Review

Interleukin-5 and IL-5 receptor in health and diseases

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Abstract: While interleukin-5 (IL-5) is initially identified by its ability to support the growth and terminal differentiation of mouse B cells in vitro into antibody-secreting cells, recombinant IL-5 exerts pleiotropic activities on various target cells including B cells, eosinophils, and basophils. IL-5 is produced by both hematopoietic and non-hematopoietic cells including T cells, granulocytes, and natural helper cells. IL-5 exerts its effects for proliferation and differentiation via receptors that comprise an IL-5-specific α and common β-subunit. IL-5Rα expression in activated B cells is regulated by a complex of transcription factors including E12, E47, Sp1, c/EBPβ, and Oct2. IL-5 signals are transduced through JAK–STAT, Btk, and Ras/Raf-ERK signaling pathways and lead to maintenance of survival and functions of B cells and eosinophils. Overexpression of IL-5 in vivo significantly increases eosinophils and B cells in number, while mice lacking a functional gene for IL-5 or IL-5 receptor display a number of developmental and functional impairments in B cells and eosinophil lineages. In humans, the biologic effects of IL-5 are best characterized for eosinophils. The recent expansion in our understanding of eosinophil development and activation and pathogenesis of eosinophil-dependent inflammatory diseases has led to advance in therapeutic options. Intravenous administration of humanized anti-IL-5 monoclonal antibody reduces baseline bronchial mucosal eosinophils in mild asthma; providing important implications for strategies that inhibit the actions of IL-5 to treat asthma and other allergic diseases.

Keywords: cytokine, eosinophil, B cells, innate immunity, acquired immunity, asthma

1. Introduction

The immune system consists of at least two categories, innate and acquired immune responses. Innate immune responses are responsible for the first line of defense against many microorganisms or tissue injury. They are mediated by macrophage/dendritic cells (DC), NK and NKT cells and leukocytes including eosinophils, neutrophils, and mast cells that recognize pathogen-associated molecular patterns (PAMPs) through germ-line-encoded pattern recognition receptors such as the toll-like receptor (TLR) or nod-like receptor (NLR) family. TLRs, expressed on a diverse variety of cells, recognize PAMPs derived from various classes of pathogens. Activation of TLRs by relevant ligands induces a conserved host defense program, which includes production of inflammatory cytokines and interferons, upregulation of costimulatory molecules, and induction of antimicrobial defenses. The NLR family is important for inflammation and tissue damage that is activated by various crystals, ATP and amyloid-β. Activation of DC by TLR ligands plays a critical role necessary for maturation and consequent ability to initiate and activate acquired immune responses.

Abbreviations: AID: activation-induced cytidine deaminase; ASC: antibody-secreting cells; BCGFII: B cell growth factor II; CSR: class switch recombination; DC: dendritic cells; EDF: eosinophil differentiation factor; IL: interleukin; PAMPs: pathogen-associated molecular patterns; SHM: somatic hypermutation; STAT: signal transducer and activator of transcription; Tbc: Mycobacterium tuberculosis; Tcf: CD4+ T helper cells; TLR: Toll-like receptor; TRF: T cell-replacing factor.

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Acquired immune responses are involved in the late phase of infection and the generation of immunological memory that is mediated by a series of interactions among T, B, and antigen-presenting cells. Activation of T cells by antigenic peptide through specific T-cell receptor (TCR) induces the release of cytokines and chemokines that augments the phagocytosis and triggers B and T cells leading to regulation of both humoral and cell-mediated immune responses.

Mature B cells expressing surface IgM as B-cell receptor (BCR) are destined to differentiate into antibody-secreting cells (ASC) after appropriate stimulation with antigen and T helper (TH) cells. The B cells are subdivided into B-1 and conventional B (B-2) cells that regulate the innate and acquired immune responses, respectively. B-1 cells can be distinguished from B-2 cells by their expression of surface markers and have numerous noteworthy characteristics, such as their self-replenishing ability, particular tissue distribution (abundant in the peritoneal and pleural cavity), V_{H} gene usage of IgM, and production of autoantibodies. B-1 cells form a minor population (less than 5%) of the total splenic B cell pool and are absent from lymph nodes. Coupled to the observation that autoimmune mice have a higher number of B-1 cells as compared to normal mice, B-1 cells may play important roles in the development of autoimmune diseases.

Activated B-2 cells respond to protein antigens and interact with TH cells, which express a TCR, resulting in proliferation and differentiation into ASC. TH cells recognize the peptide–MHC complex presented on the B cells and transiently express CD40 ligand (CD40L) on their surface, which is required for interaction with B cells through CD40 and LMP1, and produce cytokines. Antigen and TH cell stimulation of B-2 cells induces genetic events in their IgH gene loci that are essential for the generation of functional diversity in the humoral immune response and for efficient antigen elimination. Class switch recombination (CSR) replaces the heavy chain constant region (C_{H}) from C\(\mu\) to other C_{H} regions to diversify the effector function of the Ig. The process of CSR is highly regulated by cytokines, B cell activators or both. The efficiency of antigen elimination is also augmented by affinity maturation of antibodies, which is accomplished by excessive point mutations in the V-region gene by somatic hypermutation (SHM). Activation-induced cytidine deaminase (AID) is the essential and sole B cell-specific factor required for CSR and SHM.

Transcriptional regulators, including Blimp-1, Bach2, Bcl6, IRF4, Xbp-1 and Pax5 organize the transition from the mature switched B cell genetic programs to high level antibody synthesis and secretion.

Allergic diseases including asthma and atopic diseases are characterized by inflammation with pronounced infiltration of T cells and granulocytes such as mast cells, eosinophils, and neutrophils. IgE-mediated degranulation of mast cells contributes to inflammatory infiltrates and acute bronchoconstriction in the early phase of allergic inflammation, whereas recruitment of CD4\(^{+}\) T cells and eosinophils is a central feature of the late-phase response. Pulmonary allergen exposure results in both increased output of eosinophils from hemopoietic tissues and increased migration to the lung. Eosinophils are produced in bone marrow and proliferate under a wide variety of conditions, including allergic diseases, helminthes infections, drug hypersensitivity, and neoplastic disorders. T-cell-derived cytokines and eosinophils are thought to play critical roles in the induction of airways hyperreactivity and the development of lesions that underpin chronic airway wall remodelling.

