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REVIEW

Notch Signaling Pathway Interfering as a Possible Asthma Treatment: A Narrative Review

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Abstract: Asthma is a respiratory disease common among all age groups, and there is currently no cure that can be applied, as the patients react differently to the available treatments. Recent studies have shown that the Notch signaling pathway can regulate the dynamic balance between Th1 and Th2 cells, inhibit airway inflammation, reduce airway hyperresponsiveness and remodeling, and promote mesenchymal stem cell (MSCs) homing. This study conducted a comprehensive search of multiple large databases and provided a narrative review of the role of the Notch signaling pathway in asthma.

Keywords: bronchial asthma, notch pathway, remodeling, inflammation, hyperresponsiveness

Introduction

Bronchial asthma is a common chronic respiratory disease with a high incidence in patients of all ages.[1] According to the Global Burden of Disease Survey, approximately 300 million patients suffer from asthma.[2] For example, China has an overall asthma prevalence of 4.26%, with up to 45.7 million people affected, causing a significant burden on people suffering from asthma, society, and the economy.[3]

The main clinical features of asthma include breathing difficulties and wheezing.[4] These symptoms can be caused by factors such as exercise, exposure to allergens, viral infections, strong odors, cigarette smoke, exhaust gas, and laughter.[5] Some studies have suggested that immune responses caused by genetic and environmental factors play an important role in the pathogenesis of asthma,[6–8] with smoking, work environment, and high body mass index (BMI) being the three main risk factors for asthma onset. However, the specific pathogenesis of asthma remains unclear, and the effects of asthma treatments are not ideal. Therefore, new treatment strategies are required.

From an intrinsic pathological perspective, the respiratory tract of patients with asthma exhibits pathological changes, such as airway inflammation, remodeling, and hyperresponsiveness. In recent years, several studies have shown that inhibiting the Notch signaling pathway can improve associated lesions in patients with asthma and even assist in recovery by promoting the homing of mesenchymal stem cells (MSCs). Moreover, the Notch signaling pathway may be a new therapeutic target for asthma.

This review focuses on the effects of the Notch signaling pathway on asthmatic airway lesions and mesenchymal stem cell homing. We also discuss the challenges in treating asthma via the Notch signaling pathway.

Materials and Methods

We conducted a comprehensive literature search in PubMed, Embase, and Web of Science, and the search strategies used for the three databases were consistent. We used keywords such as "asthma", "Notch", "inflammation", "remodeling",

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"high reactivity", and "mesenchymal stem cells", and a combination of these words. Additionally, a free-word search strategy was applied.

Only studies published between 1990 (limited to the establishment of databases) and the end of 2024 were considered. The selected literature types were review papers, clinical trials, and animal experiments.

There were no limitations on language, author nationality, or funding status. After completion of the search, all eligible studies were immediately downloaded for screening. A total of 245 studies met the inclusion criteria. Following consecutive cross-reviews conducted by at least two authors, 162 studies were excluded due to duplicate inclusion across three databases. The subsequent discussion is based on the remaining articles.

Discussion

Mechanism of the Notch Signaling Pathway and Its Correlation With Asthma

The Notch signaling pathway is highly conserved and promotes communication between adjacent cells.[7] It can also regulate cellular activities, such as cell proliferation, development, and differentiation.[8] In mammals, the pathway involves four receptors (Notch 1–4), each made up of a single transmembrane protein with repeated structural units. These units are organized into three parts: the extracellular domain (NECD), the transmembrane (TM) domain, and the intracellular domain (NICD). In addition to the receptors, there are five ligands in the Notch signaling pathway: DLL1, DLL3, DLL4, and Jag1 and Jag2. These ligands are also single-pass transmembrane proteins.[9]

The pathway is typically activated when ligands bind to their corresponding receptors, which sets off a chain reaction.[10] This interaction triggers two cleavage events in the Notch receptors: (1) metalloproteinases (ADAMs) cut the ligand-bound NECD from the rest of the receptor; and (2) γ-secretase cleaves the transmembrane part from the NICD.[11] Once the NICD is released, it moves into the nucleus, where it binds to a transcription factor called CBF-1 (also known as CSL or RBPJ). This binding replaces the repressor proteins with coactivators, such as mastermind-like protein (MAML), turning the pathway on and starting the transcription of target genes.[12] The full mechanism of this process is shown in Figure 1.

