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Review

Study of the Notch-Aromatic Hydrocarbon Receptor-Interleukin-22 Signaling Pathway and the Pathogenesis of Immune Thrombocytopenia

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Abstract

Objectives: Immune thrombocytopenia (ITP) is an acquired autoimmune bleeding disease characterized by thrombocytopenia. This review will examine the Notch-aromatic hydrocarbon receptor (AhR)-interleukin-22 (IL-22) signaling pathway regulatory mechanisms in ITP to generate ideas for the pathogenesis and etiological investigation of the disease. **Mechanism**: Studies had shown that an abnormal imbalance of immune cells and immune factors is associated with ITP pathogenesis. The Notch-AhR-IL-22 signaling pathway disrupts the immune microenvironment *in vivo*, which contributes to the pathogenesis of ITP. **Findings in Brief**: Several studies have suggested that the pathogenesis of ITP may be mediated by multiple pathways, such as Notch signaling that induces AhR to increase direct secretion of IL-22 from $CD4^+$T cells or the Notch-AhR pathway that induces differentiation of $CD4^+$T cells into Th22 cells to enhance IL-22 expression. However, the precise pathogenic mechanisms are still unknown. **Conclusions**: ITP pathogenesis is complex, the Notch-AhR-IL-22 signaling pathway may be involved in the pathogenesis of ITP, and further research into the relationship between ITP and this signaling pathway is needed.

Keywords: immune thrombocytopenia; Notch; AhR; IL-22; pathogenesis

1. Introduction

Immune thrombocytopenia is an autoimmune disease characterized by a platelet count below $<100 \times 10^9$/L [1]. According to foreign research, the incidence of immune thrombocytopenia (ITP) in adults ranges from 1.6 to 3.9/per 100,000, with a prevalence of about 1/10,000 [2]. Uncertainty surrounds the etiology of ITP, which is closely linked to immune intolerance brought on by an immune cell and immune factor imbalance in addition to autoantibody factors [3]. By controlling the differentiation and homeostasis of immune cells and immune factors, it has been shown that the Notch-aromatic hydrocarbon receptor (AhR)-interleukin-22 (IL-22) signaling pathway can be involved in the regulation of various inflammatory responses and immune diseases, such as hepatitis B [4], gastric cancer [5], and lung adenocarcinoma [6]. Recently, it has been proposed that Notch signaling may help ITP develop by increasing the production of IL-22 in $CD4^+$T cells through AhR [7]. In this paper, we review the mechanisms of the Notch-AhR-IL-22 signaling pathway to set the groundwork for understanding the pathogenesis of the disease and to provide novel insights into ITP therapy.

2. Pathogenesis of Immune Thrombocytopenia

ITP is an autoimmune condition with a complicated etiology, and anti-platelet autoantibodies may contribute to excessive platelet destruction by the mononuclear macrophage system [8]. The pathogenesis of ITP is related to the overproliferation of helper T cell (Th) subpopulations such as Th1, Th2, Th17, Th22, and regulatory T cells (Treg), regulatory B cells (Breg), bone marrow-derived suppressor cells and other immunosuppressive cells decreased, and dysfunction of dendritic cells and natural killer cells [9–11], where abnormal B and T cells are the main features of the disease.

Naive $CD4^+$T cells are stimulated to differentiate into Th1 cells by IL-12 and gamma interferon (IFN-γ), and Th1 cells produce cytokines like IFN-γ, tumor necrosis factor-α (TNF-α), IL-2, and IL-22 that encourage B cell differentiation and proliferation. Th2 cells are induced by IL-4 and differentiated from naive $CD4^+$T cells, secreting cytokines IL-4, IL-6, and IL-10 that can synergistically control B cells with Th1 cells [12]. Sun *et al.* [13] discovered increased serum levels of Th1 cells and associated cytokines and decreased levels of Th2 cells and associated cytokines in ITP patients, indicating that an imbalance in the ratio of Th1/Th2 cells may exist be crucial in the pathogenesis of ITP. Activation of AhR can greatly promote the differentiation of $CD4^+$T cells into the Th22 cell population, a subpopulation of $CD4^+$T cells that mainly secrete cytokines such as IL-22, IL-13, IL-26, and TNF-α. In addition to cooperating with Th17 and Th1 cells in ITP, Th22 cells can also contribute to the pathophysiology of ITP by secreting IL-22 [14]. The findings from Jernas *et al.* [15] showed that elevated plasma IL-22 levels in children with

ITP are associated with Th22 and Th1 cells, suggesting that Th22 cells and IL-22 may play a key role in the pathogenesis of ITP in children. Th17 cells are a subset of pro-inflammatory lymphocytes differentiated by $CD4^+$T cells under the combined action of transforming growth factor-β (TGF-β) and IL-6, which work together to mediate inflammatory responses and autoimmune diseases by secreting IL-17, IL-21, IL-22, and other cytokines, with IL-17 serving as a marker for pro-inflammatory factors [16]. An imbalance in the expression of Th17 cells may work in concert with Th22 and Th1 cells to mediate the pathogenesis of ITP, according to a research by Zhan *et al*. [17] who discovered a significant increase in serum Th17, Th1, and Th22 cells in ITP patients and a positive correlation between Th17 and Th1 and Th22 cells.