In the 1980s, numerous attempts were made to disclose the molecular nature of T-cell derived cytokines such as T cell-replacing factor (TRF) that are involved in activated B cell differentiation in the absence of T cells. We have analyzed the roles of a T-cell-derived cytokine, at first calling it “Enhancing factor on anti-hapten antibody response” and later “TRF” on anti-hapten IgG response of T-cell-depleted mouse B cells. Recombinant monoclonal antibody (mAb) against TRF and isolated cDNA encoding the TRF active molecule were developed. As recombinant TRF exerts pleiotropic activities on various target cells beside B cells, we proposed calling TRF as “interleukin 5 (IL-5)”. Recombinant IL-5 activates mouse B cells and eosinophils for their proliferation and differentiation. In humans, the biological effects of IL-5 are best characterized on eosinophils.

This review summarizes the advances of IL-5 and IL-5R researches in studying the structure, physiologic functions, and unique mode of receptor-mediated signaling. The pathophysiology of aberrant expression of IL-5 and its receptor regarding allergic inflammation is also discussed.

2. Interleukin 5, IL-5

(1) Historical background. A factor that induces terminal differentiation of B cells to Ig-
secreting cells is originally designated as TRF. Dutton et al. as well as Schimpl and Wecker demonstrated that supernatants of mixed lymphocyte cultures or concanavalin A-stimulated T cells contain TRF activity. These TRF preparations exert remarkable effects in a number of different assays of T- and B-cell activity. TRF activity is mainly screened with the use of dinitrophenyl (DNP)-primed mouse B cells by its ability to support the anti-DNP IgG-ASC response. Biochemical characterization of TRF takes a long time partly because purification of TRF is difficult and its assay system is complicated.

Howard et al. described the first B-cell growth factor (BCGF, later referred to as BCGFI) distinct from IL-2 that had the ability to support B-cell proliferation. This BCGF synergizes with anti-IgM antibody for inducing DNA synthesis of resting B cells. Then Swain and Dutton reported the second T-cell-derived BCGF (BCGFII) active on murine B cells and distinct from BCGFI, suggesting the existence of at least two distinct factors affecting B cell proliferation. They found that TRF-containing supernatants also showed BCGFII activity for in vivo growing murine chronic B-cell leukemia (BCL1) and dextran-sulfate stimulated B cells.

We found TRF activity in supernatants of the lymph node cell culture of Mycobacterium tuberculosis (Tbc)-primed mice after stimulation with the extracts from Mycobacterium tuberculosis, which are so called purified protein derivatives (PPD). We monitored TRF activity by its ability to induce anti-DNP IgG-ASC from T-cell-depleted DNP-primed B cells in an adoptive cell transfer system. We then established an in vitro culture system to assess the TRF activity and examined the TRF-producing T cell subset. We showed that TRF-producing T cells were a different subset from Tbc-primed T cells for cognate interaction with DNP-primed B cells through DNP-PPD (Fig. 1). We also found a strain of mice, DBA/2Ha whose DNP-primed B cells are low-responders to TRF preparations, while they are good responders with Tbc-primed T cells for cognate interaction through DNP-PPD, suggesting the existence of two different subsets in activated B cells.

We developed a TRF-producing T cell hybridoma and established a reproducible TRF assay system using BCL1 cells. Cultured supernatants of the hybridoma showed TRF activity on BCL1 cells and induced their differentiation into IgM-ASC. The anti-TRF mAb does not neutralize IL-1, IL-2, IL-3, IL-4 or IFN-γ activities. Affinity-purified TRF has a molecular mass of 50 to 60 kDa under non-reducing conditions and migrates to a smaller mass (25 to 30 kDa) under reducing conditions (Fig. 2B). The reduced and alkylated TRF does not show any
activities, indicating that T-cell-derived TRF consists of homodimers and its dimer formation is essential for exerting biological activities.

The molecular cloning of cDNA encoding mouse TRF and functional assessment of recombinant TRF have convincingly demonstrated that a single molecule is responsible for both TRF and BCGFII activities. Furthermore, recombinant TRF exerts pleiotropic activities on activated T cells and eosinophils besides B cells. We therefore proposed calling TRF “IL-5”. IL-5 is a synonym of cytokine called TRF, BCGFII, IgA-enhancing factor, IL-2Ro-inducing factor, killer helper factor, EDF, and eosinophil colony stimulating factor.

(2) Cloning of the gene and its organization.
Mouse IL-5 cDNA was isolated by using the expression vector system containing the SP6 promoter. The cDNA libraries were constructed from poly(A) RNA of allo-reactive T-cell clone. Pools of recombinant plasmid DNA from the SP6 library were transcribed in vitro into mRNA using SP6 RNA polymerase. mRNA synthesized in vitro was microinjected into Xenopus oocytes and oocytes’ culture supernatants were assayed for TRF activities. Pools that scored positive in the biological assays were further divided into smaller pools, which were synthesized in the same manner until single cDNA clones capable of directing the synthesis of biologically active TRF preparations were obtained. The isolated IL-5 cDNA clone was subjected to nucleotide sequencing analyses. The mouse (m) IL-5 cDNA, thus obtained, codes for a polypeptide chain of 133 residues that contains the N-terminal signal sequence of 20 residues and the secreted core polypeptide with a molecular mass of 12.3 kDa.
cysteine residues are present in the polypeptide sequence (Table 1 and Fig. 2C). Using the mIL-5 cDNA clone as a probe, human (h) IL-5 cDNA was isolated from a cDNA library constructed with poly(A)^+ mRNA extracted from ATL-2 cells.\textsuperscript{43}) The isolated hIL-5 cDNA clone encodes a polypeptide consisting of 134 residues, containing an N-terminal signal peptide of 19 residues. The nucleotide and amino acid sequence homologies of the coding regions of hIL-5 and mIL-5 are 77% and 70%, respectively. The cDNA clone coding for hEDF is independently isolated by other groups and entire amino acid sequences are identical to that of hIL-5.\textsuperscript{44})