The association between the Notch pathway and asthma is first reflected in its regulation of T helper 1 and T helper 2 cells (Th1 and Th2 cells, respectively). Th1 and Th2 cells are differentiated from CD4 + T cells based on different regulatory transcription factors and cytokine markers. However, the main characteristics of asthma are the overexpression of Th2 cells and the reduction in Th1 cell numbers, which create an imbalance of Th1/Th2. Moreover, the Notch signaling pathway differentiates Th1 and Th2 cells[13] and may affect asthma through ligand-receptor regulation of the Th1/Th2 cell balance.[14] In addition, it is generally believed that the Notch ligand delta is closely related to the development of Th1 cells. In contrast, the development of Th2 cells is mainly related to Jagged Notch ligands. Additionally, there are other ways to increase and restore the Th1/Th2 balance in patients with tuberculosis by blocking Notch signaling using N-[N-(3, 5-difluorophenacetyl)-l-alanyl]-s-phenylglycinet-butyl ester.[15]

In contrast, another study showed that Notch signaling inhibits Th2 polarization, enhances Th1 cell differentiation, and increases the Th1/Th2 balance in mice, and this inhibits or reduces food allergy in mice.[16] In contrast, in the specific case of the Notch-1 ligand, a study found that it regulates the Th2 immune response through dendritic cells.[17] GCs and GSI may reverse the Th1/Th2 imbalance and reduce allergic pulmonary inflammation by inhibiting Notch1 signaling transduction.[18] Reducing Th2 and Th17 cytokine levels and increasing the IFN- γ Horizontal downregulation of the Notch-1 receptor and its ligand Jagged 1 and 2 expressions alleviates allergic asthma.[10]

Moreover, there is also a balancing effect between Th1 and Th2, where Th1 cells express the transcription factor T-bet and secrete the cytokines IFN- γ and TNF- α, which play a major role in the cellular immune regulation against viruses and bacteria. In contrast, Th2 cells express the transcription factor GATA-3 and secrete cytokines, such as IL-4, IL-5, and IL-13, promoting humoral immunity after pathogen infection. IFN- γ inhibits the differentiation and function of Th2 cells, while both IL-4 and IL-10 inhibit the differentiation and function of Th1 cells.

In summary, several studies have shown that the Notch signaling pathway may affect the occurrence and development of asthma by regulating the balance between Th1 and Th2 cells.

