Review Article

Interleukin-5: Modulator of innate and acquired immunity

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The interleukin-5 (IL-5)-IL-5-receptor system has been of great interest because the IL-5-receptor (IL-5R) contains the common cytokine-receptor β-chain (βc), which is shared with the GM-CSF receptor and IL-3 receptor. IL-5 is produced by type 2 T helper cells (Th2), mast cells, and eosinophils, and non-hematopoietic cells. As we discuss, IL-5 has pleiotropic actions, from enhancing the homeostatic proliferation and survival of B-1 cells through noncognate stimulation and driving the differentiation of B-1 and B-2 cells into terminally differentiated plasma cells to augmenting the survival and activation of eosinophils. Thus, IL-5 links natural and adaptive immunity specific to the epitopes of natural ligands and exogenous antigens leading to the inducion of Ig-producing cells, regulating chronic inflammation and controlling disease. The potential roles of IL-5 in immune responses, allergy and autoimmunity make it attractive candidate for use in the clinical setting.

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Key words B-1, B-2, class-switch recombination, eosinophil, allergy

Introduction

Immune responses and inflammation to pathogens involve coordinated linkages among multiple components of the lymphoid and myeloid cell lineages. These include both immediate innate immune responses, which are mediated by B-1 cells, dendritic cells (DCs), granulocytes, natural killer (NK) cells, NKT cells, monocytes and macrophages, and acquired immune responses, which are generated in the lymphoid compartment and consequently provide antigen specificity and immunological memory[1]. These coordinated linkages are accomplished through a network of cytokines whose function is to induce maturation within these lineages and control effector function, and then to turn off these responses when control of the pathogen is achieved.

Of the type-1-cytokine-family members, those with receptors that contain the common-cytokine-receptor β-chain (βc) (that is, interleukin-3 (IL-3), GM-CSF and IL-5) are integral members of this coordinated network[2,3]. These cytokines are of particular interest because their actions on eosinophil precursors are common and their actions on B cells are different. IL-5 has a prominent feature among these cytokines that can induce the proliferation of B-1 cells and enhance differentiation of B-1 and activated B-2 cells into Ig-secreting cells[3-6]. IL-5 appears to regulate both innate and acquired immunity regarding B cell triggering. B cell development, differentiation, and plasma cell development have been extensively reviewed elsewhere.

The potential roles of IL-5 in the link between the innate and acquired immune responses, and in allergy and autoimmunity make it attractive candidate for use in the clinical setting. This review summarizes the basic biology of the IL-5-IL-5R system and its potential role in the pathogenesis of various diseases.

IL-5 and signal transduction

IL-5 is produced by Th2 cells after stimulation with antigens such as *Mycobacterium tuberculosis*, *Toxocara canis*, or antigens involved in allergy and by activated mast cells[7-9]. IL-5 is an interdigitating homodimeric glycoprotein and belongs to a member of the four α helical bundle motif that is conserved among several hematopoietic cytokines[9]. IL-5R consists of two heteromeric polypeptides, namely IL-5-binding protein (IL-5Rα) and IL-5Rβ [10]. IL-5α was discovered as a novel type-1 cytokine receptor that contains four conserved cysteine residues and a Trp-Ser-X-Trp-Ser motif (where X denotes any amino acid)[11-13]. The gene that encodes IL-5Rα is located on human chromosome 3 and on mouse chromosome 6. IL-5Rβ, also known as the common β chain (βc), is shared with IL-3R and GM-CSFR[14-16]. The βc constructs functional IL-3R and GM-CSFR together with IL-3-binding protein (IL-3Rα) and GM-CSF-binding protein (GM-CSFRα), respectively[17]. IL-5Rα specifically binds IL-5, and βc transduces signals leading to the activation of tyrosine protein kinases and the expression of nuclear proto-oncogene[18,19]. The membrane proximal proline-rich sequence (PPvP motif) of the cytoplasmic domain of IL-5Rα that is conserved among IL-3Rα and GM-CSFRα is essential for signaling[18-20]. The carboxy-terminal region of IL-5Rα is critical for regulating IL-5-induced B cell homeostasis and CSR[21].