The chromosomal genes for mouse and human IL-5 are isolated using IL-5 cDNAs as probes. Nucleotide sequence analyses of the IL-5 genes as well as flanking regions show that IL-5 genes consist of four exons and three introns.\textsuperscript{42}) Conserved TATA-like motif and the lymphokine element (CLE0, CLE1, CLE2) are found at about 30 and 70 base pairs, respectively, upstream of the transcription initiation sites. The CLE0 element has been shown to be crucial for IL-5 expression.\textsuperscript{45}) As the exon–intron organization and the location of the cysteine codons of the IL-5 genes resemble those of the GM-CSF, IL-2, and IL-4, the IL-5 gene might be evolutionarily related to the genes for IL-2, IL-4, and GM-CSF genes. The genes encoding IL-3, IL-4, IL-5, IL-13, and GM-CSF are located in a cluster on mouse chromosome 11 and in the syntenic region of human chromosome 5q31.\textsuperscript{46})

During Th2 cell differentiation from naïve T cells, changes in the chromatin structure of the Th2 cytokines (IL-4/IL-5/IL-13) gene loci are induced. It is frequently asserted that the expression of IL-4 and IL-5 is coordinately controlled, implying a common mechanism of gene expression. GATA-3 antisense RNA inhibits IL-5 but not IL-4 promoter activation.\textsuperscript{47}) Furthermore, ectopic expression of GATA-3 is sufficient to drive IL-5, but not IL-4 gene expression. Hyperacetylation of histone H3 on nucleosomes observed in Th2 cells is associated with IL-5 gene expression that is STAT6- and GATA-3-dependent.\textsuperscript{48}) Interestingly, the loss of GATA-3 expression results in decreased Th2 cytokine production and reduction of histone hyperacetylation at the IL-5 gene locus but not so at the IL-13/IL-4 gene loci.\textsuperscript{48}) Collectively, GATA-3 is sufficient for optimal expression of the IL-5 gene but not the IL-4 gene.

(3) **Protein in structure.** A single polypeptide with a molecular mass of 14 kDa is secreted when mIL-5 mRNA is transiently translated in rabbit reticulocyte lysates.\textsuperscript{49}) Mouse (m) and human (h) IL-5 are disulfide-linked homodimer with a molecular mass of 50 to 60 kDa.\textsuperscript{23,42}) The large variation in the molecular weight of IL-5 is predominantly as a result of the heterogeneous addition of carbohydrate in posttranslation.\textsuperscript{50})

| 1. Gene locus         | Mouse: Chromosome 11 | Human: Chromosome 5q3.3–31.1 |
|-----------------------|----------------------|-----------------------------|
| 2. Gene structure     | 4 exons              | 4 exons                     |
| 3. Primary structures | 133                  | 134                         |
|                       | 3                    | 2                           |
|                       | 3 N-glycosylation sites | 2 N-glycosylation sites     |
| 4. Secondary structure| 4 alpha helices      | 4 alpha helices              |
|                       | 2 beta strands       | 2 beta strands              |
| 5. Tertiary structure | Interdigitating homodimer | Interdigitating homodimer |
|                       | 2 helical bundle motifs | 2 helical bundle motifs     |
|                       | 2-fold axis of symmetry | 2-fold axis of symmetry     |
| 6. Molecular weight   | 40–60 kDa (nonreduced) | 30 kDa (nonreduced)         |
|                       | 20–30 kDa (reduced)  | 15 kDa (reduced)            |
| 7. Producing cells   | Th2 cells            | Th2 cells                   |
|                       | Mast cells           | Mast cells                  |
|                       | Eosinophils          | Eosinophils                 |
|                       | Natural helper cells | NK and NKT cells            |
|                       | Non-hematopoietic cells | Reed Sternberg cells       |
|                       |                      | EBV-transformed cells       |

**Table 1. Physical properties of IL-5**

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The crystal structure analysis of hIL-5 has revealed that IL-5 is a unique member of the short-chain helical-bundle subfamily of cytokines whose canonical motif contains four helices (A–D) arranged in an up-up-down-down topology (Fig. 2D). Other subfamily members fold unimolecularly into a single helical bundle, while IL-5 forms a pair of helical bundles of two identical monomers that contribute a D helix to the other’s A–C helices. The exact origin of PP CD3-ε+ cells has not been clarified. Recently, Moro et al. identified IL-5-producing c-Kit+ natural helper cells in lymphoid clusters in adipose tissues in the peritoneal cavity. The natural helper cells, a new type of innate lymphocyte subset of Lin- c-Kit+Sca-1+IL-7Rα-IL-33Rα+ cells, proliferate in response to IL-2 resulting in the production of large amounts of IL-5 together with IL-6 and IL-13. They also produce large amounts of IL-5 upon stimulation with IL-33 or nematode infection.

To analyze the localization of IL-5-producing cells, we generated IL-5/Venus knock-in mice and found that the expression of IL-5 along with Venus was detected in IL-5/Venus T cells cultured under Th2-skewing conditions. No IL-5 but strong Venus expression was detected in IL-5/Venus/CD4+ T cells or in Th1-skewed T cells. We also identified innate IL-5-producing Venus+ Lin- c-Kit+Sca-1+ T1/ST2+ cells (referred to as innate IL-5-producing cells) in the small and large intestines, peritoneal cavity, and the lung in non-immunized IL-5/Venus naïve mice. The innate IL-5-producing cells possess several similarities with natural helper cells, but show different tissue localization (Ikutani and Takatsu, unpublished data). Innate IL-5-producing cells in the intestine proliferate in response to IL-25 and IL-33 resulting to enhance mucosal IgA production. A higher proportion of innate IL-5-producing cells is observed in the lung of IL-5/Venus C57BL/6 mice than IL-5-producing T cells, while IL-5-producing Th cells reside mainly in the peritoneal cavity in IL-5/Venus BALB/c mice. As BALB/c and C57BL/6 mice differ in the nature of the pathophysiology of allergic airway diseases and also exhibit variations in underlying mechanisms, different localization of innate IL-5-producing cells in the lung in C57BL/6 than BALB/c mice may have relevance with strain difference for asthma pathogenesis.