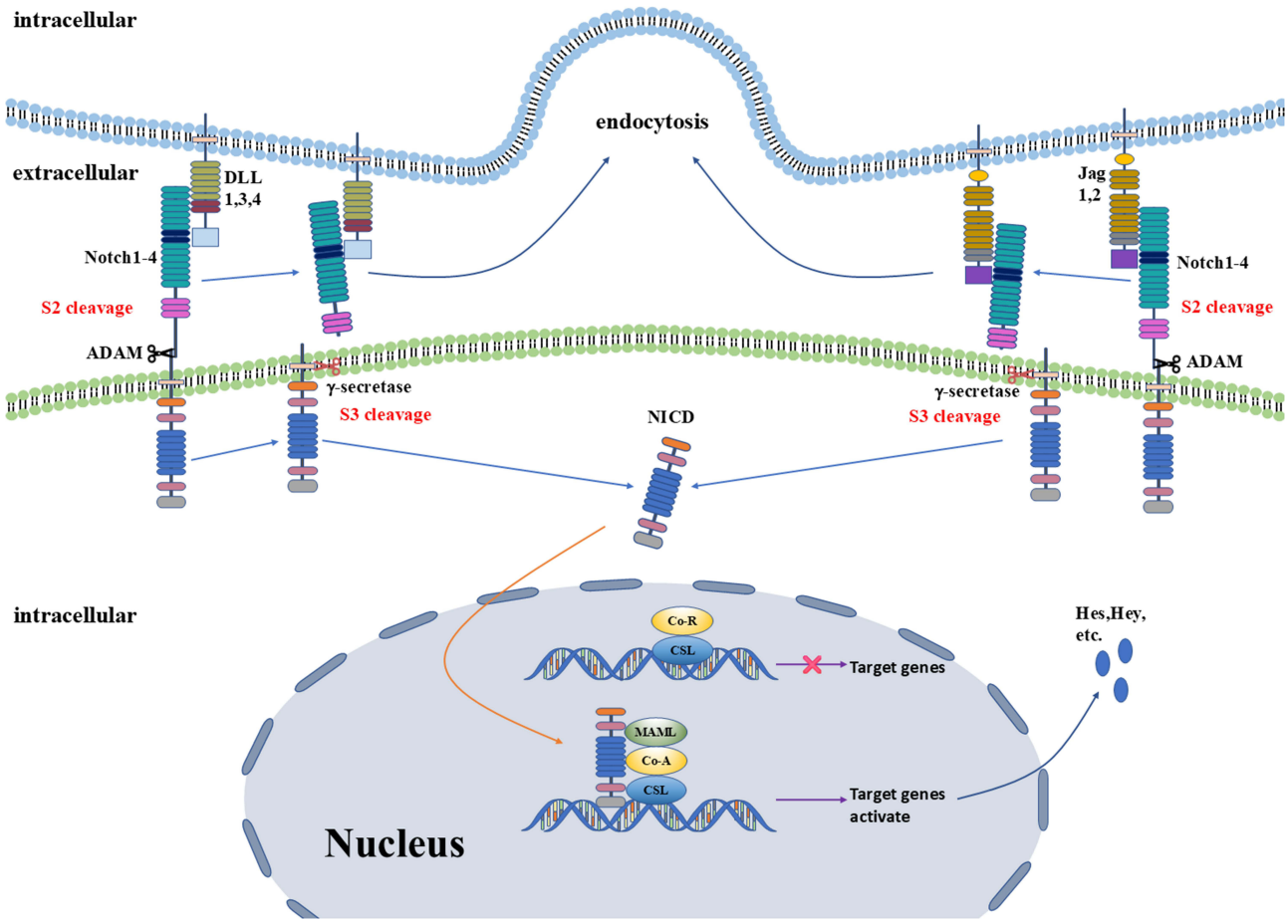

Figure 1 The operating mechanism of the Notch signaling pathway.

Mechanisms of the Notch Signaling Pathway in the Asthma Inflammation Progression

Factors That Promote Asthma Inflammation Progression

Airway inflammation is one of the main pathological symptoms of asthma. It stimulates mucus production, which promotes airway remodeling and hyperresponsiveness.[19]

Several inflammatory cells can promote or initiate airway inflammation, and T lymphocytes play an indispensable role in these processes.[20] $CD4^+$T lymphocytes differentiate into Th1 and Th2 cells under the control of transcription factors T-bet and GATA3, respectively. Under physiological conditions, the differentiation of Th1 and Th2 cells into $CD4^+$T lymphocytes maintains a dynamic balance. However, during the development of inflammation, the Th1/Th2 balance tilts towards Th2 immune inflammation, increasing Th2 cytokine levels (IL-4, IL-10, and IL-13) and decreasing Th1 cytokine levels (IFN-γ and IL-2).[21] Moreover, Th2 cytokines are crucial for inflammation.[22] Therefore, the Th1/Th2 imbalance is an important target for treating airway inflammation in asthma. Moreover, the Notch signaling pathway has an important impact on the occurrence and development of airway inflammation because the completion of this pathway is required for the signaling and differentiation of T cells.

A study on the effects of PM2.5 on asthmatic mice found that asthmatic mice exhibit Th1/Th2 immune imbalance and excessive activation of Notch signaling. For example, PM2.5 exacerbates the Th1/Th2 immune imbalance by activating the Notch signaling pathway.[21] Another study on allergic airway inflammation (AAI) driven by house dust mites (HDM) showed that airway inflammation was only alleviated in mice with RBP-J deficiency in the T cell lineage, indicating that the Notch signaling pathway in T cells is crucial for the Th2-mediated AAI response.[23] Peng et al showed that monocyte chemotactic protein-induced protein 1 (MCPIP1) can bind to the mRNA encoding GATA3 and inhibit Th2-related Notch signaling, thereby regulating Th2 cell development and differentiation and reducing Th2-mediated allergic airway