Treg is a subpopulation of T cells that specifically exerts immunosuppressive effects and is distinguished by high levels of CD25 and the forkhead/winged helix transcription factor (Foxp3) on $CD4^+$T cells [18]. Treg cells exert immunosuppressive effects through the secretion of IL-10, TGF-β, and IL-35, and they can also inhibit T cell activity by expressing cytotoxic T lymphocyte antigens on their surface [19]. Treg and Th17 cells are functionally regulated by one another, and Zhou *et al*. [20] found that in the peripheral blood of ITP patients, the levels of Treg cells and TGF-β, which play an inhibitory role, were significantly decreased, while the levels of Th17 cells and IL-17, which play a pro-inflammatory role, were significantly increased. This finding suggests that the imbalance of Th17/Treg cells was one of the causes of ITP. Numerous studies have demonstrated that immune dysregulation in ITP patients can be caused by a reduction in the amount of Treg cells, a reduction in suppressive activity, or an imbalance between Th17 and Treg cells [8,21].

B cell activating factor (BAFF) abnormalities are currently thought to be the primary humoral immune mechanism in the pathogenesis of ITP. BAFF regulates T cell activation and maturation as well as B cell differentiation, maturation, and apoptosis [22]. In addition, Toll-like receptor7 (TLR7) may be another pathogenic mechanism of ITP because it can stimulate dendritic cells to generate large amounts of BAFF and increase the production of circulating anti-platelet antibodies [23]. Breg cells have negative regulatory effects, primarily through the production of TGF-β and IL-10 to play an immunomodulatory role, and ITP patients have fewer serum Breg cells, which externally manifests as decreased IL-10 and TGF-β, which can inhibit monocyte TNF-α expression and induce Treg cell differentiation and diminish $CD4^+$T cell function [19,24]. Breg cells may play a role in the impaired immune cell suppression experienced by ITP patients, according to research by Zhu *et al*. [10] that found significantly lower levels of Breg cells, IL-10, and TGF-β in patients with ITP. In conclusion, abnormalities like a Th1/Th2 imbalance, an increased ratio of Th1, Th17, and Th22 in T-cell subsets, a decrease in Treg cell numbers, an imbalance between Th17/Treg cells, higher BAFF, and a decrease in Breg cell numbers are linked to the pathogenesis of ITP.

3. Notch Signaling System Components and the Function of Immunity Regulation

The Notch signaling pathway is an intercellular signaling pathway with great evolutionary conservation that primarily regulates cell proliferation, differentiation, migration, and apoptosis. It also plays an important role in maintaining tissue homeostasis and the stability of the internal environment [25]. Notch signaling in the mammalian immune system can regulate various cells to direct early T and B cell lineage development, control the differentiation of hematopoietic stem cells, and control the maturation of T cells and their subpopulations [26,27]. Four Notch receptors (Notch-1, Notch-2, Notch-3, Notch-4) and five ligands, three Delta-like ligands (*DLL-1, DLL-3, DLL-4*), and two *Jagged* family ligands (*Jagged-1, Jagged-2*) have been identified [28], where the ligand binds to the receptor, activating Notch signaling, which regulates the expression of related genes in adjacent cells [29]. An increasing quantity of research indicates that activating $CD4^+$T cells' Notch receptors and ligands can cause $CD4^+$T cells to differentiate into various Th-cell subsets that secrete a range of inflammatory factors and cause a variety of immune disorders [25,30]. It has been suggested that Notch signaling promotes Th1 and Th2 cell differentiation, with greater expression of the Notch ligand *DLL-1* causing Antigen Presenting Cells (APCs) to differentiate toward Th1 cells, whereas increased expression of *Jagged-1* causes APCs to differentiate toward Th2 cells [31]. Notch signaling regulates the differentiation of Th17 cells in addition to its effects on Th1 and Th2 cells. Unintervened ITP patients had an imbalance of Th17/Treg cells that leaned greater toward Th17 cells, according to Yu *et al*. [32], when Notch signaling activity was blocked, Th17 cell and IL-17 expression decreased along with a decrease in the Th17/Treg cells ratio, indicating that Notch signaling is necessary for maintaining Th17/Treg cells homeostasis and that it can be used to restore it. Another research discovered that by controlling the expression of FoxP3, the *DLL-1* ligand of Notch signaling induces the differentiation of $CD4^+$T cells into Treg cells [33]. Many investigations have shown that Notch signaling might influence the production of immune factors and the differentiation of different immune cells, causing an imbalance that may contribute to the onset of various autoimmune illnesses. For example, Ma *et al*. [34] observed increased expression of Notch-1, Notch-3, and the Notch ligand *DLL-1* in blood samples from ITP patients, while Notch-2 expression was comparatively lowered. Similar findings were made by Wang *et al*. [35] who reported that patients with acute ITP had significantly increased Notch-1 and Notch-3 expression. These findings suggest that Notch signaling can be widely expressed on $CD4^+$T cell surfaces and can

