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Review Article

IL-17 in Pneumonia: Cure or Corruption?

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Abstract

As a pro-inflammatory cytokine, IL-17 is important in the immune system against fungal and bacterial infections. The IL-17 cytokine family consists of six members that exert their effects by cooperating with five receptors that form the IL-17 receptor family. Although IL-17 is mainly a defensive factor, at times, overexpression of this cytokine will lead to inflammatory and damaging outcomes.

Pneumonia is a lower airway disease that can be caused by different agents. In this condition, IL-17 is secreted from different cells and can fight against infection or otherwise lead to progression of the disease. This article reviews the IL-17 role in pneumonia and different inflammatory pathways that it can affect.

Keywords: IL-17; Pneumonia; IL-23; Respiratory Diseases

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Introduction

IL-17 is a cytokine that takes part in inflammatory responses (1). IL-17 can induce inflammatory responses, depending on its site of secretion and the factor that induced its secretion (2).

So far, six members of the IL-17 cytokine family have been known (3), with IL-17A (or CTLA8) being the first to be discovered in 1993 (4). IL-17 receptor A was discovered and known as a receptor for IL-17A in 1995 (5). This receptor and four others, which were discovered later on, form the IL-17 receptor family (3). Both IL-17 cytokines and receptors share sequence homology (3). The special cytokine structure in this family is considered a part of the cysteine knot family with a slight resemblance to neurotrophins (6). Innate

and adaptive immune cells can produce IL-17 (7, 8, 9). Macrophages of the placenta can produce IL-17A and IL-17F during different stages of gestation (10). Mast cells, neutrophils, NK, and NKT cells can also express cytokines of the IL-17 family (6) in organs such as intestinal mucosa, skin, and lungs (11). Pneumonia is a disease in which the parenchymal cells of the lower respiratory tract get involved with an acute infection. Some microorganisms cause this infection by attacking the parenchymal cells. There are two major types of this disease: community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) (12, 13, 14, 15). Ventilator-associated pneumonia (VAP) is a kind of hospital-acquired pneumonia. Mechanical ventilation (MV) is one of the major factors in the appearance of this disease (16, 17). HAP is one of the major leading-to-death diseases among infections obtained in hospitals (15).

The elderly are more susceptible to pneumonia because of a weakened immune system, mucociliary system, and other factors (18). Another type of pneumonia appeared in patients who were in contact with the healthcare system. This category is named healthcare-associated pneumonia (HCAP) (19). Pneumonia during the neonatal period has the highest mortality rate (20). In developed countries, the risk of becoming infected by pneumonia increases with age (21). Pneumonia is the major cause of death, considering acute respiratory infections in children (22).

IL-17 has an important role in immune responses against infections caused by bacteria (such as Staphylococcus aureus and Klebsiella pneumoniae) and fungi (7, 11). IL-17 improves bacterial elimination after influenza and also promotes clearance of MRSA (23). Although IL-17 is necessary for some immune responses, excess amounts of this cytokine are related to conditions such as asthma (24), psoriasis (25), pneumonia (26), rheumatoid arthritis (27), axial spondyloarthritis (1), multiple sclerosis, systemic lupus erythematosus (28), and some other autoimmune diseases (11, 29). This review emphasizes the IL-17 cytokine family and its dual effect on pneumonia, considering both therapeutic and pathologic effects.

IL-17 Family: Receptors and Pathways

The IL-17 family shows a very special pattern of signaling. IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE are members of the IL-17 receptor family (30). The IL-17F coding gene is on the same chromosome as IL-17A (3). These receptors can be expressed by a wide variety of cells. Therefore, IL-17 is known for affecting various organs (31, 32). IL-17RA is mostly expressed in hematopoietic cells (33). IL-17B, IL-17C, and IL-17D are three cytokines in the IL-17 family that are usually produced by epithelial cells (31).

All of the IL-17R family members share a structural unit called the SEFIR domain (8, 34). The first event in the IL-17R signaling pathway is getting in contact with a signaling protein called Act1, which also has a SEFIR domain (8). This protein is well known for activating IL-17RA-dependent responses (8) but is also needed for the initiation of nearly all of the IL-17 signaling pathways that are known (35).

