IL-5- and eosinophil-mediated inflammation: from discovery to therapy

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Abstract

IL-5 was originally defined as a T-cell-derived cytokine that triggers activated B cells for terminal differentiation into antibody-secreting plasma cells, at least in mice. Concurrently, IL-5 was recognized as the major maturation and differentiation factor for eosinophils in mice and humans. Over-expression of IL-5 significantly increases eosinophil numbers and antibody levels in vivo. Conversely, mice lacking a functional gene for IL-5 or the IL-5 receptor alpha chain (IL-5Rα) display a number of developmental and functional impairments in B-cell and eosinophil lineages. In addition to the Janus kinase–signal transducer and activator of transcription pathway, the tyrosine kinases Lyn and Btk (Bruton agammaglobulinemia tyrosine kinase) are involved, and Ras GTPase–extracellular signal-regulated kinase (Ras–ERK) signals are important for IL-5-dependent cell proliferation and survival. IL-5 critically regulates expression of genes involved in proliferation, cell survival and maturation and effector functions of B cells and eosinophils. Thus, IL-5 plays a pivotal role in innate and acquired immune responses and eosinophilia. In humans, the biologic effects of IL-5 are best characterized for eosinophils. The recent expansion in our understanding of the mechanisms of eosinophil development and activation in the context of IL-5 has led to advances in therapeutic options. A new therapy currently in clinical trials uses humanized mAbs against IL-5 or the IL-5R.

Introduction

IL-5 was originally found as ‘T-cell replacing factor’ that is secreted from T cells to stimulate antibody production from activated B cells (1). IL-5 is produced by T_h,2 cells after stimulation with Mycobacterium tuberculosis, Toxocara canis or with allergens and by mast cells upon stimulation with allergen–IgE complex (2). As an active form, IL-5 makes homodimer in that two molecules are coupled in ‘interdigitated’ fashion. IL-5 messenger RNA (mRNA) is also expressed in eosinophils, γδT cells, NK and NKT cells and non-hematopoietic cells (3–6). CD4^+ c-kit^− CD3e^− IL-2Rα^+ cells in the Peyer’s patch produce high levels of IL-5 when stimulated with IL-2 (7).

IL-5 acts on target cells by binding to its specific receptor (IL-5R). The IL-5R consists of a unique α chain (IL-5Rα/CD125) and the common cytokine β-chain (βc/CD131) and is expressed on cells in various lineages, where it transduces signals for multiple functions (6, 8–11). The IL-5Rα specifically binds to IL-5 and the βc is a molecule shared with other cytokine receptors, including IL-3R and granulocyte/macrophage colony-stimulating factor (GM-CSF) receptor. The βc alone does not bind any cytokines, has relatively long cytoplasmic portion and several functional domains (11, 12) and is deeply involved in the signal transduction (Fig. 1). Intriguingly, the cytoplasmic region of IL-5Rα, particularly the membrane-proximal proline-rich sequences, is required for IL-5-induced cellular proliferation and signal transduction (13–16).

IL-5 induces terminal differentiation of activated B cells into antibody-forming cells in mice and enhances proliferation and differentiation of eosinophil precursors into mature eosinophils in mice and humans. B-1 cells, which are distinguishable from B-2 cells by their cell surface markers,
anatomical location and self-replenishing activity, constitutively express IL-5Rα and respond to IL-5 for survival, proliferation and differentiation to antibody-secreting plasma cells (17, 18). IL-5Rα−/− and IL-5−/− mice show a decrease in B-1 cells in peritoneal washouts and in B-1-cell-derived sIgA+ cells in lamina propria (19–21). B-2 cells activated by antigen or mitogens in the presence of Th cells express IL-5Rα and become responsive to IL-5 for maturation (22, 23). It still remains elusive whether human activated B cells express IL-5Rα and respond to IL-5 for maturation. In both mice and humans, IL-5Rα is expressed on mature eosinophils and basophils.

Allergic diseases, including asthma, are characterized by inflammation with pronounced infiltration of eosinophils and CD4+ T cells (24, 25). Regarding the inflammatory cells implicated in asthma, recruitment of CD4+ T cells is a central feature of the late-phase allergic response (LAR) (24, 26). Accumulating evidence indicates that classical T,2-cell-derived cytokines (e.g. IL-3, IL-4, IL-5, IL-9, IL-13 and GM-CSF) together with eotaxin play critical roles in the induction of airway hyper-reactivity and the development of chronic airway wall remodeling (27–29). In addition, newly identified cytokines, including thymic stromal lymphopoietin, IL-25 and IL-33, are involved in the induction of allergic inflammation in asthma (30–32).