The hIL-5 mRNA is detected in bronchoalveolar lavage T cells of mild atopic asthma subjects. It is also detected in HTLV-1-infected T cells, transformed human B cells by the Epstein–Barr virus, and Reed–Sternberg cells of Hodgkin’s disease with cosinophilia. The Reed–Sternberg cells are malignant cells that are essential to the diagnosis of Hodgkin lymphoma. In situ hybridization studies on cytoperaparations of Hodgkin’s disease with cosinophilia reveal striking localization of the hIL-5 mRNA to the cytoplasm of Reed–Sternberg cells and variants, while it is undetectable in a case of Hodgkin’s disease without cosinophilia. This observation indicates the IL-5 mRNA may explain the cosinophilia associated with Hodgkin’s disease.
Eosinophils infiltrating into the mucosa of patients with active coeliac disease express the hIL-5 mRNA, suggesting that eosinophils have the potential to synthesize IL-5. Mast cells, γδT cells, NK and NKT cells, and non-hematopoietic cells including epithelial cells can also produce IL-5.61)

3. IL-5 receptor

IL-5 acts on target cells by binding to its specific IL-5 receptor (IL-5R). In mice, IL-5 responsive B cells and eosinophils express small numbers (approximately 50) of high-affinity IL-5R (Kd of 10–150 pM) and large numbers (around 1,000) of low-affinity IL-5R (Kd of 2–10 nM)62),63) (Fig. 3A). Biological responsiveness to mIL-5 depends on interaction with the high affinity IL-5R. Chemical crosslinking studies of mIL-5R with IL-5 reveal that the high affinity mIL-5R consists of two distinct subunits, α and β (Fig. 3B).63) IL-5 specifically binds to the IL-5Rα subunit. We developed anti-IL-5Rα mAb, H7 that could recognize 60 kDa proteins on IL-5-responsive cells and specifically inhibit IL-5-dependent cell proliferation.64),65) Rolink and his colleagues propagated another mIL-5R mAb, R52.120, which partially inhibited IL-5-induced cell proliferation and recognized 130 kDa proteins.66) Interestingly, addition of H7 and R52.120 mAbs to the cell culture completely inhibited IL-5-induced proliferation (Fig. 3C).67) As anti-IL-3R mAb, Aic2B showed similar inhibitory activity to that of R52.120, we speculated that H7 and R52.120 could recognize IL-5Rα and IL-5Rβ subunit, respectively (Fig. 3D).

1) IL-5R α subunit. Expression cloning of cDNA encoding mIL-5Rα on IL-5-dependent early B cell line is carried out by using anti-mIL-5Rα mAb.68) Nucleotide sequence analysis of the cDNA reveals that the mIL-5Rα is a type-I transmembrane protein of 415 amino acids including an amino-terminal...
signal peptide, a glycosylated extracellular domain, a single transmembrane segment, and a cytoplasmic tail (Fig. 4A). The sequence of amino-terminal 17 amino acids of affinity purified mIL-5Rα from BCL1 is identical to that deduced from the nucleotide sequence of the mIL-5Rα cDNA, confirming the inferred amino-terminus of the mature mIL-5Rα protein. The extracellular domain of the mIL-5Rα contains two motifs that are conserved in a set of type I cytokine receptor family, a particular spacing of four cysteine residues and the tryptophan-serine-X-tryptophan-serine (WSXWS) motifs located close to the transmembrane domain. In addition, the extracellular region comprises three tandemly repeated sets of a fibronectin type III domain, while the cytoplasmic domain does not contain the consensus sequences for a tyrosine kinase domain. Interestingly, the cytoplasmic domain has a motif rich in proline, PPXP motif following the transmembrane domain that is well conserved among IL-5Rα, IL-3Rα, GM-CSFRα, prolactin and growth hormone receptor.

The carboxy-terminal region of IL-5Rα is essential for regulating IL-5-induced IgH class switch recombination. cDNAs of the hIL-5Rα subunit have been isolated from human eosinophils and a cell line, HL60. The entire nucleotide sequence of hIL-5Rα cDNAs shows considerable similarity to the coding sequence of the mIL-5Rα, and the amino acid sequence of the hIL-5Rα has about 70% homology with the mIL-5Rα and retains features common to the cytokine receptor superfamily. The cytoplasmic regions rich in proline residues following the transmembrane domain are well conserved.

COS7 transfectants expressing the mIL-5Rα cDNA bind IL-5 with low-affinity, but they do not respond to IL-5 (Fig. 4B). cDNAs coding for soluble forms of both mIL-5Rα and hIL-5Rα have been isolated. Human eosinophils express, through differential splicing, two forms of soluble
forms of hIL-5Rα (s-hIL-5Rα) in addition to the membrane-bound receptor isoform from the same hIL-5Rα locus.73) s-hIL-5Rα arises from splicing to a soluble-specific exon, which precedes the exon encoding the transmembrane domain. In the case of mice, no evidence for a “soluble” exon has been obtained, indicating that a different splice pattern is used for the generation of s-IL-5Rα in humans and mice. It is unclear whether that represents an interspecies variation or a cell-type-dependent difference. The recombinant s-hIL-5Rα binds hIL-5 with high affinity and inhibits the hIL-5 activities; however, it has not been detected in serum or in supernatants of cultured eosinophils.

The mL-5Rα genomic gene is divided into eleven exons and ten introns and spans more than 35-kb. The gene organization shows a pattern of considerable structural homology with genomic genes coding for other cytokine genomic genes such as IL-2Rβ, IL-3R, IL-4R, IL-7R, and EpoR. Chromosomal localization of the mL-5Rα and hIL-5Rα genes is mapped on the distal half of mouse chromosome 6 and human chromosome 3 (3p24–3p26), respectively.

(2) IL-5Rβ subunit. Enforced expression of mL-5Rα in IL-3-dependent FDC-P1 cells enabled them to reconstitute high-affinity mL-5R and induced proliferation upon IL-5 stimulation (Fig. 4C), indicating that IL-3-dependent FDC-P1 cells constitutively express the IL-5Rβ subunit. Anti-IL-3R mAb was shown to recognize both mL-3R (AIC2A) and a homologue protein of mL-3R (AIC2B).74) Transfection of Aic2B cDNAs into mL-5Rα-expressing L cells could induce the high-affinity IL-5R expression.75) Furthermore, enforced expression of mL-5Rα and AIC2B in CTLL enabled them to proliferate in response to IL-5. We conclude that AIC2B is the mL-5Rβ subunit that plays an indispensable role for the IL-5 signal transduction. AIC2B does not bind IL-5 in the absence of mL-5Rα.

