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Review Article

Internal Medicine Section

Role of IL-25 in Immunity

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ABSTRACT

IL-25 a 2o KDa protein mostly known as IL-17E, encoded by chromosome 14, and containing 117 amino acids. Cytokine IL-17 family consists of 6 members; IL-17A to IL-17F, among which IL-25 has a unique structure and function. The receptor of IL-25 (IL-17BR) is highly expressed in the main Th2 cells. IL-25 regulates the internal safety of adaptive immune responses which leads to begin allergic diseases and plays a role in stimulation of pulmonary mucosal cells and fibroblasts. IL-25 can also have some effects on production of other cytokines. For instance, production of IL-25 in human and mice or injection of IL-25 to animals has resulted in production of high concentrations of Th2 cytokines, including IL-4, IL-5, and IL-13. Pilot studies have shown that mRNA of IL-25 has a high expression in Th2 cells. However, the mechanism through which IL-25 leads to Th2 immune response is still unknown. Reaction between IL-25 and IL-17BR leads to activation of transcription factors, such as NF-KB, STAT6, GATA3, NF-ATC1, JUNNB, MAPK, and JNK. IL-25 has been used against the kidney damage in mice. A large number of researchers in various countries, including the U.S. and Taiwan, have stated that IL-25 is a strong inflammatory cytokine protein which is involved in allergic inflammations.

Keywords: Inflammatory cytokine protein, Th2

INTRODUCTION

Cytokine IL-17 family consists of 6 members; i.e., IL-17A to IL-17F, among which IL-25 has a unique structure and function. Most of IL-17 family members have pro-inflammatory function, while IL-25 has a different responsibility towards progress of type 2 immune responses (Th2) [1]. IL-25 also has receptors called IL-17BR which are highly expressed in vivo by production and induction of Th2 cells. Moreover, recent studies have proved that IL-25 plays a role in differentiation of Th2 and Th2 memory cells [2]. Some evidences have shown that IL-17B can bind to IL-17BR which is highly expressed in lung and gastrointestinal system either in dissolved or membrane hackled forms [3].

IL-25 was first identified by Fort et al., 2001 in a study carried out in 2001 to search for the sequence homology in cytokine IL-17 genomic DNA [4]. Among the 6 members of IL-17 family, the sequence of IL-25 is 16-20% similar to that of IL-17, revealing its unique function. IL-25 is capable of regulating immune responses, especially regulation of different types of Th2 cells. In fact, this cytokine has a stimulatory role for Th2 cells [5]. Phylogenetic analysis demonstrated a close correlation among sheep, cow, and pig IL-25. Accordingly, sheep IL-25 gene was similar to cow's gene amino acids by 81%, pig's IL-25 by 64%, and human IL-25 gene by 67% [6].

Role of IL-25 in immune adjustment

IL-25 is produced by different cells various tissues, including activated Th2 cells, eosinophils, basophils, liver cells, kidney cells, lung cells, innate immune cells resembling lung epithelial cells, macrophages (after stimulation by inhaled antigens), mast cells, bone marrow cells, fibroblasts, endothelial cells, intestinal epithelial cells, and capillary endothelial cells [4,7,8]. Overall, IL-25 regulates the internal safety of adaptive immune responses which leads to beginning of allergic diseases and plays a role in stimulation of pulmonary mucosal cells and fibroblasts. Factors, such as NFATC1 and Th2/JUNB, are moderated by regulation of GATA3 by IL-25. Thus, differentiation to Th2 cells is empowered by regulation of GATA3. Since IL-25 has numerous producer and responder cells, it plays a significant role in progress and description of the roles the cells play in beginning and spread of diseases [9].

Role of IL-25 in production and regulation of cytokines

IL-25 can also have affected the production of other cytokines. For instance, production of IL-25 in human and mice or induction and injection of IL-25 to animals resulted in production of high concentrations of Th2 cytokines, including IL-4, IL-5, and IL-13 [9-11]. Also, by activation of transcription factor NF-KB, IL-25 stimulates production of IL-8 cytokine in kidney cell lines. Nonetheless, the role of this cytokine in renal diseases is yet to be explained [12]. It has been indicated that T cells are regulated in the first transcription of IL-4 gene, resulting in an increase in production of Th2 cytokine 3 days after activation and more differentiation towards Th2 [3]. However, some studies have revealed that regulation of Th2 memory cytokine is independent from that of IL-4.

