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IL33-/ST2 Axis as a Well-Known Endogenous Defense Against Tuberculosis

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ABSTRACT

Tuberculosis (TB) infection is caused by an intracellular bacterium, Mycobacterium tuberculosis (Mtb). The disease is among the most important infectious diseases, which has dedicated most cases of morbidity and mortality to itself worldwide. The global report of World Health Organization (WHO) in 2019 shows that from 10.7 million infected people in 2018, 1.6 million died. Although the BCG vaccine has been used for about a hundred years, it is only effective in children, but is not able to produce a protective and reliable immunity against adult pulmonary TB. Hence, using an alternative vaccine with high more efficacy than BCG seems to be urgent. The IL-33/ST2 axis forms of IL-33 and ST2, and both of them are the members of IL-1 family. IL-33 is secreted as an alarm in response to cell damages and cellular stress, and ST2 causes stimulation of MyD88/NF-κB signaling pathway, which is needed for the proper response of infected cells to Mtb and other intracellular pathogens. In Th2 cells, NF-κB enters into the nucleus, and acts as a transcription factor. Finally, cytokines such as IL-4, IL-5, and IL-10 are produced which are effective in the prevention of tissue damage. Based on various information, it is recommended that IL-33 can be as a novel therapeutic candidate in post-exposure cases of TB disease.

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Introduction

Nowadays, notable progressions have been done in the diagnosis and treatment of tuberculosis (TB) infection. However, TB remains one of the major causes of morbidity and mortality worldwide. According to WHO report in 2019, from 10.7 million involved people with this microorganism, 1.6 million died in 2018 (1,2).

In addition, it is estimated that one-fourth of people in all of the words affected to latent form of TB that with time, 5-10% of them afflicted to reactivation of TB (3).

As soon as the entrance into the lung, Mycobacterium tuberculosis (Mtb) is surrounded by alveolar macrophages, and phagocytized through interaction with specific receptors. Depend on host epigenetic conditions, there are three categories of TB infections containing:1) active TB infection (ATBI) in health and immunocompromised individuals;2) aborted infection in healthy individuals, due to proper activity of classic (M1) macrophages; 3) Latent tuberculosis infection (LTBI), due to remaining in alternative (M2) macrophages (4,5).

Based on current documents, immune system changes play a pivotal role in the determination of Mtb pathogenesis, as well as in the formation of different outcomes in Mtb infection (6,7).

The IL-33/ST2 axis is one of the immune

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system components, which its role has been demonstrated in tuberculosis pathogenesis, cancer, hypersensitivity diseases, myocardial infraction, inflammatory bowel disease (IBD), as well viral diseases such as HIV and HBV (8,9).

Interleukin 33 (IL-33) is one of the classic members of the family of IL-1, which is secreted as an alarm in response to cell damages and cellular stress in non-hematopoietic cells such as endothelial, fibroblast, adipocyte cells, as well as, lung and intestinal epithelial cells, and hematopoietic cells such as dendritic cells (DCs) and macrophges (10,11).

This interleukin may have cleaved by chymase, tryptase, elastase, neutrophil serine protease. Evidence suggests that the cleaved form of IL-33 has 10-30 fold more than the complete form (12).

