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Cytoplasmic tail of IL-13Rα2 regulates IL-4 signal transduction

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Abstract

IL (interleukin)-4 and IL-13 are key cytokines in the pathogenesis of allergic inflammatory disease. IL-4 and IL-13 share many functional properties as a result of their utilization of a common receptor complex comprising IL-13Rα1 (IL-13 receptor α-chain 1) and IL-4Rα. The second IL-13R (IL-13 receptor) has been identified, namely IL-13Rα2. This has been thought to be a decoy receptor due to its short cytoplasmic tail and its high binding affinity for IL-13 but not IL-4. IL-13Rα2 exists on the cell membrane, intracellularly and in a soluble form. Recent reports revealed that membrane IL-13Rα2 may have some signalling capabilities, and a soluble form of IL-13Rα2 can be generated in the presence of environmental allergens such as DerP. Interestingly, IL-13Rα2 has also been shown to regulate both IL-13 and IL-4 response in primary airway cells, despite the fact that IL-13Rα2 does not bind IL-4. The regulator mechanism is still unclear but the physical association of IL-13Rα2 with IL-4Rα appears to be a key regulatory step. These results suggest that the cytoplasmic tail of IL-13Rα2 may interfere with the association or activation of signalling molecules, such as JAK1 (Janus kinase 1), on IL-4Rα and thus prevents downstream signal cascade. The receptor has more complicated functions than a simple decoy receptor. In this review, we discuss newly revealed functions of IL-13Rα2.

Introduction

IL (interleukin)-4 and IL-13 are pleiotropic cytokines with key roles in the pathogenesis of asthma and other atopic diseases. They induce VCAM-1 (vascular cell adhesion molecule-1) on vascular endothelium and thus direct the migration of T-lymphocytes, monocytes, basophils and eosinophils to the inflammation site [1–3]. In asthma, IL-4 and IL-13 contribute to inflammation and to airway obstruction through the induction of mucin gene expression and the hypersecretion of mucus [4]. Both cytokines inhibit eosinophil apoptosis and promote eosinophilic inflammation by inducing chemotaxis and activation through the increased expression of eotaxin [5].

IL-13 mediates its functions via its cognate receptor, a heterodimer composed of the IL-4Rα (IL-4 receptor α-chain) and the IL-13-binding protein, IL-13Rα1 [IL-13R (IL-13 receptor) α-chain 1] [6]. The IL-13Rα1–IL-4Rα complex can act as an alternative receptor for IL-4, especially in cells that lack the common γ-chain (γc) that usually forms a complex with IL-4Rα to bind IL-4 [7]. The IL-13R complex is formed in a sequential manner: IL-13 first binds to IL-13Rα1 before recruiting IL-4Rα to form a high-affinity, signalling complex [8]. In the case of IL-4 binding to IL-13Rα1–IL-4Rα, IL-13Rα1 contributes little to the overall binding affinity and its role within this complex remains unknown [9].

IL-13Rα2

A second IL-13 binding protein, IL-13Rα2, has been identified [10]. It shares 37% homology with IL-13Rα1 and binds IL-13 with high affinity, but not IL-4 [8]. Binding studies have shown that IL-13Rα2 has the characteristics of a negative regulator, with a fast association rate but an exceptionally slow dissociation rate [8]. IL-13Rα2 has a short cytoplasmic tail that lacks any obvious signalling motif and is unable to instigate a signal through the STAT (signal transducer and activator of transcription) 6 pathway. IL-13Rα2 appears to regulate IL-13, as receptor expression makes cells unresponsive to IL-13 despite the high binding affinity. This high affinity, together with the finding of soluble IL-13Rα2 *in vivo* [11], has led to speculation that IL-13Rα2 is a decoy receptor. However, it has been revealed that membrane IL-13Rα2 may have some signalling capabilities. Fichtner-Feigl et al. [12] have suggested that IL-13 can signal through IL-13Rα2 in macrophages to activate an AP-1 (activator protein 1) variant containing c-Jun and Fra-2, leading to IL-13-induced TGFβ (transforming growth factor-β)-mediated fibrosis [12]. They found that prevention of IL-13Rα2 expression reduced the production of TGFβ1 in oxazolone-induced colitis and that prevention of IL-13Rα2 expression, IL-13Rα2 gene silencing or blockade of IL-13Rα2 signalling led to marked down-regulation of TGFβ1 production and collagen deposition in bleomycin-induced

Key words: asthma, cytokine receptor, interleukin 4 (IL-4), interleukin 13 (IL-13), interleukin 13 receptor α-chain 1 (IL-13Rα1), signal transduction.

Abbreviations used: IFNγ, interferon γ; IL, interleukin; IL-13R (etc.), IL-13 receptor (etc.); IL-13Rα, IL-13 α-chain; JAK, Janus kinase; MMP, matrix metalloproteinase; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β.

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lung fibrosis. This group also showed that IL-13 signalling via the IL-13Rα2 is a key initiation point for a complex fibrotic programme in the colon consisting of TGFβ1 activation, IGF-1 (insulin-like growth factor 1) and EGR-1 (early growth-response gene product 1) expression, myofibroblast apoptosis, and myofibroblast production of collagen [13].

