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Role of Th17 Cell in Tubercle Bacillus Infection

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Abstract. Tuberculosis is mainly a kind of lung disease. Normal immune cell expression can inhibit proliferation of tubercle bacillus in the lungs, but this may also lead to chronic inflammation and pathological lesion. Th17 cell is a newly discovered CD4+ effector T cell subsets, whose differentiation and roles are influenced by various cytokines in the surrounding environment. Th17 cell plays an important role in resisting tubercle bacillus infection, but also it may cause pathological damage through the inflammatory response. Therefore, to balance two kinds of roles of Th17 cells in tubercle bacillus infection can effectively protect the body. This paper intends to do a summary on differentiation, regulation, and biological functions of Th17 cell.

1. Introduction
Tuberculosis (TB) as a major infectious disease widely spread worldwide, which seriously threat human health, about 8.5 million new patients are infected every year, of which 1.5 to 2 million die from this disease. According to the WHO report in 2010, one third of the world's people subclinical infect Tubercle Bacillus. The tuberculosis are mainly parasitic and multiply in host macrophages, so cell-mediated immune response becomes an important mechanism to control tuberculosis infection, and immune cells play an important role in immune response. T cell responses play an important role in resisting tubercle bacillus infection in protective immune responses. After host is infected with tubercle bacillus, CD4+ T cell produce a large number of IFN-γ and play an important protective role. In addition, CD4+ T cell can be differentiated into Th1, Th2, and Th17 and so on. The cytokines produced by Th1 cell promote the activation of Th1 cell and CD8T cell, activate macrophages and make them mature. Th2 cell secrete B lymphocyte stimulating factors to promote the production of antibodies, and suppress 1 type immune response. The recent research finds that Th17 cell are also linked with tuberculosis infection. Th17 cell as a subset of T cells, secrete cytokines including IL-17, IL-17F, IL-21 and IL-22. These cytokines mainly promote the production of defensins and recruit neutrophilic granulocyte and monocytes to inflammation site, and they play an important role in early host defense.

2. Induction and Differentiation of Th17 Cell
TH17 cell is CD4T cell subset that secretes IL-17 when studying autoimmune diseases. Under certain conditions, transforming growth factor-β (TGF-β) and IL-6 can induce the development and differentiation of Th17 cell, IL-1β plays an important role in the early differentiation of Th17 cell. While IFN-γ secreted by Th1 cell and IL-4 secreted by Th2 cell inhibits their activation. Unlike Th1 and Th2 cell, transcription factors for Th17 cells are mainly orphan nuclear receptors (ROR) RORγt and RORα6, RORγt and RORγ are receptors of the same subtype, which are significantly expressed by immune cells. TGF-β or IL-6 can induce the expression of RORγt and RORα, and promote the
differentiation of Th17 cell when the differentiation of Th1 and Th2 cells is blocked. While T cell that
RORα reduces expression selectively decreased the expression of IL-17 and IL-23R and reduces the
effects on EVE7.

3. Role of IL-17 and Th17 cell in Tuberculosis
When tubercle bacillus invades the lungs, dendritic cells (DCs) migrate to the lymph node. T cell that
produces IFN-α and IL-17 is activated in the lymph node, and migrate to lung tissue to exert an immune
effect. Although tubercle bacillus stimulates innate immune receptor and can cause an innate immune
response, the cytokines produced play an important role in obtaining cellular immunity

In order to investigate the role of IL-17 in protective immune responses in the early stage, infection
model of respiratory tract was used to investigate its effects on neutrophilic granulocyte recruitment
and tissue repair9. Recent research have shown that when bacteria parasitized in the cells infecting the
body, IL-17 can strengthen immunity, but the effect is not as obvious as when extracellular bacteria
invades. For example, after infection with Salmonella, bacteria in the liver and spleen of IL-17-
deficient mice multiply rapidly, and neutrophilic granulocyte cannot normally recruit. However, it is
unclear whether this mechanism affects the immunity directly10. The effects of IL-17 and Th17
cellchemotactic factor were studied by mouse models, and their function was influenced by the
infection stage and the infection amount. Low-dose tubercle bacillus are injected into the body, it did
not affect the organism's control pathogenic bacteria amplification in the absence of IL-17 and IL-2311.
When high doses of tubercle bacillus infect the respiratory system, mice which lack IL-17 cannot
control the multiplication of pathogens12. In the early stage of tubercle bacillus, especially when a
large number of tubercle bacillus invade the body, IL-17 is mainly secreted by γδT cell, the expression
of IL-17 mRNA is detected in the lung tissue one day after the injection of BCG into the respiratory
tract of mice, at this time γδ T cell also express TCR peptide chains of Vγ4 and Vγ613. When low-dose
tubercle bacillus invades the body, γδ T cells secrete IL-17, which is an antigen-dependent process.
First, dendritic cells secrete IL-23 under the action of tubercle bacillus and induce γδT cells to produce
IL-17, and then Th17 cell produces a large amount of IL-1714. The above conclusion shows that
γδT cells are the major immune cells produced by IL-17 during the early stage of tubercle bacillus
infection, however, the number of tubercle bacillus infection and the influence mechanism of invasion
route which γδT cell secretes IL-17, and how the subsequent immune cells and cytokines mediate IL-
17 and play a protective role, which need further research.