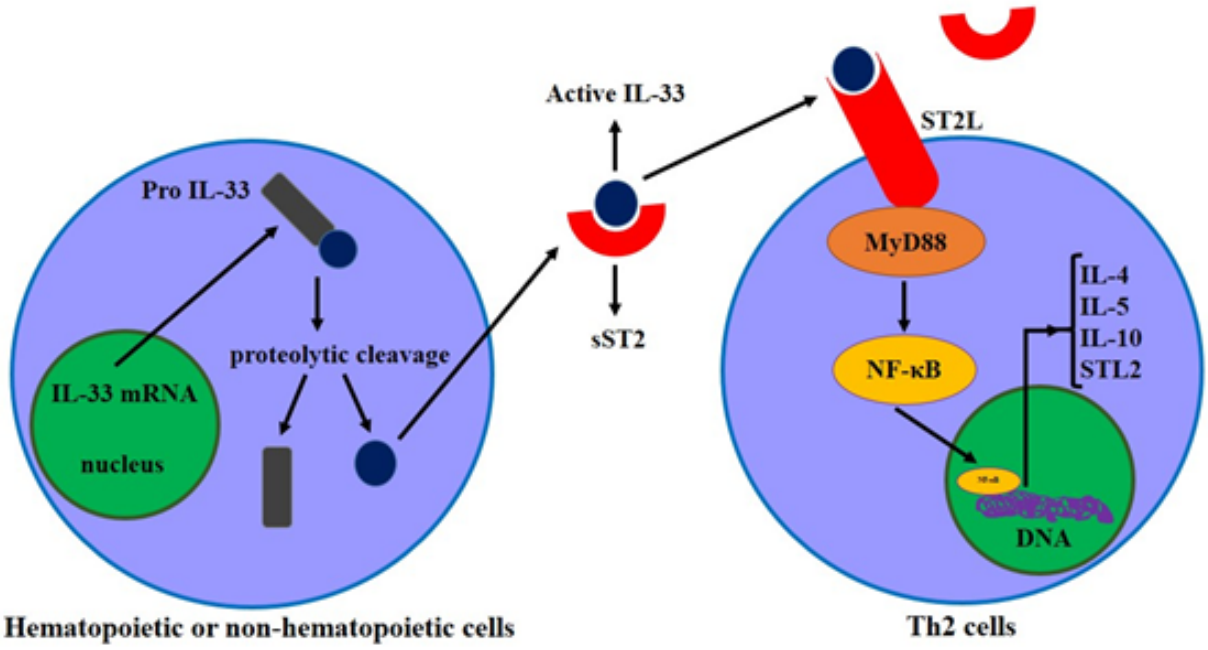
The function and specific receptor of IL-33 were unknown until recent; but recently it has been determined that IL-33 is a pleiotropic cytokine. The immune-modulator function of cytokine is mediated via its specific receptor, Serum stimulation-2 (ST2), which is expressed on the surface of many immune cells including NK cells, CTLs, DCs, basophils, eosinophils, T regulatory (T reg) cells, Th1, Th2, iNKT cells, mast cells, B cells, neutrophils and macrophages (9, 13).

ST2 (or tumorigenicity 2) first was introduced by Tominaga et al. in 1989. ST2 is one of the members of family of IL-1 which is expressed in four forms such as ST2L (a membrane receptor), sST2 (a soluble factor as decoying the ST2L receptor), ST2V (a variant of ST2), and ST2LV (a variant of ST2). Of these, ST2 and sST2 have more studied, so that ST2 causes stimulation of MyD88/NF-κB signaling pathway, but sST2 causes down-regulating of it (9,14, 15).

ST2 is expressed on the surface of many cells, and regulates derivative responses from Th2, T reg cells, and IgE production. (8,9,16).

The sST2 compared to ST2 has a unique region containing 9 amino acids which lead to increase proinflammatory cytokines such as IL-1β, TNF-α in epithelial and monocyte cells (8, 17).

Overall, IL-33/ST2 axis through the affecting on cellular signaling pathways causes to form various massages in immune system cell lines. Among these massages can be mentioned to increase in T reg cells number, stimulate the production of cytokines such as IL-4, IL-5, and IL-10, as well as suppression of IFN-γ and IL-2 in Th2 cells, boost production of TGF-β and IL-4 in Th9 cells, enhance the production of IL-12 in CTLs, production of IL-13, IL-5, and IgM in B1 cells, and also increased production of IL-17 and IFN-γ in NK and iNKT cells (9, 18, 19) (Figure 1).