Expression of IL-13Rα2 varies across cell types and can be induced by inflammation and cytokines [14,15]. A role for IL-13Rα2 as a potent modulator of inflammatory responses in asthma is suggested by the IL-13- and IL-4-dependent up-regulation of IL-13Rα2 in primary bronchial epithelial cells and the demonstration that overexpression of IL-13Rα2 in primary airway cells decreases IL-13-dependent STAT6 phosphorylation and eotaxin production [16]. Daines et al. [17] demonstrated that IL-13Rα2 is largely an intracellular molecule, which is rapidly mobilized from intracellular stores after treatment with IFNγ (interferon γ) [17]. Up-regulation of IL-13Rα2 surface expression in response to IFNγ was rapid, did not require protein synthesis, and resulted in diminished IL-13 signalling. Furthermore, there appeared to be communication between the intracellular pools and the cell surface as prolonged treatment of cells with trypsin revealed an ongoing decrease in total cell IL-13Rα2 [18]. The authors suggest that this continued decline in IL-13Rα2 was due to mobilization of the cytoplasmic IL-13Rα2 to the surface where it was susceptible to trypsin-mediated cleavage.

Soluble IL-13Rα2 has been postulated as a critical endogenous modulator of IL-13 responses. Specific blockade of IL-13 by soluble IL-13Rα2 to allergen challenged mice reversed airway hyperreactivity and mucus production [19], but the mechanism for the generation of soluble IL-13Rα2 remains unclear. Soluble cytokine receptors can be generated by several mechanisms, including the proteolytic cleavage of membrane-bound receptor proteins from the cell surface and alternative splicing of mRNA transcripts. Matsumura et al. [20] reported that endogenous MMP(s) [matrix metalloproteinase(s)] solubilize IL-13Rα2 in airway epithelial cells, whereas Chen et al. [21] demonstrated that soluble IL-13Rα2 can be produced by means of direct cleavage by MMP-8 and that MMP-8 contributes to the solubilization of IL-13Rα2 in BALF (bronchoalveolar lavage fluid) in house dust mite-treated mice. Furthermore, this group showed that exposure to mould or house dust mite allergens resulted in degradation of surface IL-13Rα2 [22]. This reduction in receptor levels may contribute to the pathogenesis of allergic disorders in individuals with allergy because of the loss of IL-13Rα2 inhibition of IL-13 responses. They also found that an alternatively spliced transcript of the mouse IL-13Rα2 gene generates biologically relevant soluble IL-13Rα2 protein *in vitro*, which can effectively block IL-13-dependent STAT6 activation [23]. Thus these results indicate that the generation of soluble IL-13Rα2 can occur from an alternative transcript encoding a soluble form in addition to the cleavage of membrane-bound IL-13Rα2.

We have observed that expression of IL-13Rα2 in primary human fibroblast cells varied considerably between volunteers [24]. There is a correlation between IL-13Rα2 baseline levels and eotaxin release, suggesting that IL-13Rα2 is able to regulate IL-13-mediated effects in fibroblasts. IL-13-mediated eotaxin release from fibroblasts with low levels of IL-13Rα2 was significantly higher than that from fibroblasts with high receptor expression. Fibroblasts with high surface levels of IL-13Rα2 were virtually unresponsive to IL-13 as the amount of eotaxin released from these cells was not significantly different from the untreated control [25]. The natural variability in IL-13Rα2 expression remains unclear as there are no known polymorphisms in the promoter region of the IL-13Rα2 gene. Receptor expression was not linked to the age or sex of volunteers and there was only a slight association with atopy. However, in light of recent reports, differences in cumulative environmental allergen exposure or in the intrinsic regulation of the production of soluble IL-13Rα2 could lead to decreased IL-13Rα2 in subjects and increased susceptibility to IL-13. A variant of IL-13, R110Q, has been associated with atopy and atopic diseases such as atopic dermatitis and rhinitis [26,27]. We have also demonstrated that IL-13Rα2 has a lower affinity for R110Q and thus is unable to regulate this cytokine as effectively as wild-type IL-13, thus leading to a more sustained response than that observed for wild-type IL-13 [28]. If this is then linked with a natural variation in IL-13Rα2, the ability of R110Q to contribute to an allergic response is dependent not only on its reduced affinity for IL-13Rα2, but also on naturally occurring levels of IL-13Rα2. Thus IL-13Rα2 may represent an important biomarker for asthma and allergic diseases.