The effect of IL-25 on the cells leads to activation of some transcription factors, such as GATA3 and phosphorus STAT6, which is moderated by IL-4. In fact, IL-4 might activate STAT6 for regulation of GATA3, eventually resulting in differentiation towards simple Th2. Moreover, the effect of IL-25 on memory cells leads to activation of transcription factors, such as GATA3, C-maf, and TUNB. It should be noted that IL-25 is mostly involved in activation of the transcription factors independent from IL-4 [13].

Role of IL-25 in production of antibodies

IL-25 is an effective factor in production of antibodies and blood cells. This cytokine also increases serum production of IgG1, IgE, and IgA antibodies, blood eosinophils, and eosinophil infiltration in liver. Besides, it leads to production of large amounts of mucus and mucosal cells [14,15].

Role of IL-25 in expression of chemokines

Production of IL-25 in pulmonary epithelial cells leads to induction of expression of chemokines, such as TARC, eotaxin, and Macrophage-Derived Chemokine (MDC), which have a role in renewal of eosinophils and Th2 cells [16].

Signaling pathways in IL-25

Pilot studies have shown that mRNA of IL-25 has a high expression in Th2 cells. However, the mechanism through which IL-25 leads

to Th2 immune response is still unknown. IL-25 probably affects polar Th2 cells. As mentioned before, IL-17BR is the receptor of IL-25. Reaction between IL-25 and IL-17BR leads to activation of transcription factors, such as NF-KB, STAT6, GATA3, NF-ATC1, JUNNB, MAPK, and JNK [3,11,15]. In addition, TRAF-6 acts as a mediator for the interaction between IL-25 and IL-17BR and also plays a role in expression of IL-25 [15].

An alternative pathway proposed by Chun K et al., is the direct effect of IL-25 on human eosinophils which leads to high expression of IL-25 receptors. Evidence has revealed an increase in expression of Intracellular Adhesion Molecules (ICAM1) and a decrease in expression of ICM3 and L-selectin in the eosinophils affected by IL-25 [17].

Respiratory smooth muscles express receptors for IL-25, as well. In general, regulation of IL-25 through respiratory challenges reduces respiratory resistance. Therefore, IL-25 signaling in respiratory smooth muscles cells results in an increase in bronchospasm [18].

Also, alveolar macrophage-like cells (CD11C+) present high expression levels of IL-25, its receptor (IL-17BR), IL-13, and eotaxin-2 after induction with IL-25 [19].

Role of IL-25 in inflammation

It has been revealed that CD4 and STAT6 cells are required for increase of IL-25 concentration and antigen stimulant eosinophils in respiratory tracts. In other words IL-25 has reduced respiratory tract allergic inflammation through Th2 cells associated with respiratory tract [4]. However, some studies also have reported that CD4 T cells are not necessary for production of Th2 cytokine which stimulates IL-25. Also, some evidences have demonstrated a decrease in antigen stimulant allergic inflammation and cell hyperplasia in respiratory tracts following injection of IL-25RS which neutralizes the biological activities of IL-25 [13,17,20]. Some findings proved that IL-25 is produced not only in infectious or helminth infection sites, but also in allergic inflammation respiratory tract [19]. In addition to different types of inflammatory cells, pulmonary epithelial cells may also be affected by allergens, such as ragweeds and aspergillus fungi, resulting in production of IL-25 agents [2]. Overall, it can be concluded that production of IL-25 from different cell types might play a role in beginning and progress of allergic diseases.

Role of IL-25 in Asthma

Overall, most allergic diseases result from irregularities in type 2 immune system. Several studies have confirmed that the Th2 cells and mucosal cells, macrophages, eosinophils, basophils, and pulmonary epithelial cells are the hidden producers of IL-25 [2].

