisms are responsible for the production of γc, what are biological functions of γc, and how γc is involved in regulating key inflammatory and immune response have been unclear. Our recent publication demonstrated that γc expression was upregulated upon TCR stimulation and was generated by alternative splicing, which led to only identical extracellular domain to the membrane γc with unique short amino acid sequence in the absence of transmembrane and intracellular domain [11]. A cysteine in unique γc tail induced disulfide bonding and was more functional in regulation of cytokine signaling than monomer or mγc, resulting in effectively outcompeting mγc for binding to other γc cytokine receptors. Although, in this study, we showed that TCR stimulation upregulates γc expression [11], further studies will be required to understand what intrinsic factors activate the alternative splicing for γc generation upon TCR stimulation and what extrinsic factors except for TCR stimulation regulates γc expression.

Role of γc in cytokine signaling

In homeostatic condition, γc overexpression dampened IL-7 signaling, resulting in impaired thymopoiesis and naïve T cell survival [11]. In this regard, physiological level of γc seems contributing to T cell homeostatic mechanisms as well as conventional one that limiting IL-7 is maximized their availability by IL-7R downregulation [6]. In stimulatory condition, enhanced level of γc produced by activated T cells dampened IL-2 signaling and promoted Th17 differentiation in vitro and in vivo because IL-2 can suppress Th17 cell differentiation [12], resulting in exacerbation of autoimmune disease as shown by higher clinical score for EAE pathology in γc transgenic mice. On the contrary, γc deficient animal resisted the induction of EAE and displayed improvement of inflammatory autoimmune disease [11].

Concluding remarks and future directions

This study adds significant insights into the cytokine regulatory mechanisms by which γc is highly released by activated T cells and negatively regulates γc cytokine signaling, resulting in modulation of T cell homeostasis and differentiation. Furthermore, our report demonstrated that γc is generated by alternative splicing and dimerized form of γc is effective in regulatory activity. The dramatic amelioration of EAE or IBD in the absence of γc indicates that block of γc dimerization might be an innovative therapy in autoimmune disease patients. Therefore, these data may lead to the generation of novel therapeutic targets for the treatment of inflammatory autoimmune diseases, as γc is genetically conserved in human and circulating levels of γc have been linked to autoimmune diseases patients [13, 14]. Furthermore, the therapy using γc would be applied and expanded to immune-associated diseases like cancer and infection.

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Conflict of interest

The authors declare that there is no conflict of interest.

References