Review

The Interleukin-21 (IL-21) Signal and Allergic Immune Response

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Abstract: Interleukin-21 (IL-21) is a member of the common γ (γc) chain family of cytokines, mainly produced by Th17 cells and natural killer T (NKT) cells. It plays pleiotrophic immunomodulatory roles through acting on various target cells including T cells, B cells, NK cells, macrophages and dendritic cells. IL-21 may be involved in pathogenesis of some autoimmune and malignant diseases. IL-21 signal counteracts IL-4 and inhibits IgE class switch recombination (CSR) in B cells, in which the inhibitor of differentiation 2 (Id2) is induced by IL-21, and essentially contributes to the IgE CSR regulation. Exogenous IL-21 drastically suppresses anaphylactic and local allergic reactions in animals. Molecular understanding of the IL-21-mediated suppression of allergic responses may provide important information for development of novel diagnostic and therapeutic modalities to control allergic diseases.

Key Words: Interleukin-21, Id2, IgE, Class switch, Allergy.

The IL-21 and IL-21 signal

IL-21 is a four-α-helix bundle cytokine with a significant amino acid sequence homology to IL-2, IL-4, and IL-15[1]. It exerts a variety of immunomodulatory functions through interaction with the cell surface IL-21 receptor (IL-21R) complex that is composed of two polypeptide chains, the IL-21R and common γ (γc) chain. The former has sequence homology with the β component of the IL-2R complex and possesses the WSXWS motif. IL-21 binds to the IL-21R even in the absence of γc chain, but IL-21R alone is not capable of transmitting a signal. The γc chain is an essential signal transducing subunit shared by the receptor complexes for IL-2, IL-4, IL-7, IL-9 and IL-15[1]. Binding of IL-21 to the IL-21R/γc complex leads to phosphorylation of the Janus kinase (Jak) 1 and Jak 3, and the phosphorylation of the IL-21R at tyrosine 510, subsequently leading to the recruitment and phosphorylation of the signal transducer and activator of transcription 3 (STAT3)[2]. The activation of STAT3 is essential for the IL-21 signaling[2]. STAT4 and STAT5 are also phosphorylated upon IL-21 stimulation, but their activation are relatively weak and transient, in sharp contrast to IL-2 and IL-15 signals that strongly activate

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STAT5 but not STAT3. Moreover, Ras-Raf-MAPK and PI3K pathways are also activated by the engagement of the IL-21R complex[3].

IL-21 is produced by activated $CD4^+$ T cells, including Th1, Th2, Th17 and T follicular helper cells[4]. Among them, Th17 cells most notably produces IL-21, which subsequently acts on Th17 in an autocrine fashion[5-7]. Meanwhile, natural killer T (NKT) cells are another producer of this cytokine[8]. $CD8^+$ T cells also produce IL-21 under certain conditions[9].

Parrish-Novak et al. reported that IL-21 cooperates with IL-2 or IL-15 to enhances NK cells, while IL-21 provokes differentiation of bone marrow NK cell progenitors in cooperation with IL-15 or flt3 ligand[10]. IL-21 also enhances proliferation of mature B and T cells, when combined with CD40 and CD3 antibodies, respectively.

IL-21 signal may play a crucial role in the commitment of naïve $CD4^+$ T cells to Th17 differentiation. IL-21 provokes TGF-β- and IL-6-stimulated $CD4^+$ T cells to produce IL-21, while inducing expression of RORγt, the Th17-specific transcriptional factor, and IL-23R[5-7]. Acting on naïve $CD4^+$ T cells, IL-21 suppresses expression of STAT4, attenuates susceptibility to IL-12, and suppresses production of interferon-γ (IFN-γ)[11][12], so that Th1 differentiation may be inhibited. IL-21 also prevents TGF-β-mediated induction of regulatory T (Treg) cells.