The IL-5Rβ has a relatively long cytoplasmic portion and contains motifs conserved among cytokine receptor families. It does not bind any cytokines, but it contributes to the signaling molecule for the IL-5, mGM-CSFR and mL-3R. Thus it is called the common β subunit (βc).74) Receptors for IL-5, IL-3, and GM-CSF are composed of a ligand-specific α subunit and a shared βc as a signal-transducing subunit (Fig. 4D). Cytoplasmic domains of both IL-5Rα and βc are essential for the signal transduction.76)–78) In humans, KH97, a homologue of mouse AIC2 could reconstitute high affinity hIL-5R with hIL-5Rα72) and transduce IL-5 signals. As KH97 has been shown to be the β subunit of hGM-CSFR and hIL-3R,74) KH97 is the hβc and common signal transducing molecule for hIL-5, hIL-3, and hGM-CSF. The X-ray structure of the hβc is an intertwined homodimer in which each chain contains four domains with approximate fibronectin type-III topology.80) By fluorescence resonance energy transfer imaging, βc subunit is demonstrated to exist as preformed homo-oligomers and the IL-5 stimulation induces βc assembly in the presence of IL-5Rα.81)

Martinez-Moczygemba and his colleagues demonstrated that following cytokine ligation, βc signaling is terminated partially by ubiquitination and proteasome degradation of its cytoplasmic domain, resulting in the generation of truncated βc products, termed βc intracytoplasmic proteolysis (βcIP).82) The truncated IL-5R complex (IL-5Rα and βcIP) is degraded in the lysosome.

(3) Regulation of IL-5R expression on progenitors for B cells and eosinophils. IL-5Rα expression is readily detectable on mouse B-1 cells and eosinophils.85),83) B-1 cells in the mouse peritoneum respond to IL-5 resulting in survival and differentiation to ASC.54),83) IL-5 transgenic mice show marked increase in proportion and numbers of B-1 cells with concomitant hypergammaglobulinemia and autoantibody production.83) They also show increase in the number of eosinophils in the peripheral blood (Fig. 5A), and eosinophil infiltration in various tissues (Fig. 5B and 5C). Passive administration of anti-IL-5 or anti-IL-5Rα mAb into IL-5 transgenic mice decreases the elevated levels of B-1 cells and eosinophil numbers in peripheral blood to normal levels (Fig. 5C).89) IL-5Rα deficiency causes decrease in numbers of B-1 cells and eosinophils in the peritoneal cavity up to one-third of wild-type littermates (Fig. 6A).85) In IL-5Rα−/− mice, serum levels of IgM and IgG3 are decreased (Fig. 6B). The frequency of IgA-ASC in mucosal effector sites such as intestinal lamina propria in IL-5Rα−/− mice is reduced. IgA-committed sIgA+ B-1 cells, but not sIgA+ B-2 cells in the inductive site such as Peyer’s patches are also decreased (Fig. 6C),89) indicating the importance of the IL-5/IL-5R system for the development of sIgA+ B-1 cells in mucosal tissues. Hyperreactivity in the airways of mice that were immunized and challenged with ovalbumin were ameliorated in IL-5Rα−/− mice (Fig. 6D). These
results imply the involvement of IL-5 in the early development of B-1 cells and eosinophils.

A key question is when and how IL-5R expression is triggered in B-1 cell progenitors. IL-5R cells are found in the lineage marker negative (Lin−) fraction in fetal bone marrow, but not in CD19+ B220− B-1 progenitor cells. There are IL-5R cells in the fetal liver that do not differentiate into B-1 cells in vivo, while IL-5R− CD19+ B220− fetal liver cells differentiate into B-1 cells. CD19+ B220− B-1 progenitor cells in the fetal liver may acquire inducing signals for IL-5R expression during migration from the fetal liver to and maturation in the bone marrow microenvironment. IL-5 is important for proliferation and survival of mature B-1 cells.

Most mouse resting B-2 cells constitutively express βc and less than 5% of them express IL-5R. Once B cells are activated by T cells and antigen through BCR and CD40, they express IL-5R and become responsive to IL-5 resulting in integration into the plasma cell differentiation program. Corcoran and colleagues reported that Oct-2 contributes to, but does not entirely control IL-5R levels. Oct2 binds directly to the promoter of the IL-5Rα gene to activate its transcription specifically in mouse B cells and enhances the ability of the B cells to differentiate into ASC under T cell-dependent conditions, through direct genetic regulation of the gene encoding IL-5Rα. The CD38 ligation of splenic B cells also induces increase in the proportion of IL-5Rα+ B cells. In our analysis, the region between bp −250 and −111 from proximal to the transcriptional start site is involved in the regulation of IL-5Rα expression.CD38-stimulated mouse B cells. A complex of transcription factors including E12, E47, Sp1, c/EBPβ, and Oct2 together with unidentified protein coordinately bind to the promoter of the mIL-5Rα gene and regulate the IL-5Rα expression.

Eosinophilic progenitors and mature eosinophils in mice and humans constitutively express IL-5Rα. The IL-5Rα expression in the bone marrow cells is one of the most critical issues in the eosinophil lineage commitment. The RFX family of DNA binding proteins binds to the cis element of IL-5Rα promoter. Although expression of RFX1, RFX2, and RFX3 homodimers and heterodimers is ubiqui-
tous, they contribute to the activity and lineage specificity of the IL-5Rα promoter in cooperation with other factors. As for down-regulation of IL-5Rα, all-trans retinoic acid suppresses eosinophilopoiesis by down-regulating membrane-bound IL-5Rα and up-regulating s-IL-5Rα.

The IL-5Rα+ cells in the fetal liver are able to differentiate into eosinophils in vitro culture under the influence of cytokine cocktails. In the normal bone marrow, Lin−Sca-1−CD34+ fraction containing a small number of cells expressing IL-5Rα and a low level of c-Kit, which are blasts cells with scattered eosinophilic granules, respond in vitro to IL-5 or SCF, IL-3, IL-9, GM-CSF, Epo, and Tpo, leading to differentiation exclusively into eosinophils. They are eosinophil progenitor cells (EoPs). In the bone marrow of mice infected with *Trichinella spiralis*, Lin−Sca-1−IL-5Rα−CD34+c-Kitb cells significantly expand in number, while numbers of granulocyte/monocyte progenitors and common myeloid progenitor are not affected. Thus, Lin−Sca-1−IL-5Rα+CD34+c-Kitb EoPs may be involved in the physiological eosinophil development.