Figtre 1. Interaction between secreted IL-33 and Th2 cell surface. Pro IL-33 is produced by hematopoietic and non-hmatopoietic cells. This protein is cleaved and active IL-33 secreted from the cells, and carried by sST2 toward ST2L on the surface of Th2 cells. Following activation of MyD88 and then NF-κB, this transcription factor enters into the nucleus and stimulates the production of cytokines such as IL-4, IL-5, and IL-10

Based on current information, the footprint of IL-33/ST2 axis has been recognized in many disorders, and also by the effect on a wide spectrum of immune system cells, this axis is able to change the consequence, and is even used as a diagnostic or therapeutic biomarker (8, 9,18-20).

Given that the controversial results, our knowledge about the role of IL-33/ST2 axis in TB pathogenesis is limited. Therefore, the main goal of this study was evaluation of IL-33/ST2 role in the final outcomes of tuberculosis.

Methods

In the present study, we collected all documents about expressive changes of IL-33/ST2 axis, serum IL-33 and ST2 level in different forms of TB disease, and also effects of enhancing or knockout of this axis from Scopus, PubMed, and Web of Science databases.

It is notable that, the search was done by use of keywords such as Interleukin-33 AND Tuberculosis, ST2 AND Tuberculosis, Interleukin-33 AND TB vaccine, Interleukin-33 AND Biomarker, Interleukin-33 AND Diagnosis, Interleukin-33 AND Pleural effusion, ST2 AND Pleural effusion, Interleukin-33 AND Lung infection, and ST2 AND Lung infection; all meta-analysis and review articles were deleted from our study. Following the collection of all information, IL-33/ST2 axis evaluated in terms of different aspects including changes in serum levels during different forms of TB, and its ability as a therapeutic and diagnostic biomarker.

Result

Although IFN-γ and Th1 cell responses are known as the main arm of the immune system, it is notable that the severe and non-controlled responses of Th1 cells and classic macrophages (M1 macrophages) may lead to type IV hypersensitivity. Mostly, severe responses cause tissue damages and caseous necrosis of granuloma, and consequently, Mtb gets out of the TB cavity and causes military TB (21).

Therefore, excessive responses of Th1 should be modulated by TH2 cells, alternative macrophages (M2 macrophages), and T reg cells, and finally, a proper balance created between Th1 and Th2 responses (22, 23). However, many studies have shown that the increased count of T reg and Th2 cells in active and disseminated TB patients (24, 25). Overall, access to a full immunity against Mtb is very complex, and is not dependent on Th1 and IFN-γ responses. In addition, Th2 and T reg cells through the equilibration of Th1 reactions, and also the prevention of hypersensitivity reactions have pivotal role during Mtb infection (26).

According to what was mentioned on the one hand, and available evidence in the other hand, it is demonstrated that ST2 receptor has a great role in protection in support of Th2 cells response, and induction of T reg cells. Hence, as a new approach, this receptor is accounted for prediction and protection of final disorders of TB infection; if this has received less attention (27).

Administration and knockout effects of IL-33/ST2 axis

Wieland et al. designed a project about the effects of IL-33/ST2 axis in infected mouse to Mtb. They contaminated two groups of mice, wild type (WT) and ST2 KO (ST2 knockout) by 150 colony-forming unit (CFU) of Mtb. Assessments showed that clinical manifestations and production of IFN-γ have no significant difference in both groups, and they claimed that ST2 has a very limited role during Mtb infection (28).

Although in previous studies it had been demonstrated that depletion of ST2-secretory cells induce the resistance against Leishmania major, but Wieland's study disproved this hypothesis in about Mtb infection (29).

Pineros et al. observed that in infected mice to Mtb, following stimulation of Th2 cells with allergens, infection is controlled more appropriately. They infected both BALB/c and ST2 KO groups with Mtb, and then exposed them to ovalbumin (OVA). They showed that allergens caused increase activity in ST2-secretory Th2 cells, as well as significantly less CFU than other groups. In addition, due to higher levels of inflammatory cytokines in this group, they recommended that IL-33 can be as a novel therapeutic candidate in infection with Mtb (30).