The effect that cytokine IL-22 impact on IL-17 and Th17 cells after tubercle bacillus infection, which has a certain influence. IL-22 mainly plays a role through IL-22 receptors expressed on
epithelial cell and hepatocytes, and promote tissue regenerate and protect tissues15. Liang SC and so on
found that TGF-β signal induce Th-17 secrete IL-17 and IL-17F, meanwhile secreting IL-22 under the
action of IL-6, it shows that the production of IL-22 is likely to induced by Th-17 cell differentiation
factor16. However, when Scriba TJ studied whether generation of IL-17 and IL-22 is induced tubercle
bacillus, he found no IL-17 protein in bronchoalveolar lavage fluid of TB patients, but found a large
amount of IL-22 protein, IL-17 is inhibited by IFN- produced by Thl cell in vitro, while the production
and effects of IL-22 and IL-17 are independent for each other, When one factor is lost, which is
replaced by another to protect the body3. Although there are a lot of reports that IL-17 and Th17 play
an important role in the immune response, how to improve the cellular immune response and the
mechanism of recruiting neutrophils in the formation of granulomatous tissue remains to be further
studied.

4. IFN-γ and TH17 Cell
When Matthew P. R. Berry and so on studying 393 transcripts of whole blood of TB patients, and they
obtain 86 transcripts that were different from other disease infections. Further research has found that
the expression of these transcripts is controlled by the IFN-induced gene profile17. TH1 cells which
secrete INF play an important role in controlling proliferation of tubercle bacillus, and it mainly play a
role by inducing macrophage activation mechanism and activating CD48+cytotoxic cells. Studies have
shown that when tubercle bacillus infects INF-deficient mice, it fails to activate T cell and neutrophils and causes granulomatous responses that impair the body\(^{19}\). It shows that IFN plays an important role in tubercle bacillus infection. After the tubercle bacillus infect dendritic cells, and induced secretion of INF and differentiation and proliferation of IL-17 cell, although these two types of cells can proliferate in the early stage of tubercle bacillus infection, and, when low-dose tubercle bacillus infect, there may be opposite regulation role between the two\(^{20}\). Andrea Cruz and so on use the INF INF-deficient mice model to explore the problem. The number of TH17 cells in INF-deficient mice was significantly increased after injecting BCG. In addition, further studies showed after adding exogenous INF, IL-12 secreted from bone dendritic cells increased while the amount of IL-23 decreased, and the cell activation ability that cell induce TH17 also reduced \(^{21}\). Teresa M. Wozniak and so on in order to illustrate the role of Th17 cell in the immune response during tubercle bacillus infection, the RAG-/- mice which infect tuberculosis are used to find in the absence of IL-23 and IL-12, proliferation of TH17 cell and TH1 cell are inhibited, and cannot produce immune protection. In the presence of IL-23 and IL-12, TH17 and TH1 cells were activated and induced significant immune protective power against tubercle bacillus infection. At the same time, when INF lack and the tubercle bacillus decrease, the survival time of Th17 cell obviously prolong, and strengthen inflammatory infiltration by increasing neutrophile granulocyte, which shows that TH17 cell can still produce immune protection against tubercle bacillus when INF is deficient. As mentioned above, it needs IL-12 when cell which secrete IFN play a role, IL-23 plays an important role in TH17 cell proliferation, the existence of INF may inhibit the activation of TH17 cell and the production of IL-17.