Similar to IL-3 and GM-CSF, IL-5 activates the JAK family tyrosine kinase JAK1 and JAK2 that constitutively bind to βc and IL-5Rα, respectively. These kinases induce the rapid tyrosine phosphorylation of various cellular proteins including βc, SH2/SH3-containing proteins, Btk and Btk-associated molecules, STAT1 and STAT5, PI3K, and MAP kinases, and activate downstream signaling molecules[18-20,22-25]. The tyrosine phosphorylation of JAK2 and STAT5 is essential for the IL-5-dependent signal transduction of both B cells and eosino-phils[23,24].

IL-5 activates Btk that is essential for IL-5 signaling in B cells. Btk was originally identified as a gene responsible for human X-linked agammaglobulinemia (XLA)[26], which is characterized by a near absence of peripheral B cells, low concentrations of serum Igs and varying degrees of bacterial infection. A spontaneous Btk mutation (R28C) in mice produces X-linked immunodeficiency (*xid*)[27,28]. Similarly, XLA, B cells from XID mice as well as $Btk^{-/-}$ mice, show impaired B cell development and function[29]. XID mice have defects manifested by a decrease in the overall number of B cells, low levels of circulating IgM and IgG3, and failure in responding to type II thymus-independent antigens[30]. In XID mice, the B-1 population is largely absent and B-1 cells are functionally compromised in response to stimulation via the BCR or CD38[31,32]. XID B cells are hyporesponsive to IL-5, IL-10, and LPS[33-35]. In particular, B-1 cells in XID mice show a decreased number of IL-5R-expressing cells and impaired IL-5-induced differentiation of $IL\text{-}5R\alpha^{+}$ B cells to IgM-producing plasma cells[36]. Thus, the impaired IL-5 responsiveness of B cells in XID mice is due to an abnormality in IL-5-induced Btk-mediated signaling.

Despite the biological importance of Btk in B cell differentiation, the precise function of Btk at the biochemical level remains unclear. We isolated a protein called BAM11 that binds to the PH-domain of Btk[37]. BAM11 is murine homologue of human LTG19/ENL, a fusion partner of MLL/ALL-1/HRX, in infantile leukemia cells. The forced expression of BAM11 inhibits not only the IL-5-induced proliferation of early B cells but also Btk activity both *in vivo* and *in vitro*. Btk localizes not only in the cytoplasm, but also in the nucleus[37,38]. The nucleocytoplasmic shuttling of Btk has implications regarding potential targets inside the nucleus, which may be critical in gene regulation during B cell development and differentiation. The enforced expression of BAM11 enhances the transcriptional activity of the synthetic reporter gene. Ectopic Btk expression together with BAM11 enhances BAM11's transcriptional co-activation activity that is required for both the intact PH domain and kinase activity of Btk[39]. This " positive-negative mutual regulation system " between BAM11 and Btk may elucidate a novel mechanism of B cell signaling through BCR and IL-5R. The enforced expression of TFII-I, another Btk-binding protein with transcriptional activity, together with BAM11 and Btk, further augments BAM11- and Btk-dependent transcriptional co-activation. Furthermore, BAM11 can be co-immunoprecipitated with the INI1/SNF5 protein, a member of the SWI/SNF complex[39]. Btk may regulate gene transcription in B cells by activating BAM11 and the SWI/SNF transcriptional complex via TFII-I activation.