### 4. IL-5R-mediated signaling

IL-5 stimulation induces rapid tyrosine phosphorylation of cellular proteins including the βc, SH2/SH3-containing proteins such as Vav and She, Btk and Btk-associated molecules, JAK1/JAK2 and STAT1/STAT5, PI3K, and MAP kinases that activate downstream signaling molecules (Fig. 9). Activation of tyrosine kinases and signal transducer and activator of transcription (STAT) protein plays an indispensable role in the IL-5 signaling. Regarding the negative regulation of IL-5 signaling, STAT5-induced cytokine inducible SH2 protein (CIS) and JAK2-binding SH2-containing protein (JAB, also called SOCS1) play a role in eosinophils, which are one of the feedback loops of IL-5 signaling. IL-5 also activates NF-κB in activated
B-2 cells and eosinophils, which is dependent on TNFR-associated factor 6 (TRAF6). IL-5 enhances the gene expression of c-Myc, c-Fos, c-Jun, Cis, Cish1/Jab, and pim-1 in B cells. The JAK/c-Myc pathway is indispensable for IL-5-induced cell proliferation and anti-apoptosis, and IL-5-induced up-regulation of c-Myc is dependent upon JAK1 and JAK2 activation.

(1) JAK and STAT pathway. Binding of IL-5 to IL-5R on mouse B cells and eosinophils from mice and humans activates JAK1/2 and STAT1/5. Analyses of JAK kinase activation domain in the cytoplasmic domain in human eosinophils revealed that JAK2 was constitutively associated with hIL-5R, regardless of IL-5 stimulation. JAK1 was constitutively associated with βc and was able to associate with hIL-5Rα only after cells were stimulated with IL-5. As with the IL-5R system, JAK2 and JAK1 are reported to constitutively associate with the hIL-3Rα and βc, respectively in the hIL-3R system. The region of hIL-5Rα necessary for JAK2 binding is located in amino acid residues 346-387 including proline-rich sequences of the cytoplasmic domain (Fig. 9B). These results indicate that the downstream region of motif rich in proline (PPXP motif) in hIL-5Rα is indispensable for significant JAK2 binding and signal transduction. The JAK1 N-terminus binds to conserved regions of proline-rich motif (Box 1 and Box 2) of βc, but signal activation requires JAK1 C-terminus.

By using COS7 transfectants expressing intact βc and a kinase-negative form of JAK1 and JAK2 (DN-JAK1 and DN-JAK2, respectively), we demonstrate that over-expression of DN-JAK2 completely inhibits IL-5-induced activation of both JAK2 and JAK1, tyrosine phosphorylation of βc, and cell proliferation. Overexpression of DN-JAK1 completely inhibits JAK1 activation, but it does not suppress JAK2 activation. These results imply that JAK2 activation is critical and indispensable for inducing tyrosine-phosphorylation of βc and activation of JAK1.

It is worthwhile to note that inhibition of βc proteasome degradation results in prolonged activation of βc, JAK2, STAT5, and SHP-2 in which JAK kinase activity is required for the direct ubiquitination of the βc cytoplasmic domain and proteasome degradation.

(2) Btk activation. Btk is the gene responsible for human X-linked agammaglobulinemia (XLA), which is characterized by a near absence of peripheral B cells, low concentrations of serum Igs and varying degrees of bacterial infections. Btk is a cytoplasmic tyrosine kinase expressed in myeloid, erythroid and B lineage cells except plasma cells. IL-5 induces tyrosine phosphorylation and activation of Btk in an
Fig. 8. Schematic illustration of our model regarding transcriptional regulation of the mIL-5Rα gene. The mIL-5Rα gene has multiple promoter regions. The region from −250 to −115 of mIL-5Rα gene is important for B-cell-specific transcriptional activation. Nucleoproteins binding to the −250 to −115 region are specifically detected in mIL-5−/− B cell lines and activated B cells. E12/E47, C/EBPβ, Sp1, Oct-2, and unknown protein bind to the region and participate in transcriptional activation. Binding of C/EBPβ to the −250−−115 region is found in eosinophils.

Fig. 9. Signal transduction through IL-5R. (A) Comparison of amino acid residues among IL-5Rα, IL-3Rα, and GM-CSFα and their functional domains. (B) Molecular basis of IL-5 signal transduction in human eosinophils. IL-5 stimulation of eosinophils activates JAK2/STAT5 and Ras–MAP kinase pathways leading to induction of the expression of genes involved in eosinophil growth, survival, and activation. Activation of JAK2 is critical for IL-5 signaling. Spred-1 is a negative regulator of Erk activation and regulates IL-5-induced eosinophil activation. (C) IL-5 stimulation of mouse B cells activates three different signaling pathways, namely JAK2/STAT5, Btk, and Ras–MAP kinase leading to induction of the expression of genes involved in B cell proliferation and survival, and differentiation.
IL-5-dependent mouse pro-B cell line.\(^{94,103}\) A spontaneous mutation of Btk (a single amino acid mutation at R28C in the pleckstrin-homology domain) in mice produces X-linked immunodeficiency (\(xid\)). The B cells from \(xid\) and Btk\(^{−/−}\) mice show impaired B cell development and hypersensitivity to IL-5, IL-10, and LPS and fail to proliferate in response to stimulation via the BCR or CD3\(^{ε}\).\(^{95}\) Activated B cells from transgenic mice expressing IL-5R\(α\) in the \(xid\) background do not respond to IL-5 for differentiation into IgG-ASC.\(^{95}\) It is not clear whether Btk is involved in IL-5 signaling in human peripheral B cells or whether the B-cells from XLA patients respond to IL-5, because human peripheral B cells from healthy volunteers express few IL-5R\(α\), if any.

We identified Btk-associated molecule (BAM)\(11\), which binds to the pleckstrin-homology domain of Btk.\(^{104}\) BAM11 is a murine homologue of human LTG19/ENL, a fusion partner of MLL/ALL1/HRX, in infantile leukemia cells. Forced expression of BAM11 in B cell progenitors inhibits Btk activity and IL-5-induced proliferation. BAM11 may negatively regulate Btk-dependent mouse B cell triggering. BAM11 has transcriptional co-activator activity that is enhanced by Btk through pleckstrin-homology and the kinase domain of Btk.\(^{105}\) (Fig. 9C). As BAM11 is co-immunoprecipitated with the IN1/ SNF5 protein, a member of the SWI/SNF complex, IL-5 might regulate gene transcription in B cells by activating Btk, BAM11 and the SWI/SNF transcriptional complex.