5. Influence of Treg Cell on TH-17 Cell

A kind of CD4+CD25+T cell subsets have been found in humans and mice, which have significant immunity suppression effects, and it can act on various target cells in different ways, Therefore, the body's immune response is finely regulated, it is called regulatory T cells (Treg cells), and includes an enhancement of Treg cell activation in the immune response mechanism against Tubercle Bacillus\(^{23}\). Marin and so on show that Treg cells are CD4^+CD25^hiFOXP3^+CD45RO^+CD127^-, with phenotypic analysis, although he demonstrated that Treg cells can be induced during tubercle bacillus infection, the role of Treg cell has not yet been clearly explained in the immune pathological mechanisms of tuberculosis. Both the latent infected person and apparent TB infected person, the consumption of Treg cells can make cells which produce INF-\(\gamma\) increases, and has no influence on Th7 cells, at the same time, neutrophile granulocyte which produce IL-10 does not impact on the above two kinds of cells. In summary, the above experimental results show that the Tregs cell inhibit the immune protection, of Th1 cells in the patients with dominant tuberculosis, it had no significant effect on Th17 cell. Shahin Shafian and so on obtains similar conclusions\(^{24}\), and proved that in tuberculosis patients, Treg cell can recognize the specific antigen of tubercle bacillus, meanwhile limiting the immune response. Even if there is a large number of Tregs cell in tuberculosis patients, the inflammatory response process may show the adaptive immune response with selective inhibition, it also shows that Tregs cells are highly inhibitory to cells which produce IFN-\(\gamma\), and have less inhibitory ability on cells which produce IL-17, so cells which produce IL-17 persist in inflammatory tissues for a long time, and cause inflammation response to be long-term or relapse. IL-17 once known as a pro-inflammatory factor\(^{25}\), because it plays an important role in inducing the production of cytokines and chemokines and chemotactic factor, it is beneficial to recruit immune cells including neutrophils, and reach the tubercle bacillus infection site to play a role, so researchers believe that it is involved in the early stages of the fight against tubercle bacillus infection. At present, the role of Tregs in the incubation period of tubercle bacillus and its relationship with other immune cells are not yet clear. More research is needed to illustrate this problem; it is used as a biomarker for preventing tubercle bacillus infection.

6. Influence of IL-23 on TH17 in Tubercle Bacillus Infection

IL-23 is an important factor IL-17 in the inflammatory response of TH17 cell. After infect tubercle bacillus, intensity of inflammatory response which lack IL-23 weaken, with the further development
of the disease, inflammatory response gradually strengthened, the deposition extent of fibrin decreases, this kind of phenomenon is similar in wild mice and mouse lack IL-23p19 gene. Although some experiment proved that after infected tubercle bacillus, IL-23 and IL-17 plays an important role in recruiting neutrophile granulocyte and maintaining body balance, but mice which lack IL-23 did not change the number of neutrophile granulocyte. Thus, il-23 and il-17 play a complex role in mediated inflammatory responses of mycobacteria. IL-23 and IL-17 induced by tubercle bacillus infection play a crucial role in regulating the relationship between Th1 cell and Th17 cell.

Th1 cell and Th17 cell ARE induced by the same dynamics In the early stages of tubercle bacillus infection, but the number of Th1 cell is 5 to 10 times as many as Th17 cell. Th17 cell is quickly suppressed by Th1 cell in the BCG infection model, and the comparison between BCG and tubercle bacillus is likely to involve the differentiation induction of IL-12 and IL-23. When BCG infects dendritic cells, IFN-γ significantly increased the production of IL-12p70, while reducing the production of IL-23. On the contrary, IL-17 limits production of IL-12 when IL-23 is abundant. These conclusions show that the cross-regulation among IL-12, IL-23 and INF-γ, IL-17 plays an important role in the inflammatory response caused by tubercle bacillus.

7. Discussion
Tuberculosis is still one of the diseases that cause death by a single pathogen infection, in order to get a better vaccine; we need to further clarify the immune response mechanism after tubercle bacillus infects the body. Although IL-23/IL-17 did not play a role in the proliferation process of controlling tubercle bacillus in the early stage, however, recent data show that this response axis plays a crucial role in the vaccine-induced protective response. This effect of recruiting immune cells to infected lesions is mainly mediated by chemotactic factor gradients, but due to over-recruitment of inflammatory cells and phenotypic changes, which cause the production of large amounts of IL-23 and IL-17, and result in immune pathology damage. Therefore, the delicate balance of the response between Th1 and Th17 cell in the body plays a very important role against tubercle bacillus infection. In order to find an effective way to prevent tubercle bacillus infection, we need many scientific workers to further clarify the protective and pathological mechanism of Th7 cell, and play the immune effect with minimal side effects.

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