In addition to the JAK2/STAT5 pathway, the Ras/ERK pathway has also been implicated in the signaling of IL-5. IL-5 stimulation of eosinophils results in hyperactivation of the Ras/ERK signaling pathway[25,40]. Sprouty family proteins are negative

regulators for several growth factor-induced ERK activations. Yoshimura and his colleagues cloned an additional Sprouty-related family of novel membrane-bound molecules, Spreds[41]. Like Sproutys, Spred-1, Spred-2 and Spred-3 also down-regulate Ras/ERK signaling. Inoue and his colleagues generated Spred-1$^{-/-}$ mice and demonstrated that mice lacking Spred-1 developed a more severe allergic reaction to inhaled antigens due to the increased number of eosinophils in the lungs[42]. T cells, by contrast, are unaffected by the lack of Spred-1. Spred-1$^{-/-}$ mice show increased responsiveness, especially of the ERK signals, to IL-5 and the subsequent overexpression of IL-13 in eosinophils. Spred-1 may moderate eosinophil activation normally mediated by IL-5.

Role of IL-5 in the innate immune response

1) Regulation of innate B cell response

In contrast with B-2 cells, which are supplied from progenitors in the bone marrow throughout life, B-1 cells maintain their number in adult animals by their self-replenishing capacity. In the adult, these self-replenishing B-1 cells are clearly enriched in the peritoneal and pleural cavities in the mouse, and a low frequency is seen in the spleen, but B-1 cells are virtually absent from the lymph nodes, Peyer's patches (PP), and peripheral blood, where most conventional B-2 cells are localized. B-1 cells are the primary source of natural IgM Ab, although they can become Ig-producing cells for all isotypes. A number of specificities of natural IgM Ab have been identified in the B-1 repertoire, including specificities for LPS, phosphorylcholine, phosphatidylcholine, and complement-binding Abs[43]. The antibody repertoire of B-1 cells is dominated by a restricted set of V genes, and they have been considered carriers of " natural " immunity.

IL-5Rα is a good marker of B-1 cells as well as B-1 progenitors[44,45]. B-1 progenitors can be developed in long-term bone marrow culture of 2-3-wk-old mice along a stromal cell-dependent IL-5-sensitive pathway[46], which can bifurcate to CD5$^+$ macrophages under the influence of GM-CSF. Transgenic mice expressing the IL-5 gene exhibit an increase in the number of B-1 cells in both the peritoneal cavity and the spleen with concomitant hypergammaglobulinemia and autoantibody production[47]. Similarly, IL-5 responsive B-1 cells are increased in spontaneously autoimmune NZB and (NZB x NZW) F1 mice[48]. Together with the observation that autoimmune mice have a higher number of B-1 cells compared to normal mice, B-1 cells play a role in the development of autoimmune diseases.

IL-5$^{-/-}$ and IL-5Rα$^{-/-}$ mice show a severe reduction in B-1 cells in neonates in the peritoneal cavity. B-1 cell numbers return to the normal range in adult life[49,50]. Interestingly, the administration of anti-IL-5 mAb into WT adult mice, T cell-depleted mice, or mast cell-depleted mice results in a reduction in the total number and cell size of B-1 cells to an extent similar to IL-5Rα$^{-/-}$ mice, while the total number and size of B-2 cells are not changed[51]. Cell transfer experiments of B-1 cells into WT and RAG2$^{-/-}$ mice have demonstrated that B-1 cell survival in WT mice and homeostatic proliferation in RAG2-deficient mice are impaired in the absence of IL-5Rα. Significant IL-5 mRNA expression was detected by RT-PCR in the lungs, spleen, and small intestine of WT mice, RAG-2$^{-/-}$ mice, TCRδ$^{-/-}$β$^{-/-}$ mice, and W/W^v mice. IL-5 may be secreted in cells other than Th2 or mast cells and act on B-1 cells in the mucosal tissues.

B-1 cells in the peritoneal cavity serve as an important source of IgA-producing plasma cells at mucosal sites. The role of B-1 cells in IgA production in the gut is supported by evidence that mice with selective B-1 cell reduction show a decreased frequency of IgA-producing cells in the LP, and B-1 cell-derived IgA is specific for commensal bacteria[51,52]. In IL-5Rα$^{-/-}$ mice, the number of sIgA$^+$ B-1 cells from the effector site are significantly reduced, and IgA levels in mucosal secretions are reduced[53], indicating the critical role of the IL-5-IL-5R system in IgA secretion in the mucosal tissues for common mucosal immune system-independent sIgA$^+$ B-1 cell development. Concerning Cμ to Cα CSR in the mucosal tissues, Faragasan et al. demonstrated that culturing LP sIgM$^+$ B cells together with LP stromal cells enhances the preferential switching and differentiation of B cells to sIgA$^+$ plasma cells[54,55]. sIgA$^+$ B cells in the gut lamina propria may be generated *in situ* from B220$^+$ sIgM$^+$ B cells.