IL-17A signaling involves two cytokine receptors, IL-17RA and IL-17RC, which form a receptor complex together (36, 37). Further, Act1 acts as an enzyme and ubiquitinates TNF-receptor-associated factor 6 proteins, which activate the nuclear factor κB (NF-κB) cascade. During significant procedures, NF-κB increases the production of various pro-inflammatory molecules. This signaling pathway creates a negative feedback system against itself (8).

Act1 can also initiate MAPK and C/EBP signaling procedures (36). Moreover, this protein can moderate some of the inflammatory responses of IL-17 signaling by binding with the stem loop of selective mRNAs and stabilizing them (36).

IL-17A and IL-17F have different roles in the body, such as stimulating neutrophil proliferation, chemotactic attraction of immune cells (e.g., neutrophils and monocytes), mucus production, and stimulating the production of inflammatory cytokines (31). Inflammatory responses of IL-17A and IL-17F can be intensified by their synergic collaboration with cytokines like TNFα, IFNγ, and IL-1β (31).

In addition to antibacterial and antifungal features, IL-17 can have various roles in organs like the liver (38), kidneys (39), lungs, etc. IL-17 increases the recruitment of neutrophils at the site of injury by increasing the secretion of inflammatory substances.

IL-17E, also called IL-25, has a distinctive role

compared to other family members. While other family members assist neutrophilic responses, IL-25 affects the secretion of cytokines like IL-4, IL-5, and IL-13, which are related to type 2 immunity. This cytokine helps promote type 2 immunity (8).

IL-17A, IL-17F, and IL-17AF signal through the same receptor, but IL-17A creates a stronger signal compared to IL-17F (8). IL-23 is one of the important cytokines in stimulating immune responses derived from IL-17 signaling (32). IL-23 is a member of the IL-12 family, which activates Th17 cells as an important source of IL-17 secretion. This pathway has an important role in autoimmune diseases (8).

IL-4 and IFNγ have negative feedback on the population of Th17 cells and the IL-17 produced by them (40). Studies have shown that the IL-17/IL-17R signaling pathway can have positive or negative effects on cancer cells (41).

IL-17 in Lungs

IL-17 is secreted by Th17 cells at sites of cellular damage as a proinflammatory cytokine (42). Th17 cells are part of the CD4+ subset and secrete cytokines such as IL-23, IL-22, and IL-17 (43). This secretion depends on cytokines such as IL-6, IL-1β, and TGF-β. IL-17 has the ability to induce the secretion of specific cytokines: IL-6, IL-1β, and TNF-α. This whole cycle works against pathogenic factors in the lungs (42).

Epithelial cells and fibroblasts have important roles in the infection and inflammation of lung tissue by producing and secreting different chemokines and cytokines. These roles can be protective by cooperating with innate and adaptive immunity; however, they can worsen the condition by over-expressing inflammatory chemicals, especially IL-17 (44).

IL-17: Cure

Pneumonia can be caused by agents such as Mycoplasma pneumoniae (MP) (45), Streptococcus pneumoniae (13), Klebsiella pneumoniae (11), and other agents such as Staphylococcus aureus and Haemophilus influenzae.

Mycoplasma pneumoniae (MP) is a common cause of community-acquired pneumonia (CAP) and can cause infection in individuals of all ages, mostly children (45, 46, 42, 47). IL-17 is an important protective agent against MP infection (46). Serum levels of IL-17 in atopic children are meaningfully lower than in non-atopic children during the acute phase of MP infection, which can lead to more severe lung damage and a greater risk of asthma (46). So, measuring IL-17 serum levels in atopic children with MP pneumonia is very helpful in avoiding acute asthma attacks (46). IL-23-induced production of IL-17A and IL-17F acts as a defensive agent in infection with Mycoplasma pneumoniae (48).

A study has shown that in children with Mycoplasma pneumoniae pneumonia (MPP), the level of IL-17 in serum is significantly higher than in healthy children. Also, in these patients, the amount of IL-17 in bronchoalveolar lavage fluid (BALF) will noticeably increase. This study declares that patients with refractory MPP (RMPP) have noticeably larger amounts of IL-17 in their BALF than patients with general MPP (GMPP) (42).

Streptococcus pneumoniae is an agent causing airway diseases, especially through its cooperation with the influenza virus (49). This pathogen is the most common bacterial cause of pneumonia (50, 51).