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inflammation.[24] Previous studies have found that in an asthmatic mouse model driven by ovalbumin, GSI can effectively block Notch signaling in bronchoalveolar lavage (BAL) cells, inhibit the production of Th2 cytokines, and ultimately inhibit Th2-related airway inflammation.[25] Moreover, the study by Hu et al also achieved similar results. In another study, a Th1/Th2 imbalance was observed to tilt towards Th2 cells. Furthermore, these results suggest that GSI and GC can inhibit Notch1 signaling, reverse Th1/Th2 imbalance, and alleviate airway allergic inflammation.[26] Alex et al showed that, in a mouse asthma model driven by HDM, SAHM1 competitively binds to nuclear complexes at the MAML interface, thereby inhibiting the Notch signaling pathway and downregulating the expression of key Th2 transcription factors and intracellular IL-4 in bronchoalveolar lavage fluid T cells, which concomitantly suppresses airway inflammation.[27]

Correlation Between the Notch Signaling Pathway and Airway Hyperresponsiveness

Airway hyperresponsiveness (AHR) is a key characteristic that distinguishes bronchial asthma from other eosinophilic airway inflammations and is considered one of the main pathological features of asthma. It mainly manifests as airway stenosis and increased airway resistance caused by nonspecific environmental stimuli, drug agonists, and inflammatory mediators, resulting in excessive bronchoconstriction.[28]

AHR is closely related to airway inflammation, and the number of inflammatory markers such as eosinophils, mast cells, and T lymphocytes in the airway mucosa can indicate the development of AHR in a patient. In the induction process of AHR, $CD4^+$T cells and $CD8^+$T cells are deeply involved, whereas the Notch pathway mediates T cell differentiation and plays an important role.

Several proteins are associated with AHR onset and severity. For example, Nieuwenhuis et al showed that pituitary tumor transforming 1 interacting protein (PTTG1IP) and mastermind-like protein 3 (MAML3) are involved in Notch signaling and are associated with the severity of adult asthma AHR.[29] In addition, Okamoto et al found that the Notch signaling pathway plays an important role in $CD8^+$T cell-mediated AHR and inflammation and identified Delta1 as an important regulatory factor in allergic airway inflammation.[30]

Furthermore, IL-17A produced by Th17 cells can stimulate the development of AHR by directly acting on smooth muscles in the airways,[31] whereas blocking IL-17 expression can alleviate AHR.[32] Moreover, Zhang et al showed that inhibiting the Notch signaling pathway could alleviate formalin-inactivated respiratory syncytial virus-enhanced AHR by inhibiting Th17 cell responses.[33] Another study found that inhibiting the Notch pathway in obese mice with asthma could regulate the expression of IL-17 in $CD4^+$T (Th17) cells and improve the AHR response.[34] An interesting approach was completed by Yao et al's study, where they found that *Mycobacterium vaccae* can reduce AHR and inflammatory response in an ovalbumin-driven asthma mouse model by inhibiting the Notch signaling pathway.[35]

Additionally, many studies have suggested that an immune imbalance of Th1/Th2 cells is an important factor in developing AHR. For example, Shin et al found that Heat Shock Protein 65 (HSP65) can induce the expression of the Notch ligand Delta1 in BMDCs and tilt $CD4^+$T cells towards Th1 cytokines, thereby reducing AHR and airway inflammation.[36] In another study, the interaction between the Notch ligand on $CD4^+$T cells and Jagged1 on Antigen-presenting cells (APCs) was found to play an important role in Th2 differentiation and initiate IL-4 production, which promotes the development of AHR and airway inflammation. Moreover, inhibition of Notch signaling in $CD4^+$T cells can prevent the development of AHR and airway inflammation.[37] In summary, the Notch signaling pathway is important in developing AHR in asthma.

Notch Signaling Pathway and Airway Remodeling

In asthma, airway remodeling is often considered the result of inflammatory damage to the bronchi caused by exposure to allergens or other environmental hazards.[38] Moreover, inflammatory damage can be observed, including epithelial damage, infiltration of inflammatory cells,[39] mucinous gland hyperplasia, deposition of collagen and proteoglycans in the subcutaneous basement membrane, angiogenesis, and increased airway smooth muscle (ASM) masses.[40]

Emerging evidence has implicated dysregulation of the Notch signaling pathway in the pathogenesis of chronic pulmonary disorders,[41] some studies specifically suggesting its potential role in modulating airway remodeling processes observed in asthma. Hu et al demonstrated that the LIM domain protein KyoT2 inhibits Notch1 and reduces Hes1

expression by competing with NICD to bind to CSL, thereby reducing airway remodeling.[42] Li suggests that inhibiting Notch1 can downregulate the expression of both the Notch-1 intracellular domain (NICD) and Hes1 while upregulating TNF- α, and this promotes the expression of PTEN in cells, which inhibits TNF-α Induced proliferation and migration of ASM cells and restores airway remodeling.[43]