Interestingly, the B-1 cells of IL-5Rα$^{-/-}$ mice showed defective proliferation and Ig production upon LPS stimulation *in vitro*, and there were significant differences in serum and fecal IgA levels in LPS-treated WT and IL-5Rα$^{-/-}$ mice[51]. In addition, enhanced IgA production in feces induced by the oral administration of LPS was not observed in IL-5Rα$^{-/-}$ mice. As the expression levels of TLR4/MD2 and RP105 on IL-5Rα$^{-/-}$ B-1 cells are comparable with those on WT B-1 cells, the IL-5-mediated signaling pathway may couple with the LPS-induced signaling pathway. The IL-5 stimulation of WT B-1 cells, but not IL-5Rα$^{-/-}$ B-1 cells, enhances CD40 expression and augments IgM and IgG production after stimulation with CD40L

or Th cells[51]. These results illuminate the role of IL-5 in the homeostatic proliferation and survival of mature B-1 cells and in IgA production in the mucosal tissues in a Th-dependent[56] as well as a Th-independent manner, which is distinguished from the systemic immune compartment.

2) Promotion of eosinophil growth and differentiation

IL-5 stimulates eosinophil precursors in the bone marrow and induces their differentiation into mature eosinophils[56]. Iwasaki et al. reported that eosinophil lineage-committed progenitors (EoPs) are phenotypically isolatable in the steady-state murine bone marrow[58]. Purified granulocyte/monocyte progenitors (GMPs) gave rise to eosinophils as well as neutrophils and monocytes at the single cell level. Within the short-term culture of GMPs, the eosinophil potential was exclusively found in cells activating the transgenic reporter for GATA-1, a transcription factor capable of instructing eosinophil lineage commitment. These GATA-1-activating cells possessed an IL-5Rα$^+$ CD34$^+$ c-Kit^{lo} phenotype. Normal bone marrow cells also contained IL-5Rα$^+$ CD34$^+$ c-Kit^{lo} EoPs that gave rise exclusively to eosinophils. EoPs significantly increased in number in response to helminth infection, suggesting that the EoP stage is physiologically involved in eosinophil production *in vivo*. IL-5$^{-/-}$ and IL-5Rα$^{-/-}$ mice unexpectedly have morphologically normal eosinophils that are present in the reduced proportion, one-third of WT mice[49,50]. Infection of IL-5Rα$^+$ mice with *Angiostrongylus cantonensis* shows the delayed expulsion of worms, suggesting that IL-5-induced eosinophils play a critical role in protective immunity against some types of nematode infection[49].

Asthma is characterized by a variable degree of airflow obstruction, airway hyperresponsiveness (AHR), mucus overproduction, and chronic airway inflammation[59]. In humans, the biologic effects of IL-5 are best characterized for eosinophils. In addition to inducing the terminal maturation of eosinophils and the eosinophilic bronchopulmonary inflammation of asthma, IL-5 prolongs eosinophil survival by delaying apoptotic death, increases eosinophil adhesion to endothelial cells and enhances eosinophil effector function[59]. Th2 cells are the predominant lymphocyte population that infiltrates the airways of people with asthma, and the cytokine products of Th2 cells play an essential role in airway eosinophilia, AHR, and serum IgE in animal models. In both mice and humans, pulmonary allergen exposure results in both increased output of eosinophils from hemopoietic tissues and increased migration of these cells to the lung. It is the accumulation of activated eosinophils during the late-phase response to allergen exposure that ultimately results in progressive inflammatory tissue damage. Thus, AHR may be classified as the immune disease caused by linkage between the innate and acquired immune response. Spred-1$^{-/-}$ mice exhibited exaggerated allergen-induced AHR, eosinophilia, IL-5 production, and mucus secretion in a murine allergic asthma model[42]. Since injection of IL-5, but not IL-13, into the lungs of Spred-1$^{-/-}$ mice caused increased recruitment of eosinophils, it is conceivable that the down-regulation of Spred-1 in the airways plays a significant role in prolonged airway eosinophilia and asthma phenotypes partly in association with IL-5 signals.