regulate the immune function and differentiation of different immune cells like Th1, Th2, Th17, and Treg, which can contribute to the pathogenesis of ITP by upsetting immune cells and immune factor homeostasis.

4. Immunomodulatory Effects of AhR

AhR is a ligand-dependent transcriptional protein that forms protein complexes with chaperone proteins to keep its cytoplasmic location [36]. When AhR binds to ligands, it moves from the cytoplasm to the nucleus where it forms a heterodimer with the aromatic hydrocarbon receptor nuclear transporter (ARNT) [37]. It has been demonstrated that AhR plays a critical part in the development of embryonic and adult tissues, reproduction, and endogenous metabolism in addition to promoting chemical and microbial defenses [38]. AhR and its signaling networks are connected to the secretion and production of some factors associated with inflammation [39]. Additionally, AhR serves as an environmental sensor and is crucial for both immune modulation and immune damage [40]. One of the key transcription factors for the development of Th cell subpopulations, AhR regulates the expression and differentiation of T and B cells, as well as the T cell immune process. AhR can alter the number of immune cells in the body and take part in the body's immune response by activation by binding to various ligands [36]. It has been shown that AhR signaling may affect the intercellular homeostasis of Th17/Treg cells, with the exogenous ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) activating AhR and causing the differentiation of Treg cells and the endogenous ligand 6-formylindolo [3,2-b]carbazole (FICZ) promotes Th17 cell differentiation after AhR activation, which causes dysregulation of the homeostasis of Th17/Treg cells and upregulation of immune factors implicated in disease development, such as IL-17 and IL-22 [41]. The differentiation and homeostasis of Th17 and Treg cells may be dependent on AhR ligands, and variations in AhR expression can disrupt the balance of these two T-cell subpopulations, resulting in the onset of autoimmune diseases, according to a study by Singh *et al*. [42]. One research discovered in a mouse model that the coordinated function of the AhR and typical TGF-β signaling pathways in differentiation is crucial for the differentiation of $CD4^+$T cells into Th17 cells [43]. It was also discovered that AhR is required for the release of IL-22 and that AhR is a direct target of miR15a/16-1 in $CD4^+$T cells, where IL-22 is inversely correlated with the release of miR15a/16-1 [38]. It has been found that AhR is essential for IL-22 secretion, and AhR is a direct target of miR15a/16-1 in $CD4^+$T cells, and IL-22 secretion is negatively correlated with miR15a/16-1, and this gene overexpression can reduce the synthesis of IL-22 by inhibiting AhR [44]. Additionally, the connection between AhR and Notch signaling has been discovered in mouse $CD4^+$T cells, and it can be utilized to regulate the cell cycle, proliferation, and differentiation. Notch signaling boosts the release of IL-22 through AhR, and IL-22 expression is decreased by AhR antagonists in reaction to Notch signaling activation, and TCDD activation of AhR raises the levels of Notch-1 and Notch-2, tentatively revealing a functional link between AhR and Notch pathway was revealed and the role of AhR as a bridge in the Notch-AhR-IL-22 signaling pathway [45,46].