In addition, overexpression-induced SOX18 promotes Notch1 expression and enhances TNF- α, stimulating the proliferation and migration of airway smooth muscle cells and promoting airway remodeling.[44] Moreover, other studies have shown that using γ- Gamma Secretase Inhibitor (GSI) prevents the activation of the Notch pathway, which can reduce both the loss of multi-ciliated cells and the surge of secretory cells, thereby improving the respiratory epithelial function and promoting benign regulation of airway remodeling.[45]

Other factors that could contribute to asthma include excessive mucus production or issues clearing it, and several proteins involved in mucus secretion and consistency. MUC5AC is a mucin protein that is highly expressed in airway epithelial cells and is one of the main components of airway mucus. Recent studies have shown that NOTCH3 is a regulator of MUC5AC production and that an increase in NOTCH3 in asthmatic airway epithelial cells may be a potential driving factor for excessive MUC5AC production.[46] In a Notch2 knockdown mouse model of HDM disease mediated by antisense oligonucleotides (ASO), goblet cell and mucus production were significantly reduced, and airway remodeling was inhibited.[47] Regulatory T cells (Tregs) suppress the Notch signaling pathway, inhibit angiogenesis, and improve airway remodeling through both DLL4 signaling and EC crosstalk, ultimately improving lung function.[48]

On the other hand, brominated domain protein 7 (BRD7) is a key component of the switch/sucrose non-fermentable complex involved in chromatin remodeling and transcriptional regulation. BRD7 inhibits TNF by downregulating the Notch pathway- α. Moreover, inducing the proliferation and migration of airway smooth muscle cells can inhibit airway remodeling.[49] In human trials, a study on asthmatic children's airway epithelial cell cultures found that Notch signal activation, to some extent, led to the disrepair of the cultured cells. Inhibition of the Notch pathway can partially eliminate the ability of airway epithelial progenitor cells to promote airway remodeling.[50]

In conclusion, similar to its effects on airway inflammation and hyperresponsiveness, inhibition of the Notch pathway also has a beneficial impact on airway remodeling, as shown in Figure 2.