Role of IL-5 in the acquired immune response

The generation of antibody-forming cells (AFCs) and the secretion of antibodies after antigen challenge *in vivo* is a complex process that is still not completely understood. The development of AFCs is associated with the regulated loss of lineage-specific surface markers. In mice, AFCs formed *in vivo* can be identified by their high expression of syndecan-1 (CD138) in conjunction with low B220[60]. Syndecan-1$^+$ cells are shown to 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) mRNA and a reduction in AID, B cell lymphoma 6 (Bcl-6) and paired Pax5 mRNA[61-67]. Blimp-1 is considered a " master regulator "for plasma cell differentiation[62,65]. IL-5 potently induces the maturation and differentiation of activated B-2 cells into IgG- and IgA-producing plasma cells. In many cases, IL-5 synergistically enhances IgG, IgA, and IgE production with other cytokines such as IL-4 and TGF-β[68,69]. IL-5 induces neither germ-line Cα transcripts nor the formation of IgA-specific switch circular DNA. TGF-β induces IgA production by LPS-stimulated murine B-2 cells and is synergized with IL-5 to enhance IgA synthesis. TGF-β acts on sIgA$^-$ cells to induce CSR from Cμ to Cα of IgH, determined by the expression of sterile transcripts and sIgA expression[69].

CSR in B cells is an important process for the generation of functional diversity of the humoral immune response. CSR results in the replacement of the Cμ constant region with other CH sequences. The mode of B cell activation also affects the outcome of cytokine stimulation with respect to the efficiency and direction of CSR[70]. CSR to the expression of a particular CH gene isotype is preceded by transcriptional activity at the respective Ig gene locus, known as the accessibility model[71,72]. Cytokines are able to rapidly and selectively up-regulate steady-state levels of specific germline CH RNA. CSR between Sμ

and another S region 5' to a CH sequence is mediated by a DNA recombination event that moves the VDJ segments to a new position upstream of the isotype being expressed. It includes looping out and deletion of all CH genes except for the one being expressed. The deleted DNA forms circular structures termed" switch circles "that may contain reciprocal recombination products consisting of the 3' section of an S region joined to the 5' section of the S region of the new isotype. The involvement of AID has been shown in the regulation or catalysis of the DNA modification step of CSR[73-75]. The switch of the Ig isotype from IgM to IgG, IgE, or IgA, is highly regulated by cytokines such as TGF-β, IL-4 and IFN-γ, B cell activators such as CD40L and LPS or both. However, it has remained elusive whether IL-5 has the ability to induce μ to γ1 CSR in mitogen-stimulated B-2 cells.