Regulation of IL-13 and IL-4 signalling

The exact mechanism by which IL-13Rα2 regulates IL-13 is still under investigation. It has been suggested that IL-13Rα2 present on the cell surface competes with the IL-4Rα/IL-13Rα1 complex for IL-13. We have previously characterized the binding of IL-13 to its receptor components and shown that IL-13Rα2 binds IL-13 with a significantly higher affinity than IL-13Rα1, a property that is derived primarily from its extremely low dissociation rate [8]. Thus, once IL-13 has been captured by IL-13Rα2, it is effectively sequestered from the lower-affinity IL-13Rα1 signalling receptor. Alternatively, a soluble form of the receptor might be present in interstitial spaces, where it can sequester IL-13 to limit its bioavailability and suppress activation of receptor complexes on the cell surface. The presence of a soluble form represents a potential mechanism for IL-13Rα2 to have effects on cells distant from its production. Daines et al. [18] reported that soluble IL-13Rα2 released from transfected cells was unable to inhibit IL-13 signalling in untransfected cells, probably because the level of soluble receptor was low [18]. However, during inflammation the levels may be higher and therefore functionally relevant. The inhibitory effects of the IL-13Rα2 on IL-13 appeared to be rapid and persistent but could be overcome by increasing concentrations of IL-13. Thus the ability of IL-13Rα2 to quench IL-13 responses is dependent on both the level of expression of the receptor and the amount of IL-13 present.

IL-13Rα2 is overexpressed in a vast majority of high-grade astrocytomas, and it has been proposed as a tumour-specific antigen [29]. Studies of the expression of the membrane-anchored form of IL-13Rα2 in tumour cells suggest that it also functions as a negative regulator of IL-13 in these cells. However, it has been shown that it not only competes with IL-13Rα1 for binding of IL-13, but it also promotes IL-13 internalization, resulting in marked suppression of IL-13 activity [30]. This property has been exploited for tumour targeting by using an IL-13 *Pseudomonas* exotoxin fusion protein. This is a highly specific cytotoxin to medulloblastoma cell lines expressing IL-13Rα2 and has led to the proposal that IL-13Rα2 might serve as a tumour-specific antigen for active immunotherapy of brain tumours [31]. Similarly, lung fibroblasts isolated from the most severe form of idiopathic interstitial pneumonia (usual interstitial pneumonia) exhibit increased expression of IL-4 and IL-13 receptor subunits, and these can be targeted with an IL-13 *Pseudomonas* exotoxin fusion protein [32]. Significantly, this effect was dependent on expression not only of IL-13Rα2, but also of IL-4Rα.

The variability in the level of IL-13Rα2 on the surface of primary epithelial cells is inversely correlated to their responsiveness not only to IL-13 but also to IL-4, despite the fact that IL-13Rα2 does not bind IL-4. Increased levels of IL-13Rα2 on the cell surface lead to a significant inhibition of both IL-13- and IL-4-mediated effects. The addition of neutralizing antibodies to IL-13Rα2 prevented the inhibition of the IL-13-stimulated responses and surprisingly IL-4-mediated responses as well [25]. The involvement of IL-13Rα2 in the regulation of IL-4 is supported by evidence that IL-13Rα2 forms a complex with IL-4Rα when cells are exposed to IL-4. The fact that IL-13Rα2 associates with IL-13Rα1 when cells are exposed to IL-13, but not IL-4, rules out the possibility that IL-13Rα2 inhibits IL-4 signalling by sequestering IL-13Rα1 [33]. Similarly, IL-13Rα2 is unable to bind IL-4, and therefore it would be unable to inhibit IL-4 signalling by sequestering the ligand.

The cytoplasmic tail of IL-13Rα2 regulates IL-4

A more likely explanation is that the short cytoplasmic tail of IL-13Rα2 might interfere with the association or activation of signalling molecules, which, in turn, prevents downstream signal cascade. The intracellular domain of IL-4Rα contains a membrane-proximal Box-1 sequence that serves as a docking site for JAK (Janus kinase) 1. It may be this site at which IL-13Rα2 is able to regulate IL-4 responses, as blocking the interaction of this signalling molecule with its receptor complex completely inhibits the JAK/STAT6 signalling pathway. A similar mechanism has been linked to the abnormal proliferation of glioblastoma cells, in which IL-4-mediated antitumour activity in rodent experimental gliomas is abrogated by aberrant expression of IL-13Rα2 by the glioblastoma cells [33]. This involves the cytoplasmic tail of IL-13Rα2, which partly blocks IL-4-mediated activation of STAT6 and upregulates the activation of STAT3, although the latter does not require a direct physical interaction between STAT3 and IL-13Rα2 [34]. Furthermore, although glioblastoma cells fail to express the alternative IL-4Rα/common γ-chain receptor complex, this form of IL-4R is present on both epithelial cells and fibroblasts, suggesting that IL-13Rα2 has the ability to inhibit IL-4Rα in either signalling configuration.

Conclusion

The IL-4/IL-13 pathway is an extremely important mediator of inflammatory responses. Small genetic differences such as the expression of the IL-13 variant, R110Q, or environmental exposure to allergens can lead to the dysregulation of IL-4 and IL-13 that contributes to an asthmatic phenotype. Thus a complete understanding of how IL-13Rα2 regulates these two important cytokines may lead to the development of a novel therapy for asthma that selectively targets these cytokines. Previous attempts to augment either IL-4 or IL-13 have been relatively unsuccessful due to their shared receptor system. By targeting IL-13Rα2, which has the ability to regulate both molecules, the problem of subverting an alternative pathway can be overcome. Such a multifunctional interaction would identify the transmembrane form of IL-13Rα2 as a powerful suppressor of Th2-mediated responses.

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