The protective effect of IL-17 against Streptococcus pneumoniae colonization can be seen 14 days after the onset of this disease (49). IL-17 increases the rate of pathogen elimination in the nasopharynx (50). Th1 and Th17 cells are activated during Mycoplasma pneumoniae infection. Although their secreted cytokines are part of the immune system, they can lead to tissue damage (43). IL-17-deficient animals have shown more nasal colonization of Streptococcus pneumoniae. The changes in the nasal microbiome caused by this cytokine can enhance immune responses against these colonies (52). Influenza A virus will increase patients' susceptibility to Streptococcus pneumoniae superinfection. This virus disrupts the production of IL-17A (53).

Th17 cells react against the primary Streptococcus pneumoniae colonization and help to prevent further damage (49).

In pneumonia caused by Klebsiella pneumoniae, the expression of IL-17 will increase and help to remove the pathogen (11). Also, IL-23-mediated IL-17 secretion helps the immune system control K. pneumoniae infection (54). Among mice

infected by Klebsiella pneumoniae, those with IL-17RA deficiency demonstrate an increased mortality rate (55).

A study reported increased levels of IL-17 in mice with Pneumocystis pneumonia (PCP). This study suggested that IL-17 can have protective roles against PCP. As an underlying mechanism, an increase in the level of IL-17 was shown to reduce the amount of IL-10, which is well known for being an anti-inflammatory cytokine. Although the down-regulation of IL-10 will help inflammation, it can lead to lung tissue damage (56).

In epithelial cells, IL-17 participates in enhancing barrier cohesion, production of anti-pathogen factors, and protection of mucosal tissue (33).

Chemokines like IL-8 and CXCL5 are released from epithelial cells after stimulation by IL-17. These chemicals are important in host defense (57).

IL-17A and IL-17F play major roles in the recruitment of neutrophils. IL-17A can modify several actions of neutrophils, such as reactive oxygen species (ROS) generation and neutrophil extracellular trap (NET) release. Also, IL-17A is necessary for the IFN-γ signaling pathway to take place (58).

Influenza A virus can cause the production of miR-155, which further inhibits the defensive effects of the IL-23/IL-17 signaling axis by down-regulating the differentiation and functioning of Th-17 cells. This event will increase patients' susceptibility to secondary infection with Staphylococcus aureus (59). It is reported that the reduced amount of IL-17 can promote inflammation caused by Staphylococcus aureus (60).

In mice affected by the VAP form of Pseudomonas aeruginosa, the animals that were oxygenated by mechanical ventilation had lower concentrations of IL-17A and IL-17F compared to those mice without mechanical ventilation (16). This indicated that IL-17 plays a protective role during acute Pseudomonas aeruginosa infection in the lungs (61).

In smokers, IL-17 and GRO-α signaling pathways will diminish and lead to bacterial colonization (62). In **Table 1**, a list of IL-17 positive effects is provided for a better perspective.

IL-17: Corruption

IL-17 can also activate a strong inflammatory response, which may cause tissue damage (42).

The excessive secretion of IL-17 in the lungs may have a major role in the incidence of refractory Mycoplasma pneumoniae pneumonia symptoms (42).

In patients with intense CAP, the amount of IL-17 is reported to be increased (63). Approximately 30% of community-acquired pneumonia per year is due to Mycoplasma pneumoniae infection (64). Different studies indicate that IL-17 can contribute to the pathology of Mycoplasma pneumoniae infection, but the exact mechanism

Table 1. Positive effect of IL-17 on body parts other than lungs

Cytokine/signaling pathway	Tissue/organ/disease	Effect of cytokine
IL-17A	-	will increase the expression of chemokines such as CXCL1, CXCL2, and IL-8 (CXCL8), which can recruit immune cells such as neutrophils[8].
IL-17B	Intestine	Acts as a proinflammatory cytokine and increases the population of neutrophils in the area of the damage
	mucosal inflammation	acts as an anti-inflammatory cytokine and stop IL-25 signaling pathway[8]
IL-17C	intestine skin	Anti-microbial and defensive role
	nervous tissue	helps rebuild nervous tissue in damage caused by Herpes simplex virus[8]
IL-17E	-	Increased secretion during helminth infection[8]
IL-17F	-	protective agent against mucocutaneous candidiasis[8]
IL-17/IL-23 axis	-	Help ease the symptoms of fungal infection of the skin with Candida albicans[11]