Eosinophils possess distinctive granule proteins, including major basic protein, eosinophil peroxidase and eosinophil-derived neurotoxin. In both mice and humans, IL-5 induces terminal maturation of eosinophils, prolongs eosinophil survival by delaying apoptotic death, possesses eosinophil chemotactic activity, increases eosinophil adhesion to endothelial cells and enhances eosinophil effector functions (28, 33). However, attempts to inhibit accumulation of eosinophils in the airways of asthmatics by targeting IL-5 have only had limited success (34).

In this review, we will describe recent progress in several aspects of eosinophil function in allergic inflammation in conjunction with the function of IL-5. We will also discuss the role of IL-5 in allergic inflammation as a novel molecular target for therapy of allergic inflammation with particular emphasis on anti-IL-5 therapy.

IL-5 in eosinophil differentiation and survival

Eosinophils diverge from hematopoietic stem cells (HSCs). The effects of IL-5 on eosinophils largely fall into four categories, namely differentiation, migration, activation and survival. As for differentiation, IL-5 is not an inducer of eosinophil lineage commitment but rather an enhancing factor for differentiation and proliferation of eosinophil progenitors (EoPs) (32, 35–37). Although helminth infection-induced eosinophil production was impaired, IL-5-deficient or IL-5R-deficient mice showed a steady state of eosinophilopoiesis, suggesting that factors or cytokines other than IL-5 may be involved in, or compensate for, the constitutive generation of eosinophils at basal levels (19, 20).

IL-5-mediated signal transduction

It is well accepted that IL-5Rα expression in the bone marrow cells is one of most critical issues in eosinophil lineage commitment (Fig. 2). The regulatory factor X (RFX) family DNA-binding proteins were shown to bind to cis element of IL-5Rα promoter (38). Although expression of RFX proteins

Fig. 1. Signal transduction pathways of IL-5 in the eosinophils. IL-5 and its two receptor chains (IL-5Rα and βc) are shown in the cell membrane, and signals in the cytoplasm and nucleus are indicated. Red ovals represent signaling molecules and purple rectangles show the effect of each signal. STAT* indicates STAT1, STAT3 or STAT5. Molecules specific to IL-5 signaling in B cells or reported only in B cells, such as Btk and Vav, are omitted.

Fig. 2. Differentiation of eosinophils in fetal and adult hematopoiesis. EoPs are GMPs that express IL-5Rα. Note that sub-population of ProB cells also express IL-5Rα and differentiate to B-1 cells. Since lineage commitment is not final and can be reversed in certain environment even at CLP stage, reversibility of progenitors is shown by background green structure. CMP, common myeloid progenitor; Eo, eosinophil; Neu, neutrophil; Baso, basophil; Mono, monocyte; MEP, megakaryocyte/erythroid progenitor; MK, megakaryocyte; Ery, erythrocyte; ELP, early lymphoid progenitor; ETP, early T-cell progenitor; ProT, progenitor T cell; T, T lymphocyte; CLP, common lymphoid progenitor; ProB, progenitor B cell; B, B lymphocyte.
is ubiquitous, they are suggested to act as lineage-specific activators in cooperation with other factors. Although Oct2 was found to be indispensable for expression of IL-5Rα in B cells (39), a lineage-specific activator of IL-5Rα transcription in eosinophils so far remains obscure. As for down-regulation of IL-5Rα, all-trans retinoic acid is reported to suppress eosinophiliopoiesis by down-regulating membrane-bound IL-5Rα and up-regulating the soluble form of IL-5Rα (40).