IL-21 also exerts regulatory functions on NK cells, DCs and macrophages. IL-21 signal facilitates induction of cytotoxic T lymphocytes (CTL)[13], and synergizes with IL-7 or IL-15 to enhance proliferation of $CD8^+$ T cells[14]. IL-21 up-regulates expression of IL-4Rα and IL-13Rα1 in macrophages, while inducing expression of CXCL8 that promotes migration of neutrophils[15]. IL-21 suppresses differentiation of murine bone marrow-derived DCs in vitro, whereas IL-21-stimulated DCs no longer provoke T cells to exert contact hypersensitivity reaction in vivo[16]. When human monocyte-derived DCs are stimulated with IL-21, SOCS-1 and SOCS-2 expression is elevated, while toll-like receptor (TLR) signal is attenuated. Moreover, IL-21 suppresses lipopolysaccharide (LPS)-induced production of TNF-α, IL-21, CCL5 and CXCL10 in the human monocyte-derived DCs[17].

IL-21 exerts variety of actions on B cells. IL-21 may either positively or negatively regulate proliferation of B cells depending on the presence or absence of CD40[18-20], BCR[18][21], LPS or CpG DNA[18][20] signals. In the presence of BCR and CD40 stimuli, IL-21 provokes naïve and memory B cells to differentiate into postswitch antigen-secreting cells (plasma cells)[22][23]. IL-21 augments proliferation of B cells that has received BCR and CD40 signals, whereas IL-21 suppresses growth of, and induces apoptosis in, B cells that has received TLR-4 or 9 signal[18][24]. This apoptosis is Bcl-1-sensitive, dependent on the caspase pathway, and mediated through induction of Bim, Bcl-6 and JunK, as well as through down-regulation of Bcl-xL[18][24]. IL-21 up-regulates expression of Blimp-1 and facilitates terminal differentiation of B cells to antibody producing cells[25][26]. Recently IL-21R signal was found critical for the development of memory B cell response[27].

IL-21 and diseases

Reportedly, the IL-21 signal was involved in the regulation of growth, survival and activation of lymphoma cells, while it promoted proliferation of acute T cell leukemia and multiple myeloma cells[28]. Meanwhile, IL-21 induced apoptosis in B cell chronic lymphoma cell. Acting on the Epstein-Barr virus (EBV)-transformed B cell lines, IL-21 transiently enhanced proliferation, followed by subsequent induction of growth arrest and apoptosis, while expression of Granzyme B was up-regulated by IL-21

in EBV-transformed B cells[9)28)].

We previously reported in vivo action of IL-21 on anti-tumor immunity. By transfecting mouse IL-21 (mIL-21) gene into mice bearing preestablished lung metastasis of RLmale1 lymphoma, we showed that IL-21 induced both CTL and NK cyotolytic activities[29)]. We also demonstrated, using a head and neck squamous cell carcinoma model, that IL-21 elicited not only cellular immune responses mediated by CTL and NK cells but also humoral immune responses in which tumor-specific IgG antibody was produced and partially contributed to tumor rejection[30)].

It has been suggested that IL-21 signal may be involved in the pathogenesis and progression of some autoimmune, including systemic lupus erythematosis, rheumatoid arthritis, multiple sclerosis[31)32)]. IL-21 may also be involved in some skin diseases such as psoriasis[9)33)] and infectious diseases. For an example, IL-21 may play important roles in anti-virus immune response, by affecting primary and memory anti-virus $CD8^+$ T cell responses[34)].

IL-21 and allergic reactions

Recent studies on human genome epidemiology suggested that the IL-21 signal may influence IgE production and be involved in allergic phenotype. Hecker et al. reported significant correlation between a single nucleotide polymorphism (SNP) of the IL-21R gene locus, i.e., T-83C, and elevated IgE levels in healthy female volunteer[35)]. Chatterjee et al. found that the C5250T polymorphism was significantly associated with atopic asthma and serum total IgE level[36)].