is not known yet (65). The concentration of IL-17 and the number of Th17 cells in patients with refractory Mycoplasma pneumoniae pneumonia is higher than in patients with macrolide-responsive MP pneumonia and healthy individuals (66). Th-17 cells and the cytokines they secrete, such as IL-17, are associated with inflammatory allergic responses in patients with asthma (45, 67). IL-17 can have a major role in the development of asthma in children (46). IL-25 is reported to have associations with the pathology of asthma. IL-25 is required by chemosensory bronchial epithelial cells. These cells need IL-25 to recognize pathogen-associated antigens and promote asthma (8).

Mucosal-associated invariant T cells in bronchoalveolar lavage are hyper-inflammatory cells that will be activated in the respiratory mucosa and contribute to infection by producing IL-17 (63).

It is reported that the number of IL-17A receptors on nasopharyngeal epithelial cells is higher in mice infected with both Streptococcus pneumoniae and influenza at the same time. In the same study, it was shown that the number of colony-forming units of Streptococcus pneumoniae was noticeably lower in the lungs, blood, and nasopharyngeal epithelial cells of IL-17-deficient WT mice. The IL-17-deficient mice also had a lower mortality rate (49). IL-17C/IL17RE is another signaling pathway in this family. IL-17C is expressed by epithelial cells, and IL-17RE acts as a receptor. Studies have shown that during infection with Streptococcus pneumoniae, IL-17C/IL-17RE increases the recruitment of neutrophils in damaged lung tissue and elevates the amount of inflammation caused by these cells (68).

Treg and Th2 cells neutralize the effects of Th1 and Th17 cells after the patient has recovered from an inflammatory disease. This procedure takes place in order to suppress the destructive effects of the inflammatory cytokines (43).

In patients with acute lung injury (ALI) and acute respiratory distress syndrome (ARDS), the secretion of IL-17 is increased. This increased amount has connections with worsened tissue injury in the lungs and increased mortality (2).

Elevated amounts of IL-17 have been seen in diseases such as MERS and COVID-19 (2).

Increased amounts of IL-17 are associated with the development of chronic obstructive pulmonary disease (COPD). Inflammation and emphysema of the lung are two symptoms resulting from IL-17 signaling in animal models of COPD induced by cigarette smoke (69). Respiratory syncytial virus (RSV) is a pathogen associated with the fast development of COPD. It has been reported that in mice with E/LPS-injured lungs, the level of IL-17 and IL-23 will increase. In addition, exhaustion of IL-17 before the infection alleviates complications of the disease (70).

During inflammation, IL-33 propels the ST2+ILC2 cells to produce IL-17. Therefore, these cells exacerbate the inflammatory status (71).

IL-17 can intensify the effects of IL-13. A study shows that compared to mice exposed to intratracheal IL-13, those that were given both IL-13 and IL-17A had more severe inflammation, more secretion of the mucosa, and more IL-13-induced gene expression (72).

IL-17A-mediated signaling pathway in the lung will lead to increased oxidative stress by upregulating the activity of iNOS and downregulating the activity of Glutathione peroxidase (GPx) (73). This disparity between oxidant and anti-oxidant levels will lead to more severe neutrophil inflammation in the lungs. Based on this information, the use of antioxidants can be a therapeutic approach for this condition (73).

In lung inflammation, ROS molecules are overproduced and cause neutrophil cell death by activating NET synthesis. As a result, the cellular contents of neutrophils may be released into the surrounding tissue and cause damage (58).

In pneumonia caused by Pseudomonas aeruginosa, the expression of IL-17A will lead to the secretion of IL-17C from epithelial cells. As a result, IL-17C will intensify the gathering of neutrophils and inflammatory pulmonary responses (74). In addition, IL-17-mediated neutrophil recruitment and cytokine secretion can initiate inflammatory reactions in CF (75).

The density of IL-17B will increase noticeably during community-acquired pneumonia. IL-17B will stimulate gene expression and production of IL-8 in epithelial cells (76). IL-17B can affect bronchial epithelial cells directly (44). Lung fibroblasts do not respond to IL-17B stimulation despite expressing IL-17RB (44).