5. Notch-AhR-IL-22 Signaling Pathway is Involved in the Development of ITP

Immune thrombocytopenia is currently a diagnosis of exclusion, and the condition's pathogenesis is still a hot subject of study among experts and scholars. It has recently been suggested that the Notch-AhR-IL-22 axis is one of the mechanisms involved in the pathogenesis of ITP, which has a fine regulation of the immune and inflammatory responses and is made up primarily of cis-acting components and trans-conduction systems, the cis-element consists of members of the δ and *Jagged* gene families in Notch ligands, while the trans expression system is composed of Notch receptors Notch1-4 bound to *DLL* and *Jagged* proteins [25,47]. In humans and mice, the Notch-AhR-IL-22 axis exists with organ-specific gene expression profiles, and the Notch and IL-22 signaling pathways are primarily linked hierarchical fashion via Notch-induced endogenous AhR ligands [47]. IL-22 is a cytokine that has both pro-inflammatory and anti-inflammatory effects, and it is primarily produced by $CD4^+$T cells, and when IL-22 is secreted alongside other inflammatory factors such as IL-17, IFN-γ, and TNF-α, its pro-inflammatory properties are increased, mediating a variety of inflammatory or autoimmune diseases [48,49]. Furthermore, IL-22 raises the levels of cytokines like IL-1 and IL-18, which regulate platelet apoptosis and cause thrombocytopenia [17]. Wang *et al*. [35] proposed that the Notch signaling pathway might promote IL-22 expression in $CD4^+$T cells by activating AhR, and this research discovered that inhibiting the Notch signaling pathway could significantly reduce IL-22 secretion by $CD4^+$T cells and AhR-mRNA expression in ITP patients, however, $CD4^+$T cell differentiation to Th17 cells was unaffected, indicating that Notch signaling was directed at the IL-22 factor secreted by $CD4^+$T cells.

In the intricate network of inflammatory molecules involved in ITP pathogenesis, Th22 cells are also important in the Notch-AhR-IL-22 signaling cascade, and IL-22 is the main Th22 cell effector molecule [17]. Zeng *et al*. [50] showed that Notch signaling regulates IL-22 transcript levels, and overexpression of the activated Notch- AhR pathway induces $CD4^+$T cell differentiation into Th22 cells, which not only increases circulating IL-22 secretion but also works synergistically with Th17 and Th1 cells to disrupt the body's immune cell homeostasis. Previous research has shown that the Notch signaling ligand *jagged-1* can increase IL-22 secretion by promoting Th22 cell expression, as well as raise AhR and IL-22 mRNA and protein levels to

participate in the development of ITP [51]. As was stated earlier, Notch signaling and AhR individually regulate the immune cell differentiation and homeostasis, which results in an imbalance in the number of Th1, Th2, Th22, Th17, and Treg cells *in vivo*, and the pathogenic process of ITP can also be mediated by several pathways, such as Notch signaling that induces AhR to increase direct secretion of IL-22 from $CD4^+$T cells or the Notch-AhR pathway that induces differentiation of $CD4^+$T cells into Th22 cells to enhance IL-22 expression (see Fig. 1 for details).

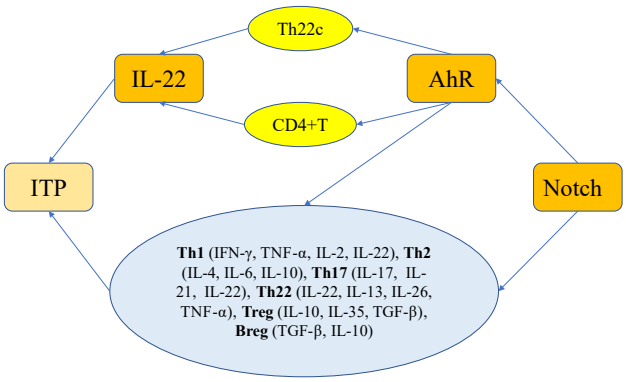

Fig. 1. Notch-induced AhR regulation of IL-22 secretion signaling pathway in ITP. Notch signaling and AhR individually regulate the immune cell differentiation and homeostasis, which results in an imbalance in the number of Th1, Th2, Th22, Th17, and Treg cells *in vivo*, and the pathogenic process of ITP can also be mediated by several pathways, such as Notch signaling that induces AhR to increase direct secretion of IL-22 from $CD4^+$T cells or the Notch-AhR pathway that induces differentiation of $CD4^+$T cells into Th22 cells to enhance IL-22 expression. Abnormalities like a Th1/Th2 imbalance, an increased ratio of Th1, Th17, and Th22 in T-cell subsets, a decrease in Treg cell numbers, an imbalance between Th17/Treg cells, and a decrease in Breg cell numbers are linked to the pathogenesis of ITP.