There are some inconsistent reports on the influence of IL-21 on generation of IgE-producing B cells. Mice genetically deficient for IL-21R[26)] or IL-21[37)] exhibited more abundant production of IgE than did wild type mice in response to immunization with antigens. IL-21 reduced serum IgE levels in antigen-primed mice. Meanwhile, the cytokine suppressed IgE production in murine splenic B cells activated in vitro by LPS plus IL-4 due to the inhibition of IgE CSR[25)]. Another report demonstrated that IL-21 enhanced production of IgE by unfractionated peripheral blood mononuclear cells (PBMC) or B cells cultured in the presence of CD40 antibody and either IL-4 or IL-13[38)]. In this report, however, IL-21 suppressed the IgE production by PBMC stimulated by PHA and IL-4[38)]. Another report showed different notion that IL-21 rather elevated IgE production and proliferation of IgE producing B cells when the cytokine was added to PBMC or tonsilar B cells stimulated by CD40 antibody and IL-4[39)]. Also, when murine B cells was cultured with CD40 antibody and IL-4, IgE production was either increased or decreased by additional IL-21 depending on the cell density in the culture[39)]. It was also reported that IL-21 failed to inhibit IL-4-induced IgE CSR in human B cells derived from peripheral blood or spleen, but down-regulated IgE production through induction of IFN-γ[40)]. The IFN-γ-mediated inhibition of IgE synthesis by IL-21 was associated with a polymorphism in the IL-21R gene[40)].

IL-21 signal counteracts the IL-4 signal and abolishes IgE CSR in B cells

As described above, it remained controversial whether IL-21 directly acts on B cells and suppresses IgE CSR, while molecular mechanisms underlying the connection between IL-21 signal and IgE CSR had not been clarified. So we examined in vitro action of IL-21 on B cells that were provoked to undergo CSR. Splenic B cells from AKR/J mice were stimulated with IL-4 and LPS, so that significant amount of various classes of immunoglobulin was produced. An addition of recombinant mouse IL-21 (rmIL-21) significantly, and specifically, inhibited the production of IgE, clearly showing that IL-21

canceled the effect of rmIL-4 and LPS that otherwise induced IgE producing B cells[41].

To figure out the molecular basis of the IgE suppression, splenic B cells derived from normal mice were cultured in the presence or absence of LPS, rmIL-4 and rmIL-21, and RT-PCR analysis was performed to detect germ line Cε transcript. An addition of both rmIL-4 and LPS significantly up-regulated germ line Cε transcript, indicating that these stimuli provoked B cells to undergo IgE CSR. In contrast, an addition of rmIL-21 almost completely abrogated the germ line Cε transcript, suggesting effective obstruction of IgE CSR by rmIL-21 that counteracted IL-4 and LPS signal[41].

The IgE CSR is a critical step in IgE-based allergic reaction. Although the mechanism of CSR has not been completely understood, it has been widely accepted that the germ line Ig heavy chain gene transcript and the activation-induced cytidine deaminase (AID) plays pivotal roles for the CSR[42-45]. Three transcriptional factors, Paired box protein 5 (Pax5)[46], E2A[47] and STAT6[48][49] positively regulate both the AID and germ line Cε transcription. Pax5 is constitutively expressed in B cells except for terminal differentiated plasma cells, and further up-regulated by CD40-mediated signal[50]. E2A is induced by LPS, IL-4 plus anti-IgM, or IL-4 plus CD40[51], while STAT6 is activated by either IL-4 or IL-13 signal[52].

We further analyzed which molecule is involved in the IL-21-mediated suppression of these pathways. It was demonstrated that the inhibitor of differentiation 2 (Id2) is transcriptionally induced by IL-21 and the Id2 was essential and sufficient for the IL-21-mediated abrogation of IgE CSR[41]. Id proteins contain the helix-loop-helix (HLH) motif but lack a DNA binding domain[53][54]. They antagonize the transactivation functions of the E proteins, which otherwise regulate many aspects of hematopoiesis as well as lymphocyte proliferation and survival through modulating gene expression program[53][55-57]. It was found that the balance between Id2 and Pax5 is pivotal for the regulation of AID gene expression[58] and that Id2 negatively regulate IgE CSR[59].