After activation of mammary cells associated with IgE in a mouse model of asthma, a transverse relationship was observed between IL-25 and IgE. According to such findings the highest production was seen 24 h after lung infection in asthma patients. It has been suggested that production of IL-25 by airway macrophages might play a role in regulation of inflammatory responses in lungs. [3].

IL-25 target cells in allergic responses

Fort et al., reported that NBNT cells were the main target cells of IL-25 [4]. In respiratory system's allergic responses, IL-25 is responsible not only for production of Th2 cytokine, but also for secretion of type 2 inflammatory chemokine. Moreover, IL-25 receptor is continuously present in pulmonary cells, such as fibroblasts and pulmonary mucosal cells, representing the main duty of these cells. It should be mentioned that the presence of IL-17BR in human lungs' fibroblasts is mostly regulated by TNF-α [21].

Some evidences indicated that CD4 cells can be target cells IL-25 and respond through induction of Th2 cytokine. They also activate naïve peribronchial lymph node, anti-CD3, and anti-CD28 cells and increase production of IL-4, IL-5, and IL-13 in the presence of IL-25, but they have no effects on production and secretion of INF-α. [22,23].

Role of IL-25 in viral respiratory diseases

Respiratory Syncytial Virus (RSV) increases the risk of progress in asthma among children. Up to now, several studies have been performed on the effects of deficit and decrease in NK cells in the children suffering from RSV. Yet, the important issue is how decrease in the number of NK cells in RSV infection leads to inhibition of INF-α production, progress of Th2, and increase of IL-25, eventually resulting in allergic diseases [24]. A research conducted by Gerard Aie et al., in 2010 indicated that increase of Th2 reactions and effect of IL-25 derived from respiratory tract epithelial cells enhanced the expression of notch ligand jagged on DC cells, inflammation, and asthma [25].

In fact, RSV is not only a symptom of asthma, but it also strengthens the relationship between viral hit at the beginning of life and childhood asthma [26,27]. Overall, clinical studies have demonstrated that deficiency and functional disorders in NK cells might play a role in bronchitis stimulating RSV which is related to progress of asthma in children. The results have also shown that cytokines obtained from mucosal cells, such as IL-25, may improve immunity on mucus surface [28].

Low amounts of INF-α in the absence of NK cells in the infected mice resulted in a considerable increase in IL-25 derived from mucosal cells. This proves a unique reverse relationship between these factors. In fact, in the absence of NK cells, RSV enhances the amount of IL-25 in the respiratory epithelial tissue. IL-25 plays a key role in development of Th2 cells and inflammation in response to RSV through increasing the expression of notch ligand jagged on lymph nodes DC cells [29].

The effect of IL-25 on treatment of autoimmune diseases

In kidney patients, macrophages are the essential mediators for chronic inflammatory reactions. Macrophages and T cells dense accumulation are the specific characteristics of kidney disease in humans and animals and are associated with histology and functional damage [30]. Adriamycin nephropathy (AN) is a kidney disease which leads to urinary loss of proteins. This disease is stimulated by Adriamycin which is similar to the central part of glomerular sclerosis. In AN, inflammatory infiltrations are mostly composed of macrophages and T cells. In a study conducted by Qicao et al., 2011 Reported that urinary loss of proteins significantly increased in the AN mice compared to those with AN, that had been treated with IL-25. In addition, glomerular sclerosis significantly decreased in a mouse with AN treated with IL-25 compared to a healthy mouse in the control group. The number of small tubes also significantly reduced in the mice with AN, that had been treated with IL-25 compared to the control group. Besides, the interstitial volume significantly decreased in a mouse receiving IL-25 compared to a mouse with AN in the control group [31].

Generally, the immunization effect of IL-25 can originate from stimulation of Th2 reactions. According to the studies conducted so far, monocytes and macrophages reacting with IL-25 act in live tissues by low regulation of meta-inflammatory cytokines and high regulation of anti-inflammatory cytokines. Besides, IL-25 could considerably control the roles of other macrophages activated by LPS, such as phagocytes [31].