The concentration of IL-17A and IL-17F also

increases during community-acquired pneumonia and stimulates bronchial epithelial cells to secrete different cytokines (44).

The inflammation caused by adenoviral IL-1β can be avoided by deactivating IL-17RA (77).

Recruitment of large numbers of neutrophils due to IL-17 signaling can damage the lung tissue by inducing smooth muscle contraction (78).

In **Table 2**, a list of IL-17 negative feedbacks is provided for a better perspective.

Table 2. negative feedback of IL-17 on body parts other than the lungs

Cytokine/signaling pathway	Tissue/organ/disease	Effect of cytokine
IL-17	cornea	induce inflammation of the cornea in conditions such as fungal or viral keratitis. This cytokine worsens diseases related to dry eye[79]
	rheumatoid arthritis	The amount of IL-17 in the patients' circulation is considerably high. Also, polymorphism in IL-17 genes can increase susceptibility to this disease[80].
	psoriasis	IL-17 can contribute to the manifestation of psoriasis. This cytokine increases the multiplication of keratinocytes through the Act1 signaling pathway[8].
	skin	tumorigenesis[8]
	schizophrenia	Studies have shown that the level of serum IL-17 is higher in patients with first-episode schizophrenia[32].
	liver	In vitro, IL-17 prompts the primary hepatocytes to produce IL-6. Also, IL-17 and TNFα together induce neutrophil attraction in conditions such as acute Hepatitis. Cells that secrete this cytokine can contribute to diseases such as Acute liver failure (ALF) and chronic liver diseases (CLD) such as Autoimmune hepatitis, Primary Biliary Cirrhosis, and Primary Sclerosing Cholangitis[38].
	neuroinflammatory diseases	Patients with neuroinflammatory diseases have higher numbers of Th17 cells in their bloodstream than patients without this condition. Also, highly elevated levels of Th17 can be seen in cerebrospinal fluid during neuroinflammatory diseases[7].
IL-17RB pathway	-	Studies on mouse models have shown that the IL-17RB pathway helps preserve cancer cells[8].
IL-17B	intestine	The amount of IL-17B will increase significantly during intestine inflammation in rat[76].
	lupus erythematosus	Compared to the control group, IL-17B is more concentrated in patients with lupus erythematosus, and the concentration of this cytokine is higher in the active phase of the disease[76].
	pancreatic cancer rheumatoid arthritis	contributes to the pathology of these diseases[44]
IL-17C	kidney	IL-17C can contribute to renal tissue damage through IL-17RE. CD4+ T cells express the IL-17E receptor abundantly[81].
IL-17/IL-23 signaling pathway	psoriasis	may take part in the pathogenesis of interstitial pneumonia[82].

Therapeutic Approaches to Suppress IL-17

There are various therapeutic approaches designed to suppress IL-17.

Secukinumab is a drug prescribed for psoriasis, psoriatic arthritis, and ankylosing spondylitis (83). This drug is an IL-17A neutralizer. Ixeki-

zumab, a drug neutralizing IL-17, is prescribed for plaque psoriasis (6). Brodalumab also acts as an antagonist for the IL-17 receptor (6).

Conclusions

Briefly, IL-17 is a double-edged sword. This cytokine works as a pro-inflammatory cytokine. Inappropriate concentrations induce immune responses against the pathogen. However, the inflammatory responses induced by IL-17 will also destroy the tissue itself. IL-17 also has a dual effect on the lungs in infections caused by Mycoplasma pneumoniae, Streptococcus pneumoniae, and Pseudomonas aeruginosa. IL-17 takes part in these pathological infections, first as a defender and then as an attacker. IL-17 does its role by propelling other cells to produce different cytokines and through different signaling pathways. Knowing about these pathways is important because they can lead us to novel therapeutic approaches.

In previous research, the deficiency in the production of IL-17 or its receptor has been reported to result in milder forms of infection (42). These reports indicate the therapeutic properties of IL-17 antagonists. It is suggested that studying the impact of IL-17 and its cooperating cytokines, such as IL-23, can lead to the development of new therapies for pneumonia (54). However, it must be considered that the complete elimination of this cytokine will definitely cause severe problems for the immune system (2).

Conflict of interests

There is no conflict of interests.

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