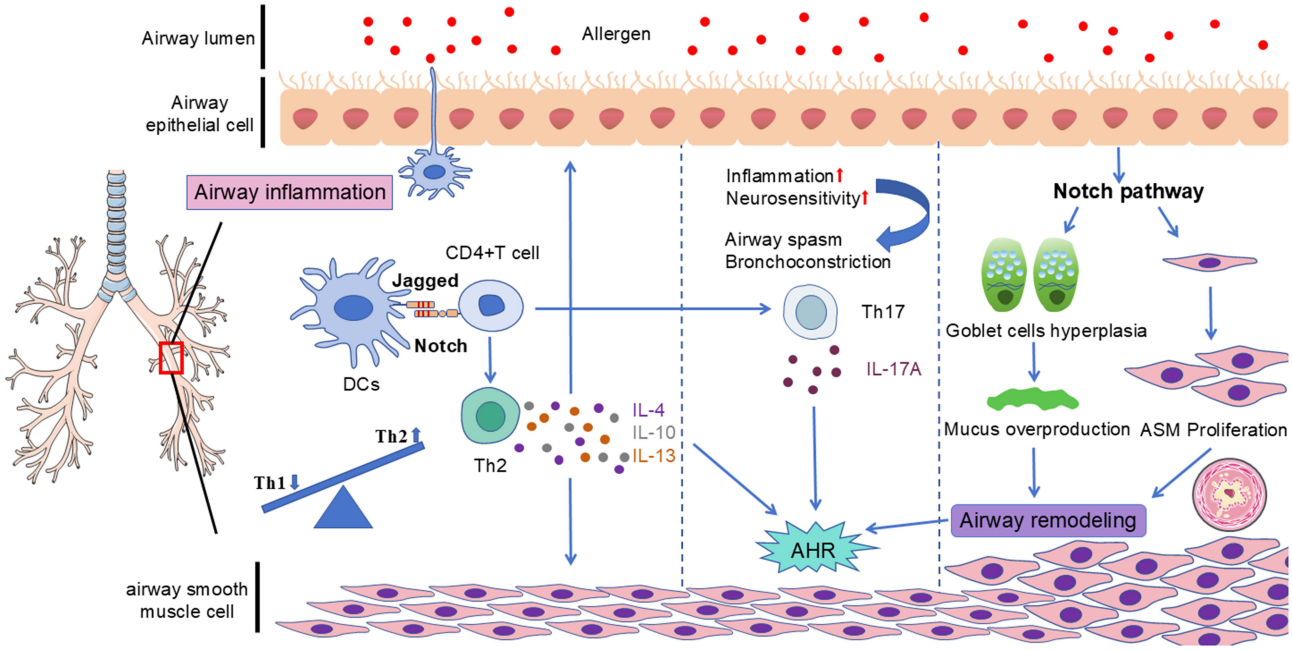

Figure 2 Notch Signaling Pathway in Alleviating Airway Inflammation, Remodeling, and Hyperresponsiveness in Asthma.

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Notch Pathway and Homing of Mesenchymal Stem Cells

Recent studies have highlighted the therapeutic potential of mesenchymal stem cells (MSCs) in asthma treatment, particularly through their interaction with the Notch signaling pathway. MSCs are multipotent cells that can differentiate into various cell types, including osteoblasts, adipocytes, and chondrocytes, and play a crucial role in tissue repair and immune modulation.[51] Moreover, MSCs have the characteristics of "homing." Homing is a process in which the combination of SDF-1 and CXCR on the surface of MSCs drives them to accumulate at the damaged site, producing a repair effect.[52] Initially, Selectins on endothelial cells mediate the rolling of MSCs along the vascular wall, where CD44 enhances adhesion and facilitates their firm attachment. To enable extravasation, matrix metalloproteinases (MMPs) degrade the extracellular matrix, allowing MSCs to penetrate the endothelial barrier. Firm adhesion is stabilized by the interaction between VLA-4 on MSCs and VCAM-1 on endothelial cells, supporting transmigration into lung tissues. Once in circulation, MSCs migrate toward inflamed airway regions in response to SDF-1, which binds to CXCR4 receptors on MSCs, guiding them to the injury site, as shown in Figure 3.

The Notch signaling pathway is known to play a pivotal role in tissue repair and cellular differentiation.[53] MSCs, through Notch signaling, can contribute to airway remodeling by promoting the regeneration of epithelial cells and inhibiting excessive fibrosis. Specifically, Notch activation in MSCs may help suppress the pathological processes of excessive fibroblast proliferation and collagen deposition, key contributors to fibrosis in asthmatic airways. Additionally, MSCs can secrete various cytokines and growth factors, such as TGF-β and VEGF, which may further aid in tissue regeneration and reduce fibrosis.[54]

The homing of MSCs to inflamed tissues is critical for their therapeutic effects. In asthma, chronic airway inflammation and remodeling create a microenvironment that could be targeted by MSCs. In recent years, studies have shown that blocking the Notch1 Signaling pathway can increase CXCR4 expression in bronchial epithelial cells, increase the combination of SDF-1 and CXCR4, and enhance the migration ability of MSCs. Xie et al interfered with Notch signal transduction by adding the Notch signal inhibitor GSI or the gene deletion RBP-J, which increased CXCR expression in MSC and promoted the MSCs migration to SDF-1 enriched sites.[55] In addition, CXCR7 overexpressed in