Experimental Autoimmune Encephalomyelitis (EAE) is an inflammatory autoimmune disease in Central Nervous System (CNS) which involves high levels of IL-17, IL-18, INF, and TNF cytokines and low levels of Th2 cytokines, such as IL-13 and IL-4 [13,29]. Studies have indicated that the more the immune system is balanced towards Th2, it leads to suppression of autoimmune responses [3,9], because Th2 responses lead to several signals preventing the production of Th1-dependent IFN [30,31]. IL-25 is

mainly expressed by microglia in CNS cells in normal conditions. Researchers have demonstrated that the disease was intensified in the mice without IL-25 compared to those receiving IL-25 [6].

Role of IL-25 in treatment of cancer

A large number of researchers in various countries, including the U.S. and Taiwan, have stated that IL-25 is an inflammatory cytokine protein which is involved in allergic inflammations. These two teams announced IL-25 as one of the strongest cytokines [32].

In 2005, the researchers of University of California mentioned that cultured mammary epithelial cells induced cytotoxic effects in human breast. By isolation of IL-25 from the normal human epithelial cells, these researchers demonstrated that IL-25 binds to its specific receptor (IL-17BR) and increases its apoptotic effect in several breast cancer cells. Besides, injection of IL-25 in the mice with xenograft breast tumors resulted in a decrease in tumor cells growth. This research team continued that IL-25 essentially exists in breast tumor cells and sometimes binds to breast tumor receptor inducing apoptosis. It should be mentioned that activation of apoptosis process is possible by attachment to Death Domains (DD) [33].

IL-25 is effective in treatment of pancreatic cancer. Pancreatic cancer is the 8th and 9th cause of mortality in males and females around the world. Almost 5% of such patients can survive 1-5 y after treatment with chemotherapy; therefore, it is one of the life-threatening cancers. Pancreatic cancer mostly occurs in the transmission tract of digestive enzymes to the small intestine. Besides, its development is usually resistant against most cancer treatments; e.g. lack of reaction to apoptosis stimulants [34].

Considering the role of IL-25 in induction of apoptosis without affecting the healthy cells, researchers decided to use IL-25 for treatment of pancreatic cancer. IL-25 induces apoptosis and leads to tumor cell death by binding to its receptor on tumoural cells. This is carried out with cooperation of TCR respectively delta d segments (TRDD) and through activation of TNF receptor associated factor (TRAF6) signaling pathway which plays an important role in adaptive regulation and innate immunity in bone metabolism and cell apoptosis [35].

CONCLUSION

IL-25 belongs to IL-17E cytokines family and leads to production of known Th2 cytokines. These cytokines, including IL-4, IL-5, and IL-13, have a role in calling eosinophils cells, differentiation of Th0 cells to Th2 cells, producing mucus, and producing IgE from B lymphocytes. This cytokine also plays a role in creation of allergic inflammation in asthma and autoimmune diseases as well as in treatment of cancer. In asthma, IL-25 is produced by lymph cells such as Th2 as well as by non-lymph cells such as mucosal cells, macrophages, eosinophils, basophils, and pulmonary mucosal cells. The pathogenic effects of this cytokine result from its impact on mucus production and eosinophil inflammation. Since most autoimmune diseases originate from disturbance of balance between the immune cells, in case the autoimmune disease originates from Th1 cells, injection of IL-25 which leads to differentiation of Th0 to Th2 cells and production of their cytokines can be effective in improvement of the disease. IL-25 which induces apoptosis in cancer cells is a proper candidate for treatment of cancer such as pancreatic cancer. Since cytokines have different effects on different cells, IL-25 cytokine shows different effects in autoimmune diseases and cancers. Thus, further studies are required to be conducted on various cancer cell lines and autoimmune diseases to further elucidate in role of the cytokine in these diseases. For instance, these studies might involve knocking out the receptors of this cytokine in animal models of autoimmune diseases, adjacency of this cytokine to cancer cell lines at different times, and investigation its pathologic and treatment effects.