IL-5 stimulation induces rapid tyrosine phosphorylation of various cellular proteins. These include the following (Fig. 1): ζc; Src-homology 2 (SH2)/SH3-containing proteins such as Vav guanine nucleotide exchange factor, HS1 (hematopoietic lineage cell-specific protein 1) and Shc (Src-homology-domain-containing transforming protein); Btk (Bruton agammaglobulinemia tyrosine kinase) and Btk-associated molecules; JAK1 (Janus kinase 1), JAK2, STAT1 (signal transducer and activator of transcription 1) STAT3 and STAT5; phosphoinositide 3-kinase (PI3K); Lyn tyrosine kinase and mitogen-activated protein kinases (MAPKs). Phosphorylation of these molecules results in activation of downstream signaling molecules (12–15, 41, 42). In addition, IL-5 activates Raf-1 (v-raf-1 murine leukemia viral oncogene homolog 1) and the phosphatase SHP2 (Src-homology-2-domain-containing protein tyrosine phosphatase) (43).

The activation of JAK2 and STAT5 is essential for IL-5-dependent signal transduction both in B cells and in eosinophils (44, 45). IL-5 also induces the expression of CIS (cytokine-inducible SH2 protein) and JAB (JAK-binding protein) in eosinophils; this is one of the feedback loops of negative regulation of IL-5 signaling (46). In addition to the JAK2–STAT5 pathway, the Ras GTPase–extracellular signal-regulated kinase (Ras–ERK) pathway has also been implicated in signaling of IL-5 (47) and is important for IL-5-dependent cell survival, proliferation and differentiation of eosinophils. JAK2 and Lyn appear to be important for cell proliferation and survival, whereas Raf-1 seems to play a central role in regulating cell function, such as degranulation.

Our analyses of functional cytoplasmic domains of human IL-5Rα (hIL-5Rα) that regulate JAK kinase activation revealed that JAK2 is constitutively associated with hIL-5Rα regardless of IL-5 stimulation. In contrast, JAK1 is constitutively associated with ζc regardless of IL-5 stimulation and is associated with hIL-5Rα only when cells are stimulated with IL-5 (15). Both JAK1 and JAK2 are activated upon stimulation with IL-5. These results clearly indicate that JAK2 and JAK1 are constitutively associated with hIL-5Rα and ζc, respectively, and that they construct a functional hIL-5Rα–ζc complex in the presence IL-5. The region of hIL-5Rα necessary for JAK2 binding is located in amino acid residues 346–387, which include proline-rich sequences, of the cytoplasmic domain (Fig. 1).

Signaling by ζc is terminated partially by ubiquitination and proteasome degradation of its cytoplasmic domain, resulting in the generation of truncated ζc products, termed ζc intra-cytoplasmic proteolysis (ζcIP) (48). Moreover, inhibition of ζc proteasome degradation resulted in prolonged activation of ζc, JAK2, STAT5 and SHP2. JAK kinase activity is required for the direct ubiquitination of the ζc cytoplasmic region and proteasome degradation.

Spred-1 (sprouty-related enabled/vasodilator-stimulated phosphoprotein homology 1 domain-containing 1) is a negative regulator of growth-factor-mediated, Ras-dependent ERK activation. Spred-1-deficient mice show enhanced allergen-induced airway eosinophilia and hyper-responsiveness without affecting helper T-cell differentiation. Biochemical analysis revealed that Spred-1 suppresses IL-5-dependent cell proliferation and ERK activation (49), indicating that Spred-1 is a negative regulator of IL-5-induced eosinophil activation.

Activation of IL-5R upon IL-5 stimulation triggers tyrosine phosphorylation of signaling molecules in several pathways that differ between B cells and eosinophils. Btk activation is indispensable for IL-5-induced proliferation and differentiation in mouse B cells. The B cells in X-linked immunodeficiency (XID) mice, in which Btk contains a single amino acid mutation in the pleckstrin-homology domain, show impaired signal transduction through the B cell receptor and IL-5R (42, 50). Interestingly, EoPs in the bone marrow of XID mice and their mature eosinophils in the periphery are fully responsive to IL-5 leading to eosinophilia in vivo and to prolonged survival in vitro (50), indicating that Btk activation may be dispensable for IL-5 signaling in eosinophils.