Mouse CD38 is expressed in follicular B cells but is down-regulated in germinal center B cells. In contrast, human CD38 is highly expressed in germinal center B cells and is thought to play a key role in the signaling events involved in B cell development[76]. Agonistic anti-mouse CD38 mAb (αCD38) stimulation of splenic B-2 cells induces potent proliferation associated with significant expression of germline γ1 transcripts and enhanced IL-5Rα expression[23,77-79]. The CD38 ligation of B-2 cells also activates a family of NF-κB/Rel proteins[79]. The $p50^{-/-}$ B-2 cells show significant impairment of the CD38-dependent expression of germline γ1 transcripts, indicating that NF-κB plays an essential role in the induction of germline γ1 transcripts. By amplifying deleted circular DNA fragments containing reciprocal junctions, we detected μ to γ1 CSR and found an increment in the number of $sIgG1^{+}$ cells and amount of IgG1 secretion in IL-5- and CD38-stimulated B-2 cells[77]. This was observed only when the cells were stimulated with IL-5 but not with IL-3 or GM-CSF. Intriguingly, IL-4 stimulation did not induce μ to γ1 CSR at all in our experimental conditions, indicating that IL-5-induced μ to γ1 DNA recombination is IL-4-independent. μ to γ1 CSR was reproducibly detectable after four division cycles and peaked following five to six division cycles. IL-5-dependent μ to γ1 CSR and IgG1 production are severely impaired in both $Stat5a^{-/-}$ and $Stat5b^{-/-}$ B cells. IL-4 partially rescued IL-5-induced μ to γ1 CSR in $Stat5b^{-/-}$ B cells.

cDNA microarray analysis revealed that genes critically regulated by IL-5 include Ig-related genes such as the J chain and Igκ , and genes involved in B cell maturation such as AID and Blimp-1. Intriguingly, in genes, the retroviral induction of Blimp-1 and AID in CD38-activated B cells could induce IL-4-dependent maturation to Syndecan-1-expressing plasma cells and μ to γ1 CSR, respectively. The levels of the AID expression in CD38- and IL-5-stimulated $Stat5b^{-/-}$ B cells were similar to those of WT B cells. Our data support the notion that Stat5b is essential for IL-5-dependent μ to γ1 CSR and IgG1 secretion and that AID may not be the target for Sta5b. Interestingly, IL-5-dependent Blimp-1 expression was impaired in $Stat5b^{-/-}$ B cells, consistent with the data showing that stimulation of CD38-activated B-2 cells with IL-5 significantly enhances Blimp-1 gene expression[23].

IL-5 links acquired and innate immunity specific for exogeneous antigens and natural ligands

1) Contact sensitivity model

Contact sensitivity is a form of delayed-type hypersensitivity that is a classic example of *in vivo* T cell-mediated immunity. The skin sensitization of mice with reactive hapten Ag induces contact sensitivity responsiveness. Subsequent challenge at a separate skin site with the immunized hapten elicits an inflammatory response in which Ag-specific T cells are recruited locally and mediate Ag-specific inflammation. Askenase and his colleagues reported that contact sensitivity is impaired in B cell-deficient mice[80,81]. They also showed that Ag-specific IgM antibody is required to recruit effector T cells to the inflammatory site. Furthermore, they demonstrated that activated B-1 cells in the spleen and lymph nodes from 1-day post-immunized mice are able to reconstitute a defective contact sensitivity response in B cell-deficient mice[80,81], indicating the involvement of B-1 cells and Ag-specific IgM antibody in contact hypersensitivity. They postulated that IgM and challenged-Ag form local complexes that activate complements, generating C5a, leading to local vascular activation to recruit the antigen-primed effector T cells that mediate the CS response. Their findings overturn widely accepted immune response paradigms.

To examine the role of IL-5 in contact sensitivity, we immunized WT and $IL\text{-}5R\alpha^{-/-}$ mice with oxazolone (OX) with skin painting. We challenged the mice with OX by ear painting 4 days after the sensitization to elicit contact sensitivity and measured ear swelling at 24 hr. We found that the $IL\text{-}5R\alpha^{-/-}$ mice showed impaired contact sensitivity to OX regarding ear swelling, and the infiltration of inflammatory cells including eosinophils into the inflammatory skin site (A.I and K.T., unpub-

lished data). The impaired elicitation of contact sensitivity to OX in OX-immunized IL-5Rα$^{-/-}$ mice was partially reconstituted by the transfer of lymphoid cells from OX-immunized WT mice. We propose a positive role of IL-5 in contact sensitivity and hypothesize that IL-5 plays a role in B-1 cell-mediated Ag-specific IgM production and the induction of eosinophil production.