Diagnostic biomarker

Toll-like receptor (TLRs) as one of the most important components of the pattern the recognition receptor (PRR) family has a pivotal role against Mtb. Following the recognition of Mtb surface antigens by TLRs in the surface of host cell, an adaptor protein named MyD88, stimulated by TIR (Toll/Interleukin-1 receptor). In the next step, MyD88 in turn activates NF-κB signaling pathway, which leads to induction of the production of IFN-γ and other pro-inflammatory cytokines (31-33). Nevertheless, tuberculous bacilli are a successful pathogen, and through calling and stimulation of negative regulators such as ST2, single immunoglobulin IL-1R related molecule (SIGIRR), Toll-interacting protein (TOLLIP), suppression of cytokine signaling (SOCS), IL-1 receptor associated kinase (IRAK). In addition, this pathogen by containment of NF-κB signaling pathway causes to suppress of immune system response, and con-

sequently freely replication, which leads to military TB (34, 35).

One of the main side effects of pulmonary TB is tuberculous pleural effusion (TPE), which is observed in 30% of extrapulmonary tuberculosis cases (36). In order to proper treatment, TPE should be diagnosed from other pleural effusions. Considering slow growth of Mtb and low sensitivity of the culture on the one hand, and invasive sampling on the other hand, diagnosis of TPE is encountered with many limitations (37).

So scientists are looking for alternative cultivation methods. In this regard, tracking of IL-33 is one the best candidates, which has attracted a lot of attention (38). Based on scientific documentation, during the IFN-γ and TNF-α response, significant amounts of IL-33 secreted in pleural fluid, which in turn improves Th1 cells activity, and also in the presence of ST2L supports production and development of Th2 responses (39, 40).

So far, many studies have been done about the evaluation of interleukin levels in TPE patients, which seems IL-33 is a safe biomarker for differentiation of TPE from other pleural effusions (Table 1).

Table 1. TPE versus other pleural effusions.

Location	Cut-off (pg.ml)	Significant in TB	Test	Ref
South Korea	10	Yes	ELISA	(39)
China	68.3	Yes	ELISA	(41)
China	19.31	Yes	ELISA	(42)
South Korea	26	Yes	ELISA	(38, 39)
Egypt	22.5	Yes	ELISA	(38)

Unlike IL-33, the relevance of ST2 and severity of TB disease do not have certain evidence and further studies are needed (Table 2). Also, based on our studies, IL-33 serum level in active TB patients significantly is more compared to healthy individuals; although this subject did not true about the sST2.

Table 2. ST2 in TB patients vs healthy group.

Location	Cut-off	Significant in TB	Test	Ref
Japan	1.28 ng.ml	No	RT-PCR	(43)
Nether-lands	261 pg.ml	Yes	RT-PCR	(44)
South Korea	328 pg.ml	No	ELISA	(39)
Japan	2700 pg.ml	Yes	ELISA	(27)

3.3. Treatment and vaccination

One of the main concerns about the TB is the lack of an effective vaccines for the prevention of pulmonary tuberculosis in adults. In recent, the vaccine is only available vaccine against TB. The vaccine is very effective in the prevention of tuberculous meningitis and also military TB in children, but does not produce a protective and reliable immunity against adult pulmonary TB, reactivation of latent TB, and also in HIV positive patients (5,45).