IL-5 enhances gene expression of c-myc, c-fos, c-jun, Cis, Cish1/Jab and pim-1 at least in activated B cells (51). The membrane-distal region of ζc is involved in the G1 to S transition that is required for the activation of Ras, Raf-1 and MAPK as well as transcription of c-fos and c-jun but not for pim-1 and c-myc (12). The membrane-proximal region of ζc is important for cellular proliferation and induction of pim-1 and c-myc (11). Thus, activation of the Ras–MAPK pathway together with transcription of pim-1, c-myc, c-fos and c-jun are indispensable for IL-5-induced expansion of eosinophils. This signaling pathway is further divided into two: one is JAK–STAT dependent and leads to induction of pim-1 and the other is JAK–STAT independent and leads to induction of c-myc (52). Thus, activation of the Ras–MAPK pathway together with transcription of pim-1, c-myc, c-fos and c-jun appears to be responsible for IL-5-induced expansion of eosinophil numbers.

**Differentiation of EoPs**

Despite of possible involvement of IL-5 in eosinophil development, the most primitive committed EoPs and the role of IL-5 in their fate decision have yet to be defined until recently. GATA-1, a transcription factor expressed in eosinophils, has been speculated to play a role in the development of eosinophils since mice with targeted disruption of the double GATA motif within the GATA-1 locus show complete loss of eosinophils (53). Iwasaki et al. (54) have identified the most primitive committed EoPs in the mouse bone marrow granulocyte/monocyte progenitors (GMPs).

Of interest, these EoPs are Lin^-Sca1^-CD34^-C-Kit^b blastic cells, express IL-5Rα and respond to IL-5 alone or Slt (steel factor), IL-3, IL-5, IL-9, GM-CSF, erythropoietin and thrombopoietin, leading them to differentiate exclusively into eosinophils (54). However, enforced expression of IL-5Rα in GMPs does not increase the frequency of EoPs, suggesting that IL-5 does promote proliferation and differentiation of eosinophils but does not promote eosinophil lineage
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commitment. This is consistent with a report in which ectopic expression of IL-5Rα in bone marrow cells does not increase the frequency of eosinophil colony formation in the presence of IL-5 (55, 56). Thus, expression of IL-5Rα on EoPs is a consequence of eosinophil lineage commitment.

In the fetal liver, we identified two classes of IL-5Rα-positive cell populations. One of them has B-1 cell progenitor potential and expresses IL-5Rα at very low levels; the other one possesses EoP potential and expresses high levels of IL-5Rα (23, 57). Thus, this picture seems to be also applicable to fetal hematopoiesis (Fig. 2).

The next question is how lineage commitment to EoPs is regulated. Nagai et al. (58) reported that Toll-like receptors are readily expressed on HSCs and their signaling facilitates myeloid cell lineage differentiation. If innate immune signalings that induce EoPs exist, pathogen itself would be considered as candidate regulator of eosinophil lineage commitment. Elucidation of precise mechanisms of eosinophil lineage commitment will contribute to the development of brand-new therapeutic drugs for hyper-eosinophilic diseases such as asthma.

Survival and function of mature eosinophils

Regarding eosinophil migration from the differentiation site, i.e. bone marrow, to the bloodstream and eventually to effecter sites, IL-5 also accelerates this step in an adhesion molecule (CD11b/CD18; αM/β2 integrin or Mac-1)-dependent manner (59). IL-5 induces this β2-integrin-mediated adhesion via the PI3K–protein kinase Cα–MAPK pathway (60). IL-5 also increases eosinophil numbers in the blood and tissue by inhibiting apoptosis (61, 62). Recently, it was revealed that mice deficient for proapoptotic protein Bid (BH3-interacting death agonist) had increased eosinophil numbers in the bronchoalveolar lavage (BAL) after antigen challenge and that those eosinophils were resistant to FAS-induced apoptosis (63). Although production of TGF-β cytokines, including IL-5, is increased in these mice, IL-5 may directly inhibit eosinophil apoptosis via inactivation of Bid since IL-5 has been reported to block Bid activation in vitro (64). Effector functions of eosinophils include generation of reactive oxygen species and secretion of cytotoxic proteins by degranulation. IL-5 also regulates these steps via activation of Raf-1 kinase (41) (Fig. 1).

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The expression of IL-5 mRNA in bronchial biopsies of asthmatic patients is increased as compared with healthy volunteers and the predominant source of IL-5 mRNA is CD4+ T cells (65). Indeed, CD4+ T-cell activation in asthma is accompanied by increased serum concentrations of IL-5 (66). IL-5 mRNA and protein are also found in mast cells located within allergen-challenged tissues. Based on these observations, an attractive paradigm for eosinophil involvement in the LAR is as follows: (i) there is up-regulation of IL-5 synthesis by mast cells activated in an immediate hypersensitivity allergic reaction; this results in (ii) eosinophil recruitment and activation (67); concomitantly, (iii) CD4+ T cells are recruited by other inflammatory mediators of the allergic reaction and undergo antigen-specific activation and acquisition of the Th2 phenotype; this (iv) further enhances eosinophil recruitment and activation.