2) Atherosclerotic model

Atherosclerosis is a chronic inflammatory disease that is caused by the uptake of oxidized LDL (OxLDL) by macrophages on the artery wall, which in turn can form neo-self determinants recognized by specific innate and adaptive immune responses[82]. During atherogenesis, LDL is oxidized, generating various oxidation-specific neoepitopes, such as malondialdehyde-modified (MDA-modified) LDL (MDA-LDL) or the phosphorylcholine (PC) headgroup of oxidized phospholipids (OxPLs). IL-5 has been detected in human atherosclerotic lesions[83], although it is irregularly expressed. EO6, the prototypic IgM anti-OxLDL antibody that is a natural antibody secreted by B-1 cells in a T cell-independent (TI) manner and possesses the germline-encoded T15 clonotype[84], was protective against atherosclerosis. In other words, IgM natural antibodies against OxLDL protect against the development of the lesion. Binder and his colleagues demonstrated that MDA-LDL immunization induces not only MDA-LDL-specific Th2 cells that prominently secrete IL-5, but also an innate T cell-independent B-1 response that is associated with the production of IL-5 leading to the increased secretion of atheroprotective anti-phospho-rylcholine T15/EO6 antibody[85]. They also showed that IL-5 deficiency leads to decreased titers of T15/EO6 and accelerated atherosclerosis. Their data strongly suggest that IL-5 links acquired and innate immunity specific to the epitopes of OxLDL and protects against atherosclerosis, in part by stimulating the expansion of atheroprotective natural IgM specific for OxLDL[86]. Therefore, IL-5 seems to be pivotally involved in the expansion of atheroprotective T15/EO6 natural antibodies derived from B-1 cells[85,86].

Future perspectives

IL-5 has a pleiotropic effect on various target cells, as do other cytokines. The successful generation and breeding of mice in whom the genes for IL-5, IL-5Rα, or βc are disrupted indicate that none of these mutations is lethal. Although IgM and IgG levels and B cells in both the B-1 and B-2 lineages are normal in the adult mice, neonatal IL-5Rα$^{-/-}$ mice have up to an 80% reduction in the number of B-1 cells. Because anti-IL-5 treatment induces impairment of mature B-1 cell survival and homeostatic proliferation in WT mice, other signals than IL-5 may play a role together with IL-5 in regulating B-1 cell homeostasis and activation. We and others have demonstrated that IL-5 can induce anti-phosphorylcholine (PC) IgM antibody by B-1 cells. However, we did not expect Th2 cells to influence anti-PC antibody formation by B-1 cells leading to the modulation of atherosclerosis. In this context, the positive modulation of protective innate immunity to OxLDL by IL-5 and the acceleration of atherogenesis in IL-5 deficiency are interesting. Because strategies are currently being developed to inhibit IL-5 action in patients with asthma and other allergic diseases, a detailed understanding of the role of IL-5 in atherogenesis is required. It is important to re-evaluate which cell types, Th2, mast cells or others, secrete IL-5 in the lesions. These validate the therapeutic goal of skewing Th responses to atherosclerosis-associated antigens.

We delineated the eosinophil developmental pathway in normal murine hematopoiesis. Eosinophils developed with neutrophils and monocytes from single GMPs. EoPs were cells activating GATA-1 at low levels, and were prospectively isolatable downstream of GMPs as a distinct population with the Lin$^-$ Sca-1$^-$ IL-5Rα$^+$ CD34$^+$ c-Kit^{lo} phenotype. The newly identified EoPs as well as other purified progenitor populations might be useful in investigating the mechanism of commitment and differentiation of the eosinophil lineage. EoPs could also be a therapeutic target for controlling a variety of eosinophil-related disorders including allergic diseases and hypereosinophilic syndrome.

In conclusion, the structural, functional, and clinical studies described herein provide insight into the role of IL-5 in the innate immune response and disease control and provide a strong impetus to investigate how IL-5 works regarding linkage between innate and adaptive immunity specific to the epitopes of natural ligands and exogenous antigens.

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