Exogenous IL-21 suppresses systemic and local allergic responses

We examined effect of mIL-21 gene transfer on experimental peanut anaphylaxis that had been established by repetitive priming with crude peanut extract (CPE) as an allergen in combination with cholera toxin and aluminum hydroxide. After intragastric challenge of CPE anaphylactic symptoms were estimated by measuring rectal temperature as well as scoring the respiratory and peripheral circulatory disturbance, neurological manifestations, and survival of the animals. The signs of anaphylaxis were totally alleviated by intravenous transfection with the mIL-21 gene, while the untreated allergic mice showed severe systemic manifestation of anaphylactic reactions. The serum IgE level in the IL-21 gene-treated allergic animals was reduced to virtually the same level as that in normal mice. The mIL-21 gene treatment drastically decreased serum level IgE, while other classes of immunoglobulin were not significantly affected. Similar results were also obtained when rmIL-21 was injected intraperitoneally to CPE-primed mice instead of mIL-21 gene transfection.

To assess effect of IL-21 on IgE CSR, germ line Cε transcript was examined. It was clearly demonstrated that the rmIL-21 treatment drastically inhibited IgE CSR that was otherwise induced in B cell after CPE immunization. This may, at least partly, contributed to the IL-21-mediated decrease of IgE and amelioration of anaphylaxis. We also found that Id2 also plays an essential role in the IL-21-mediated inhibition of IgE CSR in vivo[41].

We also tested whether IL-21 is capable of affecting local allergic responses. Allergic rhinitis model

of mice was established by repetitively administrating ovalbumin as allergen in combination with an adjuvant. Intra-nasal administration of rmIL-21 partially, but significantly, reduced allergic rhinitis symptoms. The OVA-specific IgE was reduced in the sera, and the germ line Cε transcript was drastically inhibited in the nasal-associated lymphoid tissues (NALT) of IL-21-treated mice[60].

As the molecular mechanisms of the IL-21-mediated suppression of IgE CSR, we found that Bcl-6 that is involved in germ line Cε transcription is transcriptionally up-regulated in the NALT after rmIL-21 stimulation. Moreover, IL-21 signal significantly suppressed production of eotaxin by nasal mucosal fibroblasts, suggesting that IL-21 may interfere with migration of eosinophils. This may be another mechanism underlying the amelioration of local allergic reaction by IL-21[60].

Conclusion

Recent progress in immunology revealed that the orchestration of the four major $CD4^+$ T cell subsets, i.e., Th1, Th2, Th17 and Treg, is pivotal for homeostasis, defense against infection, and pathogenesis and progression of various disorders[61]. IL-21 is an essential player that induces and maintains Th17, while physiological and pathological significance of other roles of this pleiotrophic cytokine remains to be fully understood. Our studies suggest significant effect of IL-21 signal on IgE-based allergic reaction in vivo, and molecular basis underlying the pathway.

The present data suggest that IL-21 may offer useful therapeutic modalities for allergic disorders. The incidence of allergic disorders is drastically increasing in not only industrial but also developing countries, causing severe medical and social problems. If IgE production can be effectively and safely controlled in patients, such procedures may alleviate allergic symptoms, leading to novel therapeutic and prophylactic interventions of allergic diseases. Finally, molecular analyses on the IL-21-mediated suppression of allergic responses may provide important information that is quite useful for development of novel diagnostic and therapeutic procedures to control allergic disorders.

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〈和文抄録〉

IL-21 シグナルとアレルギー免疫応答

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IL-21 は，コモンγ鎖サイトカインファミリーに属し，主として Th17 と NKT 細胞から産生される．T，B，NK 細胞，マクロファージ，樹状細胞等に作用して多彩な免疫応答制御を司る．IL-21 はまた，自己免疫疾患や悪性腫瘍等の病態にも関与する．我々は，IL-21 シグナルが B 細胞に Id2 分子の発現を誘導し，この Id2 が必須に関与することで，IL-4 シグナルに拮抗して IgE クラススイッチを抑制することを見出した．さらに，アナフィラキシーや局所アレルギー病態を in vivo で抑制することも示した．IL-21 によるアレルギー抑制機構を分子レベルで理解することは，獲得免疫応答のネットワーク制御における IL-21 の意義を理解することにつながるのみならず，アレルギー疾患の新しい治療手段の開発につながる可能性がある．

キーワード：インターロイキン-21，Id2，IgE，クラススイッチ，アレルギー．

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