It is obvious that eosinophils are involved in the pathology of asthma because massive eosinophil infiltration is observed in the airway of asthma patients (68). In asthmatic patients, eosinophils have been detected in high numbers in peripheral blood, in bronchial mucosa and in the BAL fluid after allergen challenge (69, 70). IL-5 levels are also elevated in the serum and the BAL fluid (65). As already mentioned, the expression of IL-5 mRNA in bronchial biopsy specimens is increased in asthmatic patients as compared with healthy volunteers. Inhalation of recombinant human IL-5 by asthma patients resulted in increased eosinophil number in the sputum, bronchial hyper-reactivity and release of eosinophil cationic protein, suggesting IL-5 as a critical factor for asthma (72).

Animal models further support a role for IL-5 in the induction of eosinophil-mediated inflammation in allergies and asthma. IL-5-transgenic mice that express IL-5 in lung epithelium show infiltration of eosinophils as well as goblet cell hyperplasia, epithelial hypertrophy and airway hyper-responsiveness (73). A pivotal role for IL-5 in the LAR has been confirmed by the capacity of neutralizing anti-IL-5 mAb to inhibit antigen-induced or virus-induced airway hyper-responsiveness and eosinophil infiltration in the airways of mice and guinea pigs (74–76).

In the case of mouse models, results are somewhat controversial. Administration of anti-IL-5 neutralizing antibody or soluble IL-5Rα to sensitized BALB/c mice inhibits hyper-eosinophilia induced by antigen challenge, but does not alter bronchial hyper-reactivity (77). In contrast, target disruption of IL-5 or IL-5Rα in the mice in C57BL/6 background abrogates antigen-challenged hyper-eosinophilia and bronchial hyper-reactivity (78, 71). Thus, it is of great interest to test whether IL-5 is a major player in the pathology of asthma in humans and whether neutralization of IL-5 could be a cure for the disease.

Anti-IL-5 therapeutics

Eosinophilia is associated with a wide variety of conditions, including asthma and atopic diseases, helminth infections, drug hypersensitivity and neoplastic disorders. Early case reports and treatment of small cohorts of patients who have eosinophilia using anti-IL-5 mAbs—either mepolizumab or reslizumab/SCH55700—showed promising results. Results of humanized anti-IL-5 blocking mAb treatment in patients with mild asthma confirmed the importance of IL-5 in eosinophil-mediated inflammation in human (79, 80). Although patients given a single injection of anti-IL-5 antibody were protected from allergen-induced blood and sputum hyper-eosinophilia, they were not protected from allergen-induced LAR or airway hyper-responsiveness (79), suggesting that airway hyper-responsiveness occurs independently of IL-5 and airway eosinophilia. However, recently it was reported that long-term anti-IL-5 antibody treatment reduces incidence of exacerbations (81, 82). Since symptoms and lung function were still not improved in the long-term treatment (83), it is suggested that in humans IL-5 is rather responsive to airway eosinophil-mediated inflammation, which is closely related with asthma exacerbations.
Recently, the role of IL-5 and eosinophils in the development of airway remodeling, in an experimental model of chronic asthma, has been carefully studied by using mice lacking IL-5Rα or mice transgenic for IL-5 (84). The study has demonstrated that IL-5 plays an obligatory role in the airway remodeling observed in experimental asthma. Intriguingly, treatment of wild-type mice with anti-IL-5 antibody almost completely prevented subepithelial and peribronchial fibrosis caused by antigen inhalation. Importantly, anti-IL-5 antibody treatment has also been shown to improve airway remodeling in asthmatic patients (29, 85). Further studies are required to define the mechanism underlying IL-5- and eosinophil-mediated airway remodeling in asthma. In mouse model, administration of anti-IL-5 mAb decreases the number and cell size of B-1 cells (4). However, functional impairment of certain B-cell subset after anti-IL-5 treatment in humans has not been investigated, possibly because definition of human B-1 cell has not been established yet.