Eosinophil progenitors in the bone marrow and mature eosinophils in the periphery of \(xid\) mice fully respond to IL-5 and proliferate in vivo, indicating that Btk activation may be dispensable for IL-5 signaling in eosinophils. It is not yet clear whether mature eosinophils or eosinophilic precursors from XLA patients respond to IL-5 for proliferation or survival.

(3) Ras/ERK activation. The Ras–extracellular signal-regulated kinase (ERK) pathway has been implicated in signaling of IL-5 for maintaining cell-survival, proliferation and differentiation of eosinophils (Fig. 9B and 9C).\(^{106}\) Sprouty family proteins are identified as negative regulators for growth factor-induced ERK activation. Yoshimura and his colleagues cloned the Sprouty-related Ena/VASP homology 1-domain containing protein (Spred)-1 and identified it as a negative regulator of growth factor-mediated, Ras-dependent ERK activation. They also demonstrated that Spred-1 negatively regulated allergen-induced airway eosinophilia and hyperresponsiveness, without affecting T\(h\) cell differentiation.\(^{107}\) Spred-1 could suppress IL-5-dependent cell proliferation and ERK activation. Moreover, Spred-1 deficiency showed overexpression of IL-13 in eosinophils. Spred-1 is a negative regulator of ERK activation and may modulate eosinophil activation normally mediated by IL-5 (Fig. 9B).

5. IL-5 modulates acquired immune response

(1) Enhancement of B-2 differentiation into ASC. Signaling through CD40 in combination with T cell-derived cytokines enhances B-2 cell differentiation, accompanied with IgH class switch recombination (CSR), into the generation of ASC. In mice, ASC formed in vivo can be identified by their high expression of syndecan-1 (CD138) in conjunction with low B220. Syndecan-1\(^{+}\) cells display a gene expression profile of plasma cells, with increased expression of the J chain, B lymphocyte-induced maturation protein 1 (Blimp-1) and X-box-binding protein 1 (Xbp-1), while expressions of AID, B cell lymphoma 6 (Bcl-6) and Pax5 are decreased.\(^{12,108}\)

In the mouse, IL-4 is a survival factor for B-2 cells and an inducer of CSR, primarily to IgG1 and IgE. In contrast, IL-5 acts to increase the likelihood of differentiation of B-2 cells in the spleen into IgM-, IgG- and IgA-producing ASC and synergizes with IL-4. For example, IL-5 acts on sIgA\(^+\) B-2 cells, but not on sIgA\(−\) B cells in Peyer’s patches and to a lesser extent in the spleen to induce IgA production.\(^{86,109}\) As IL-5 induces neither the expression of germ-line C\(c\) transcripts nor the formation of IgA-specific switch circular DNA, IL-5 is not a class switching factor for IgA. Rather IL-5 acts on the B cells committed to become IgA-ASC and induces their terminal differentiation. TGF-\(β\) is an inducer of CSR for C\(μ\) to C\(α\).\(^{109}\)

(2) Induction of class switch recombination to C\(μ\) to C\(γ1\). Naive B cells undergo CSR and develop into ASC to generate the appropriate class and amount of antibody necessary for effective immunity. CSR results in replacement of the C\(μ\) heavy chain constant region with other C\(H\) sequences in activated B cells. Cytokines and mitogens are able to rapidly and selectively up-regulate steady-state levels of specific germine C\(H\) RNA. CSR between S\(μ\) and another S region 5’ to a C\(H\) sequence includes looping out and deletion of all C\(H\) genes except for the one being expressed. For example, CSR from IgM to IgG1 requires B-cell proliferation, γ1 germline expression, μ to γ1 DNA recombination, and DNA
repair. The involvement of AID that attacks DNA directly or indirectly through RNA editing has been demonstrated in the regulation or catalysis of the DNA modification step of CSR. Several proteins besides AID such as Bach2, uracil-DNA glycosylase (UNG), and 53BP1 are also involved in CSR. We have demonstrated that IL-5 induces the maturation of CD40- and CD38-activated B cells to IgG1-ASC. The CD38 stimulation of B cells induces the expression of germline γ1 transcripts, NF-κB/Rel activation, and enhancement of IL-5Rα expression. IL-5 stimulation of CD38-activated B cells further induces cell cycle progression and increase in frequencies of μ to γ1 CSR. This IL-5-dependent μ to γ1 DNA CSR is totally IL-4 independent and associated with the enhanced gene expression of AID, UNG, Bach2 and 53BP1 and with the activation of Ku70, Ku80, and DNA-PKcs that are essential for DNA repair. The IL-5-induced μ→γ1 CSR and IgG1 production is totally dependent on STAT5 activation. Carboxy-terminus of IL-5Rα is required for the IL-5-induced IgG1 production (Fig. 9A).

We conducted comprehensive analyses of the expression of IL-5-inducible genes in CD38-stimulated mouse B cells using a microarray system. A set of genes including BCL6, Aid, and Blimp-1 is critically regulated by IL-5 (Fig. 10). These genes are prone to be induced slowly after IL-5 stimulation. The Blimp-1 and Aid expression are upregulated from 24 hrs after the IL-5 stimulation, while BCL6 mRNA levels decline within 6 hrs of IL-5 stimulation. Significant levels of the J chain and γ1-μ reciprocal circular DNA expression are detectable around 48 hrs after IL-5 stimulation.

6. IL-5 in health and diseases

Emerging concepts in understanding the role of IL-5 in asthma have been discussed through the integration of results from animal studies and analyses of clinical disorders. The lack of bronchial hyperreactivity and eosinophils in the lungs of antigen-sensitized and aeroallergen-challenged IL-5 gene deficient or IL-5Rα deficient mice strengthens the linkage of IL-5 to the pathogenesis of asthma. Administration of a neutralizing mAb to IL-5 before antigen inhalation suppresses the airway hyperreactivity of mouse, guinea pig and monkey models and appears to be applicable to inhibit the development of allergen provoked airway eosinophilia and hyperreactivity.