One of the main limitations of the BCG vaccine is the inability to the induction of T memory cells and thus long-term immunity (5, 45, 46). Vaccine and its adjuvants enhance the activity of B cells and the production of antibodies, while effective immunity against TB infection is related to CMI (47, 48). Appropriate adjuvants via the effect on antigen presenting cells (APCs) stimulate CTLs and Th1 cells, and finally induce a stronger response against TB infection (49, 50). In this regard, IL-33/ST2 axis plays an important role. Nowadays it is known that this axis effect on both Th1 and Th2 cell groups, and therefore new vaccine candidates have produced based on the proposed axis. For example, blocking of ST2 by use of monoclonal antibody IgG-ST2, leads to a decline of created allergic reactions in upper respiratory tracts due to excessive activity of Th2 cells (51, 52). In recent, many of therapeutic agents such as sST2, IL-33 and ST2 inhibitors for the treatment of gastrointestinal inflammation, Graft versus host disease (GVHD), cardiovascular disorders, asthma, and chronic obstructive pulmonary disease (COPD) are in clinical trial I and II phases (9). Currently, anti-tuberculosis vaccine candidates of IL-33/ST2 axis, are more designed based on post-exposure vaccines. The root of utilizing of IL-33/ST2 vaccine is the presence of strong adjuvants such as CAF01, which are able to simulate of IL-33/ST2 signaling pathway (5, 34, 53-55). Available information show that, subsequent IL-33/ST2 signaling pathway, activated MyD88 adaptor can stimulate and enhance Th1/Th2 response. As a result, high level of IFN-γ is produced, which in turn causes activation of M1 macrophages and finally intracellular lysis of Mtb (34, 55). According to review of literatures, so far two types of vaccines have been produced from this generation (53, 56). Desel et al. designed a study based on central role of MyD88 in immunization against TB infection by subunit vaccines. They immunized different groups of MyD88-/- and Mincle-/-C57BL/6 mice against TB, by use of H1 (Ag85B-ESAT6) subunit vaccine, along with trehalose-6,6-dibehenate (TDB). In their research, they demonstrated that following injection of TDB adjuvant, expression level of IL1A and IL1B genes increase in mice. Therefore, stronger immune responses of Th1 and Th17 cells was observed in mice which had higher level of IL-1 family (IL-33

and ST2) genes (53).

According to Villarreal et al. studies, it is found that the mice which were immunized with IL-33 in addition to DNA vaccine encoding Ag85B, had higher levels of IFN-γ and TNF-α than the group vaccinated with Ag85B alone (52).

Based on what was mentioned, it is recommended that immunization with anti-tuberculosis vaccines along with supportive adjuvants of IL-33/ST2 (MyD88-dependent) signaling pathway can be accounted as a novel approach for enhancing of protective effects of post-exposure vaccines.

Discussion

Tuberculosis has one of the great public health concern in recently decades which in turn, it has more challenge such as the emergence of drug-resistant TB strains, coinfection with HIV, as well as the presence of a quarter of the world is contaminated with LTBI which 5-15 present of these were develop to active TB (57).

In relation to reactivation TB it is suggested significant documents about evaluation of T regulatory and Th2 cells count and activities in blood samples during active TB compare than LTBI phase (58). It has been concluded that immune-suppuration was occurred following support of Th2/Treg activities in reactive and primary active TB cases (58-59).

Although Th1 immunity response is crucial for elimination and clearance of Mtb within macrophages; But type 1 immunity can be cause of tissue damage and destructive if not restricted (60).

Usually, immune-system has various strategies to reduce exaggerated type I immunity response such as development and support of Th2/Treg cells (61). There is evidence which destructive epithelial cells in granuloma can produce IL-33 which could be impressed the Treg/Th2 cell activities using ST2L receptor (41,56).

The IL-33/ST2L signaling has various immune-modulatory effects that depend on immune cell lines, microenvironment stimulation signals, and epigenetic events which may result of NF_kB activation (inflammatory response) to MAPKs signaling pathway (P38 stimulation and Th2/Treg activation) (Figure 2) (13,18).

Beside of negative opinion in association with activity of Treg/Th2 cells in TB for it immune-suppuration function (58); there is numerous evidence which supported from efficient roles of Th2 cells during TB infections (62,63).

Treg/Th2 activities can be useful for TB using various function such as 1) reduction of tissue damage,2) reduction of exaggerative Th1 response,3) enhance and support of antioxidant capacity,4) development of humoral immunity for example production of antibody and making efficient antigen presenting cells (APCs), and 5) support of innate immunity response (61-65).

The IL-33 is one of the important immune-modulatory cytokines which can produce in numerous cell lines of hematopoietic and non-hematopoietic in results of infection and cell damage (9).

There are numerous studies which are relied on efficacy of IL-33 level for diagnosis and monitoring of pulmonary complication particularly tuberculosis (39-42).