Anti-IL-5 therapy has been shown to be effective in patients with hyper-eosinophilic syndromes (HES), who exhibit diverse manifestations involving lungs, heart, skin and gastrointestinal tract. A multicenter, randomized, international, double-blind, placebo-controlled trial of mepolizumab for the treatment of HES confirmed the safety and efficacy of anti-IL-5 therapy for the treatment of HES and provided the first example of successful therapy targeting eosinophils in eosinophil-mediated disorders (86). In these studies, the effect of mepolizumab on HES patients who were negative for the fusion gene FIP1L1–PDGFRA (FIP1-like 1–platelet-derived growth factor receptor α) was evaluated. The authors showed that mepolizumab treatment enabled clinically significant reductions in corticosteroid dose, and often corticosteroid discontinuation, in HES patients without major safety concerns.

Koike et al. generated mAbs directed against hIL-5Rα and characterized their antibody-dependent cell-mediated cytotoxicity (ADCC) function using hIL-5Rα-bearing cells. They reported that one of the mAb (KM1259) markedly inhibited activities associated with hIL-5/hIL-5Rα. Humanized versions of KM1259 created by complementarity-determining region grafting technology also showed potent inhibitory activity equivalent to the mouse mAb (87). They also reported their preliminary data showing that a humanized fucose-negative mAb (BIW-8405)—generated by POTELLIGENT® technology—exerted a potent ADCC activity for human eosinophil-mediated eosinophils in the absence of degranulation and release of toxic granule proteins from eosinophils (88).

Busse et al. (89) assessed the safety and biological activity of MEDI-563 (known as BIW-8405), a humanized afucosylated IgG1 anti-hIL-5Rα mAb. MEDI-563 neutralizes IL-5 activity and depletes tissue eosinophils in pre-clinical models and has an acceptable toxicological profile. They reported that MEDI-563 was well tolerated and no serious adverse events were observed. Furthermore, circulating eosinophil numbers decreased below detection limits within 24–48 h of dosing in all subjects and the effect lasted for 8–12 weeks post-dosing.

**Conclusion**

There is overwhelming evidence to support a major role for T_{h}2 cells and their products such as IL-4, IL-5, IL-9, IL-13, IL-25 and IL-31 in causing allergic inflammation. Among these cytokines, IL-5 has pleiotropic effects on various target cells, including eosinophils and B cells, and induces cell proliferation, survival and differentiation. Although anti-IL-5 antibody therapy for asthmatic patients still remains elusive, a potential of humanized anti-human anti-hIL-5Rα mAb treatment for asthmatic patients would be beneficial to eliminate, by ADCC, eosinophils and basophils localized in the inflammatory tissues. The structural, functional and clinical studies described herein and in future provide insight into the role of IL-5 in the immune response and control of inflammatory disease.

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**Abbreviations**

- ADCC: antibody-dependent cell-mediated cytotoxicity
- BAL: bronchoalveolar lavage
- Blk: Bruton agammaglobulinemia tyrosine kinase
- Bld: BH3-interacting domain death agonist
- Btk: Bruton agammaglobulinemia tyrosine kinase
- Bc: common cytokine β-chain
- Ecp: eosinophil progenitor
- ERK: extracellular signal-regulated kinase
- GM-CSF: granulocyte/macrophage colony-stimulating factor
- GMP: granulocyte/macrophage progenitor
- HES: hyper-eosinophilic syndromes
- hIL-5Rα: human IL-5 receptor α chain
- HSC: hematopoietic stem cell
- IL-5Rα: IL-5 receptor α chain
- JAK: Janus kinase
- LAR: late-phase allergic response
- MAPK: mitogen-activated protein kinase
- mRNA: messenger RNA
- Raf-1: v-raf-1 murine leukemia viral oncogene homolog 1
- Ras: Ras GTPase
- RFX: regulatory factor X
- PI3K: phosphoinositide 3-kinase
- PI3Kα: phosphoinositide 3-kinase α
- SH2: Src-homology 2
- SHP2: Src-homology-2-domain-containing protein tyrosine phosphatase
- Spred-1: Sprouty-related enabled/vasodilator-stimulated phosphoprotein homology 1 domain-containing 1
- STAT: signal transducer and activator of transcription
- XID: X-linked immunodeficiency

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