Given the regulatory role of the Notch-AhR-IL-22 signaling pathway in ITP, some studies have suggested that decreasing IL-22 levels by blocking the Notch-AhR-IL-22 axis could be used to treat or mitigate the progression of ITP. According to a study by Cao *et al.* [52] untreated ITP patients had a significantly higher percentage of serum Th22 cells than did treat ITP patients, but after high-dose dexamethasone treatment the levels of Th22 cells and IL-22 significantly decreased, and the platelet levels in the ITP patients quickly recovered. According to recent research, resveratrol, an AhR antagonist, inhibited Notch-AhR signaling, markedly decreased IL-22 levels, and slowed the pathogenesis of ITP [7]. All of the aforementioned results suggest that inhibiting the Notch-AhR-IL-22 signaling pathway's expression can reduce the amount of IL-22 secreted, which in turn suppresses the immune inflammatory response and returns ITP's immune system to normal, and perhaps blocks any link of the Notch-AhR-IL-22 axis is expected to be a potential target for immunotherapy of ITP.

6. Research Progress on the Notch-AhR-IL-22 Signaling Pathway and ITP in Pregnancy

Pregnant women, as a special group, have a considerably higher incidence of ITP than non-pregnant women due to changes in various systems and organs during pregnancy, in addition to adult women and children who are susceptible to the development of ITP [53]. ITP is the most common cause of serious thrombocytopenia before pregnancy, in the first or second trimester of pregnancy, and accounts for 1%–4% of all causes of thrombocytopenia in pregnancy [54]. Existing research suggests that the same factors that cause ITP in non-pregnant people also cause it in pregnant people. These factors include defective T-cell gene expression, specific anti-platelet antibody binding to antigens in pregnant women's plasma, impaired megakaryocyte maturation, increased platelet destruction, and insufficient platelet production [9]. Although the precise pathogenesis of ITP is still unknown, pregnancy may speed up the disease's development [55]. The special immune tolerance and immune homeostasis that occur during pregnancy may also play a role in the disease's pathogenesis [56]. Additionally, the timing of ITP can have an impact on how a pregnancy develops, increasing the risk of clinical problems like postpartum hemorrhage, neonatal thrombocytopenia, and even intracranial hemorrhage [57]. In recent years, some researchers discovered that the Notch-IL-22 pathway plays a role in the pathogenesis of ITP in pregnant mice by controlling the immune response, subsequent research confirmed that blocking the Notch-IL-22 pathway with recombinant human thrombopoietin can improve the prognosis of pregnant mice with ITP and raise the platelet levels [58]. Additionally, research on the human placenta found that early gestation Notch receptor expression levels were greater and *Jagged-1* expression levels were lower, as evidenced by the fact that *Jagged-1* expression levels were higher and Notch-1 and Notch-4 expression levels were reduced in late gestation, the Notch signaling pathway may be differentially regulated during pregnancy [59]. Additionally, it has been demonstrated that patients with ITP in pregnancy have significantly higher serum levels of TNF-α, IL-22, IL-5, and IL-6 while significantly lower serum levels of IL-12 and IL-16, indicating that the development of ITP in pregnancy is linked to an imbalance of related immune cells and immune factors [60]. According to the research mentioned above, IL-22 factors and Notch signaling may contribute to the pathogenesis of ITP during pregnancy. Despite the rarity of reports on this pathway in ITP during pregnancy, the Notch-AhR-IL-22 signaling pathway is more commonly studied in non-pregnant ITP. This can serve as an experimental basis for future studies on the Notch-AhR-IL-22 signaling path-

way in ITP during pregnancy, and the mechanism of this signaling pathway in ITP during pregnancy can also be further investigated. Given that the pathogenesis and management of patients with ITP during pregnancy are similar to those during non-pregnancy, immunotherapy regarding ITP in pregnancy might start with blocking the Notch-AhR-IL-22 signaling pathway. To thoroughly investigate the Notch-AhR-IL-22 signaling pathway's role in ITP to generate fresh concepts for immunotherapy of ITP in pregnancy.

7. Conclusions

In summary, the pathogenesis of ITP is defined by a complex immune imbalance and immune intolerance condition caused by multiple factors, pathways, and channels, and Notch signaling is involved in the development of ITP by inducing AhR expression to promote the differentiation of $CD4^+$T cells to Th22 cells and by increasing IL-22 secretion, which together disrupts the immune homeostasis *in vivo*. Understanding the pathogenic role of the Notch-AhR-IL-22 axis in ITP may set the experimental groundwork for further research into the pathogenesis of ITP in pregnancy and may also open up new possibilities for immunotherapy of ITP in pregnancy.

Author Contributions

Q-qF participated in the manuscript conception and design, participated in the drafting of the manuscript. R-xH participated in the conception and design of the manuscript, revised the important contents of the manuscript, and approved the publication. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. Both authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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