REFERENCES

[1] Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. *Immunity*. 2011;34:149-62.
[2] Rouvier E, Luciani MF, Mattei MG, et al. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability se-quences, and homologous to a herpesvirus saimiri gene. *J Immunol*. 1993;150:5445-56.
[3] Wangy YH, Angkasekwinai P, Lu N, et al. Il-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-Dc- activated Th2 memory cells. *J Exp Med*. 2007;204:1837-47.
[4] Fort MM, Cheung J, Yen D, et al. IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies *in vivo*. *Immunity*. 2001;15:985-95.
[5] Ikeda K, Nakajima H, Suzuki K, kagami S, Hirose K, Suto A, et al. Mast cells produce interleukin- 25 upon Fc epsilon RI mediated activation. *Blood*. 2003;101:3594-6.
[6] Zaph C, Du Y, Sanez SA, Nair MG, perrigoul JG, et al. Commensal dependent expression of IL-25 regulates the IL-23- IL-17 axis in the intestine. *j Exp med*. 2008;205:2191-98.
[7] Pan G, French D, Mao W, Maruoka M, Risser P, Lee J, et al. Forced expression of murine IL-17E induces growth retardation, jaundice, a Th2-biased response, and multiorgan inflammation in mice. *J Immunol*. 2001;167:6559–67.
[8] Kim M, Manoukian R, Yeh R, Silbiger S, Danilenko D, Scully S, et al. IL-17E result in eosinophilia, B-lymphocyte hyperplasia, and a ltered antibody production. *Blood*. 2002;100:2330-40.
[9] Lee, et al. IL-17E, a Novel Proinflammatory Ligand for the IL-17 Receptor Homolog IL-17RH1" *J Biol Chem*.. 2001;276:1660-64.
[10] Anton Gossenr, Anna P ecrs, vireginia Venturing, John Hopkins. Expressed gene sequences of two variants of sheep interleukin 25. *Vet Immunopathlol*. 2011;139 (2-4):319-23.
[11] Tomohiro Tamachi, et al (2006). Mechanism of asthma and allergic inflammation. Il-25 enhances allergic air way inflammation by amplifying a TH2 cell- dependent path way in mice. *J Allergy Clin Immunol*. 2006;118(3):606-14.
[12] Ikedak, Nakajima H, Suzuki K, Kagami S-I, Hirose k, Suto A, et al. Most ceus produce interkukin 25 upon activation. *Blood*. 2003;101:35,4-6.
[13] Murst SD, Muchamuel T, Gorman Dm, Gilbert Jm, Clifford T, Kwan S, et al. New IL 17 family member's promote Th1 or Th2 responses in the lung: in vivo function of the novel cytokine IL-25. *J Immunol*. 2002;169:443-53.
[14] Audusseau S, Rothenberg ME, Fiset PO, Ludwig MS, Hamid Q, et al. I-17E upregulates the expression of proinflammatory cytokines in lung fibroblasts. J *Allergy clin Immunol*. 2006;117:590-96.
[15] Umetsu DT, Mcintirej J, Akbari O, Macaubas C, Dekruyff RH. Asthma: An epidemic of dysregulated immunity. *Nat Immunol*. 2002;3:715-20.
[16] Renauld JC. New insights in to role of cytokines in asthma.*J Chin patbol*. 2001;54:577-89.
[17] Chun K. Wong, Phyllis F. Y. Cheung, Wai K. Ip, and Christopher W. K. Lam Interleukin-25–Induced Chemokines and Interleukin-6 Release from Eosinophils Is Mediated by p38 Mitogen-Activated Protein Kinase, c-Jun N-Terminal Kinase, and Nuclear Factor-κB. *American Journal of Respiratory Cell and Molecular Biology*. 2005;33(2):186-99.doi: 10.1165/rcmb.2005-0034OC
[18] Angkasekwinai P, park H, et al. Interleukin 25 promotes the initiation of proallergic type 2 responses. *J Exp Med*. 2007;204:1509-17.
[19] Tamachi T, Maezawa Y, Ikeda K, Kagami S, et al. IL-25 enhances allergic airway in flammation by amplifying a th2 cell. Dependent pathway in mic. *J Allergy clinImmuol*. 2006;118:606-14.
[20] Letuve S, Lajoie- kadoch S, Audusseau S , Rothenberg ME, Fiset Po, Ludwig Ms, et al. IL-17E upregulates *the* expression *of proinflammatory* cytokines in lung. *J Allergy Clin Immunol* 2006;117:590–96.
[21] Foster PS. Mechanism of interleukin-25 (IL-17E)-induced pulmonary inflammation and airways hyper-reactivity. *Clin Exp Allergy*. 2006;36:1575-83.
[22] Ranger AM, Hodge MR, Gravallese EM, Oukka M, Davidson L, Alt Fw, et al. Delayed lymphoid repopulation with defects in IL-4-driven responses produced by inactivation of NF-ATc. *Immunity*. 1998;8(1):125-34.
[23] Flavell RA, Li B, Dong C, Lu HT, Yang DD, Enslen H, et al. Molecular bais of T- Cell differentiation, cold spring Harbsymp. *Quant Biol*. 1999;64:563-71.
[24] Simoes EA. Respiratory syncytical virus in faction. *Lancet*. 1999;354:847-52
[25] Gerard E Kaiko, Simon Phipps, Pornpimon Angkasekwinai, Chen Dong, paul S Foster. Nk Cell Deficiency predisposes to viral- induced Th2- Type Allergic inflammation via epithelial Derived IL-25. 2010. *J Immunol*. 2010;185(8):4681-90.
[26] welliver TP, RP GaroFalo, y Hosakote, KH Hintz, L Avendano, et al. Severe human lower respiratory tract illness caused by respiratory syncytial virus and influence virus is characterized by the absence of pulmonary cy to toxic lymphocyte responses. *j infact DIS*. 2007;195:1126-36.
[27] Larranaga CL, SL Ampuero, VF luchsinger, FA Carrion, NV Aguilar, PR Morales, et al. Impaired spriatory syncytical virus, pediatr. *infect Dis J*. 2009;18:867-73.
[28] Mailliard Rb, YI Son, R Redlinger, PT Coates, A Giermasz, PA Morel, et al. Dendritic cells me diate NK cell help for Th1 on CTL responses: Two- signal requirement for the in duction of NK cell helper function. *J Immunol*. 2003;171:2366-73.
[29] Orange JS, Wang B, Terhorst C, and Biron CA. An absolute and restricted requirement for IL-12 in natural killer cell IFN-y production and antiviral defense. Studies of natural killer and T-cell responses in contrasting viral infections. *J Immunol*. 1996;156:1138-42.