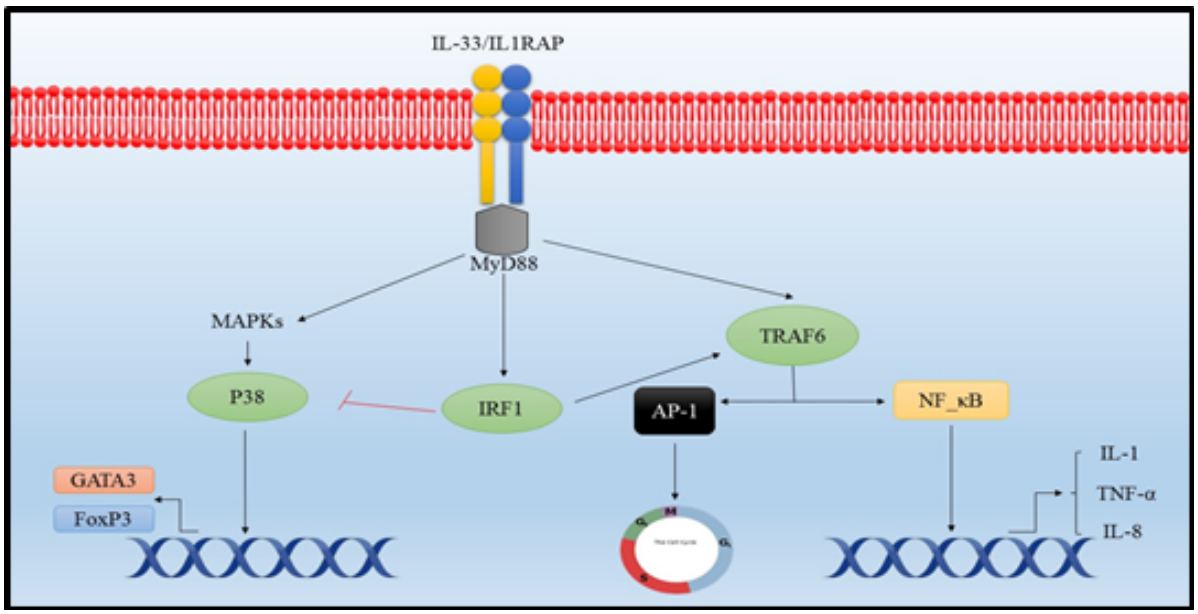


Figure 2. Immune-modulatory functions which occurred following IL-33/ST2L axis signaling pathway in TB infection; the MyD88 mediator is stimulated by IL-33/IL1RAP which induce MAPKs as well as NF_κB signaling pathways; the outcomes of these changes are influenced CD4+ T Cells differentiation, cell survival and pro-inflammatory response

It seems that IL-33 is appropriate potential biomarker for monitoring of tuberculosis during LTBI phase and treatment cases (40,42).

In the other hand, IL33/ST2L has immune-modulatory effects which is support Th2 response as well as induction of inflammatory process by triggering NF_κB signaling pathway (8-9).

In healthy condition, the type I immunity response ownregulated by Th2 activities after clearance of infectious agents and the balance between Th1 and Th2 was essential for appropriate function and hemostasis (66).

According to review of the literatures, IL-33/ST2L axis has important role in TB infection with switching between Th1 and Th2 response (57).

Moreover, due to immune-modulatory effects of this axis, the molecular targeting of the IL-33/ST2L axis can novel approach in development of immune-therapy of tuberculosis (13).

Conclusion

According to review of the literatures, IL-33 as one of the important cell-damage response can be produced by epithelial cells in results of tissue destruction which caused by Th1 response in active-TB; the ST2L is specific receptor of IL-33 which produce by immune-cells particularly Th2 cells. The IL-33/ST2L axis has immune-modulatory effects by impressed various signaling network which used to making balance between Th1 and Th2 responses and can be useful in development of novel approach in diagnosis and treatment of TB.

Conflicts of interest

The authors declare no conflicts of interest.

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