(1) Anti-IL-5 mAb therapeutics. Eosinophilia is associated with a wide variety of conditions, including asthma and atopic diseases, helminth infections, and drug hypersensitivity. Case reports and series of treatment of patients having disorders with eosinophilia with humanized anti-IL-5 mAbs (mepolizumab and reslizumab) suggest promising results.
A. Clinical trials in bronchial asthma. In asthmatic patients, IL-5 levels are elevated in the serum and the bronchoalveolar lavage fluid. In addition, increased eosinophil numbers and airway hyperresponsiveness are observed upon IL-5 inhalation by asthmatic patients. Leckie and coworkers have shown that an administration of humanized anti IL-5 mAb, mepolizumab to patients with mild asthma caused decrease in numbers of peripheral blood and sputum eosinophils, although mepolizumab exhibited no significant improvement in asthma symptoms.126) The second humanized anti-hIL-5 mAb, reslizumab is also shown to decrease blood eosinophil counts, but no significant improvement is observed in asthma symptoms or lung function in patients with severe asthma.

A large-scale clinical trial of mepolizumab in patients with moderate persistent asthma also showed that it was ineffective in improving asthma symptoms.124) As eosinophils downregulate their IL-5R surface expression, tissue eosinophils may survive in the absence of IL-5. Therefore, it is desirable to develop a stronger intervention of eosinophil tissue accumulation and survival for depletion of eosinophils from asthmatic tissues.

B. Clinical trials in hypereosinophilic syndromes. Hypereosinophilic syndrome (HES) comprises a heterogeneous group of disorders characterized by persistent peripheral eosinophilia for a minimum of 6 months, lack of evidence for other causes of eosinophilia, and organ damage and dysfunction associated with eosinophil infiltration.125) An interstitial deletion on chromosome 4q12 resulting in the formation of the Fip1-like 1–platelet-derived growth factor receptor α fusion gene leads to generation of FIP1L1–PDGFRα fusion protein. The FIP1L1–PDGFRα rearrangement results in a constitutively activated platelet-derived growth factor and represents a subset of chronic eosinophilic leukaemia. Rothenberg and his colleagues evaluated the effect of mepolizumab on HES patients negative for FIP1L1–PDGFRα by an international, multicenter randomized, double-blind, and placebo-controlled trial. They showed that mepolizumab treatment enabled clinically significant reduction in the corticosteroid dose, often corticosteroid discontinuation, in HES patients negative for FIP1L1–PDGFRα without major safety concerns.126) This provides an example of successful therapy targeting eosinophils in eosinophil-mediated disorders.

(2) Anti-human IL-5Rα mAb therapy. As eosinophil precursors and mature eosinophils constitutively express IL-5Rα, it is worthwhile attesting the potential of humanized anti-hIL-5Rα mAb for eliminating eosinophils localized in the inflammatory tissues by antibody-dependent cell-mediated cytotoxicity (ADCC). Koike and his colleagues developed humanized anti-hIL-5Rα mAb, KM1259, which exerted potent inhibitory activity on IL-5.127) They also developed a humanized fucose-negative anti-hIL-5Rα mAb (known as MEDI-563), which is recombinant IgG1 mAb and binds with high affinity to the IL-5Rα. MEDI-563 inhibits proliferation of IL-5-dependent cell lines by blocking the IL-5 binding to the IL-5Rα and shows augmented eosinophil apoptosis in vitro via ADCC. Aluacosing enhances the interaction of MEDI-563 with FcγRIIIa, the main activating Fcγ receptor (FcγR) expressed on natural killer (NK) cells, macrophages and neutrophils,128) and heightens ADCC functions by more than 1,000-fold over the parental antibody. In non-human primates MEDI-563 depleted blood eosinophils and eosinophil precursors in the bone marrow.129)

Busse and his colleagues assessed the safety profile, biological effects and pharmacokinetic activity of MEDI-563.130) They reported that adult patients with mild atopic asthma received single escalating doses of intravenous injection of MEDI-563 had an acceptable safety profile and resulted in marked reduction of peripheral blood eosinophil counts within 24 hrs of dosing at the levels of tested up-to 3 mg/Kg. Although the effect of MEDI-563 on eosinophils was reported to persist for 8–12 wks post dosing, no deteriorations of lung function were shown. Their results indicate that single escalating doses of MEDI-563 have an acceptable safety profile and result in marked reduction of peripheral blood eosinophil counts within 24 hours of dosing. This effect persisted for at least 2 to 3 months in subjects dosed in the 0.03 mg/kg to 3 mg/kg range. So far no side-effect of MEDI-563 on B cells have been reported.130)

7. Future perspectives

IL-5 is an interdigitating homodimeric glycoprotein and a member of the four α helical bundle motifs that are conserved among hematopoietic cytokines. IL-5 exerts its effects on target cells via IL-5R, comprising an IL-5α and βc subunit. The membrane proximal PPX motif of the cytoplasmic domain of both the IL-5Rα and βc subunit is essential for IL-5 signal transduction. Elucidation of the functional residues on IL-5 and IL-5R subunits will expedite the design and development of therapeutic antagonists and agonists of IL-5-mediated immune responses.
IL-5 has pleiotropic effects on various cell types and controls the production and function of myeloid and lymphoid cells. In mice, the role of the IL-5/IL-5R system in the production and secretion of IgM and IgA in mucosal tissues is highly appreciated. In humans, IL-5 acts mainly on eosinophils and their precursors; however hIL-5 might also play a crucial role in the production of IgA in human mucosal tissues. Structural, functional and clinical studies provide insight into the role of IL-5 and its receptor system in the immune response, inflammation, and disease control (Fig. 11). We also emphasize the strong impetus for investigating the means of IL-5 regarding linkage between natural and adaptive immunity specific to the epitope of natural ligands and exogenous allergens.

In aggregate, the structural, functional, and clinical studies described herein provide insight into the role of hIL-5 in health and diseases, and a strong impetus for investigating the means of modulating IL-5 effects. In concert with the efficacy of anti-hIL-5 and anti-hIL-5Ra antibody therapy in hypereosinophilic syndrome, entirely new approaches and concepts regarding patient care may emerge in the near future.

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Profile

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