[30] Saenz SA, BC Taylor, D Aritis. Welcome to the neighbodhood epithelial cell-derived cytokines license innate and adaptive immune responses atmucosal sites. *Immunol Rev*. 2008;226:172-90.
[31] Angkasekwinai P, H park, YH wang, SH Chang, DB Corry, YJ Li U, et al. Inretleukin 25 promotes the initiation of proallergic type 2 responses. *J Exp Med*. 2007;204:1509-17.
[32] Wang YH, P Angkasekerinai,N.Lu.K.S.Voo.KArima, SH Anabuchi, A Hippe, CJ Corringan, C Dong, et al. IL-25 augments types immune responses by enhancing the expansion and functions of TSLP-DC- activated Th2 memory cells. *J Exp Med*. 2007;204:1837-47.
[33] Caruso R, Stolfi C, Sarra M, Rizzo A, Fantini MC, Pallone F, et al. Inhibition of monocyte-derived inflammatory cytokines by IL-25 occurs via p38 Map kinase-dependent induction of Socs-3. *Blood*. 2009;113:3512-19.
[34] Qicao, Chang q I wang, Dong Zheng , Yawang, et al. IL- 25 In duces M2 macrophages and Rend Injury in proteinuricki deny Disease. *Basic Research* 2011. Pp.1229-1239.
[35] F Furuta, S, et al. Sci, Transl. med; published online April B.2011 D 10, 1126/ scitransl med. 300 1374.

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