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Review article

Allergic diseases: From bench to clinic - Contribution of the discovery of interleukin-5

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ABSTRACT

T helper 2 cells produce a number of cytokines including inteleukin (IL)-5, IL-4 and IL-13. Group 2 innate lymphoid cells (ILC2s) also produce IL-5 under sterile conditions. IL-5 is interdigitating homodimeric glycoprotein and a member of the four α helical bundle motifs conserved among hematopoietic cytokines. IL-5 exerts its effects on target cells via IL-5 receptor (IL-5R), composed of an IL-5R α and βc subunit. The membrane proximal proline-rich motif of the cytoplasmic domain of both IL-5R α and βc subunits is essential for IL-5 signal transduction. Although IL-5 was initially identified by its ability to support the growth and terminal differentiation of mouse B cells into antibody-secreting cells, recombinant IL-5 exerts pleiotropic activities on various target cells. For example, IL-5 is now recognized as the major maturation and differentiation factor for eosinophils in mice and humans. Overexpression of IL-5 in mouse significantly increases eosinophil numbers and antibody levels *in vivo*, while mice lacking a functional gene for IL-5 or IL-5R display developmental and functional impairments in B cell and eosinophil lineages. In mice, the role of the IL-5/IL-5R system in the production and secretion of Immunoglobulin (Ig) M and IgA in mucosal tissues has been reported. Although eosinophils protect against invading pathogens including virus, bacteria and helminthes, they are also involved in the pathogenesis of various diseases, such as food allergy, asthma, and inflammatory bowel diseases. The recent expansion in our understanding in the context of IL-5 and IL-5-producing ILC2s in eosinophil activation and the pathogenesis of eosinophil-dependent inflammatory diseases has led to advances in therapeutic options. A new therapy currently under invetigarion in clinical trials uses humanized monoclonal antibodies against IL-5 or the IL-5R. In this review, we summarize our current understanding of the functions of IL-5 and its receptor, the innate regulation of IL-5-producing cells, and therapeutic potential of anti-IL-5 and anti-eosinophil (IL-5R) antibodies.

Contents

Abbreviations: ADCC, antibody-dependent cell-mediated cytotoxicity; ASC, antibody secreting cell; AHR, airway hyperresponsiveness; βc, common β; BCGF, B cell growth factor; BCDF, B cell differentiation factor; BCL1, murine chronic B leukemia; Btk, Bruton's tyrosine kinase; COPD, chronic obstructive pulmonary disease; DNP, 2,4-dinitrophenylated; EDF, eosinophil differentiation factor; IL, interleukin; IL-5R, IL-5 receptor; ILC2, group 2 innate lymphoid cell; Ih2, innate helper 2; Ig, imunoglobulin; JAK, janus kinase; mAb, monoclonal antibody; PAH, pulmonary arterial hypertension; STAT5, signal transducer and activator of transcription 5; Th, T helper; TRF, T cell-replacing factor; VIP, vasoactive intestinal peptide.

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1. Introduction

Around 1970, many immunologists were interested in how T cell facilitates B cell differentiation into antibody-secreting cells (ASC). They found that T-cell-derived soluble mediators enhanced antibody response in an major histocompatibility complex-non-restricted manner [1] termed "T cell-replacing factor" (TRF). In the 1980s, numerous attempts were made to identify the molecular nature of T-cell derived cytokines including TRF that were involved in activated B cell differentiation in the absence of T cells. We previously analyzed the roles of a T-cell-derived cytokine, which we called "Enhancing factor on anti-hapten antibody response" [2] and later "TRF" on anti-hapten Immunoglobulin (Ig) G response [3]. We developed a monoclonal antibody (mAb) against mouse TRF [4] and isolated cDNA encoding the TRF active molecule [5]. As recombinant mouse TRF exerts pleiotropic activities on various target cells beside B cells, we proposed calling TRF "interleukin (IL)-5" [5,6]. Recombinant IL-5 activates mouse B cells and eosinophils and induces their proliferation and differentiation. In humans, the biological effects of IL-5 have been best characterized using eosinophils [7,8].

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 of high-affinity IL-5R and large numbers of low-affinity IL-5R. The biological responsiveness of IL-5 depends on interactions with the high-affinity IL-5R composed of IL-5R α and common β (βc) subunits [9–14] IL-5R α is expressed on mouse B cells and eosinophils. B cells can be subdivided into B-1 B cells and conventional B (B-2 B) cells, which regulate the innate and acquired immune responses, respectively. B-1 B cells have specific characteristics, including the constitutive expression of the high-affinity IL-5R, and differentiation into IgM-secreting cells in response to IL-5 [15,16]. Naïve B-2 B cells express low numbers of IL-5R α, if any, but fully express it upon stimulation with antigen and T helper (Th) cells. They then respond to IL-5 by differentiating into ASCs. IL-5-stimulated activated B-2 cells also undergo genetic events in their IgH gene loci for IgG1-switch recombination, where the heavy chain constant region is changed from Cμ to Cγ1 [17,18]. Although several cytokines affect eosinophil functions, IL-5 is the major cytokine involved in the regulation of blood and tissue eosinophils [7,8]. Therefore, it has been postulated that IL-5 is a therapeutic target for eosinophil-associated diseases such as asthma.

Th2 cells and mast cells are major IL-5-producing cells [6,19]. Interestingly, IL-5 expression was observed in the tissues of T cell- or mast cell-deficient mice [15]. To elucidate which cells other than Th2 cells produce IL-5 under sterile conditions, we established IL-5 reporter mice that enabled us to detect IL-5-producing cells as florescent protein Venus^{+} cells [20]. Using this system, we identified IL-5-producing non-T lymphoid cells that resided in the intestine, peritoneal cavity and lungs in naïve mice. These cells share many overlapping characteristics with natural helper cells, nuocytes and innate type 2 (Ih2) cells such as surface antigens and responsiveness to cytokines. Innate cells producing Th2 cytokine including IL-5-producing innate cells are now called group 2 innate lymphoid cells (ILC2s). Numerous studies have reported that ILC2s are involved in innate immune responses in allergy and infection [21].

Allergic diseases including asthma and atopic diseases are characterized by inflammation with the pronounced infiltration of T cells and granulocytes including mast cells, eosinophils, and neutrophils. Recruitment of CD4^{+} T cells and eosinophils is a central feature of the late-phase allergic response. Pulmonary allergen exposure results in the increased output of eosinophils from hemopoietic tissues and their increased migration to the lung [22]. T-cell-derived IL-5 and eosinophils are thought to play critical roles in the induction of airway hyperreactivity and the development of lesions that underpin chronic airway wall remodeling. In addition, thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 appear to be involved in the induction of allergic inflammation in asthma.

Eosinophilia is associated with a wide variety of conditions including asthma and atopic diseases. Data from animal models support a role for IL-5 in the induction of eosinophilic inflammation. For example, the pivotal role played by IL-5 in the late asthmatic response was confirmed by the capacity for neutralizing anti-IL-5 mAb to inhibit antigen- or virus-induced airway hyperresponsiveness and eosinophil infiltration in the airways of mice and guinea pigs [23,24]. 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 [25–27]. Results of humanized anti-IL-5 mAb treatment in patients with mild asthma confirmed the importance of IL-5 in eosinophil-mediated inflammation in humans. However, whether long-term anti-IL-5 antibody treatment can reduce the incidence of exacerbation of eosinophilic asthma remains to be determined.

As there are already outstanding reviews providing general information on IL-5 and IL-5R, this review article briefly summarize the historical background of IL-5 research and introduce recent