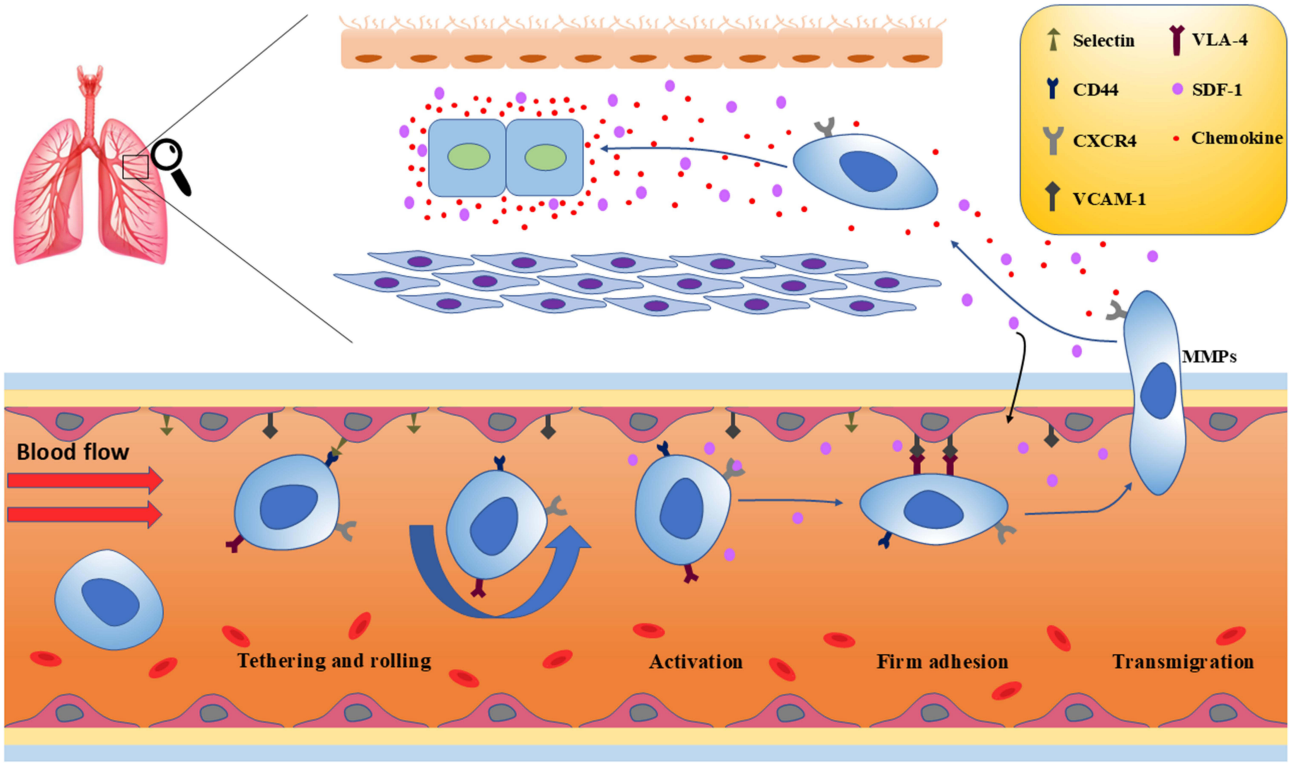

Figure 3 Homing of MSCs in Asthma.

base-2b cells can inhibit the Wnt/ β- Catenin pathway and inhibit the expression of Notch1/Jag1.[56,57] The above experiments show that inhibiting the Notch pathway can increase the expression of CXCR4[52] and positively impact the homing of stem cells, which may be conducive to rehabilitating asthma.

The role of MSCs in Notch pathway-based asthma treatment is multifaceted. By targeting the Notch signaling pathway, MSCs can modulate the immune response, enhance tissue regeneration, and improve the homing of these cells to sites of inflammation. While the interaction between MSCs and the Notch pathway holds promise for asthma treatment, several challenges remain. The complex role of Notch signaling in regulating MSC functions requires careful consideration, as both activation and inhibition of Notch signaling can have distinct effects depending on the cellular context. Furthermore, the translation of MSC-based therapies into clinical practice requires addressing concerns such as optimal cell delivery methods, dosage, and long-term safety.

Conclusions

The Notch signaling pathway can regulate the development and function of immune cells and may be a promising treatment for T cell-mediated diseases, such as asthma. Several studies have confirmed that interfering with the Notch signaling pathway can reduce airway inflammation and hyperresponsiveness, airway remodeling, and repair damaged respiratory tracts by promoting the homing of mesenchymal stem cells.

While emerging preclinical evidence suggests therapeutic potential for Notch signaling modulation in asthma management – particularly in mesenchymal stem cell (MSC) homing and immunoregulation – this approach remains in the exploratory phase. Current studies, predominantly in vitro and murine models, demonstrate Notch pathway involvement in attenuating airway remodeling (eg, via CXCR4-mediated MSC migration) and suppressing Th2-driven inflammation. However, critical knowledge gaps persist regarding: (1) tissue-specific Notch receptor/ligand dynamics in human asthmatic airways, (2) long-term safety profiles of systemic Notch inhibition, and (3) optimal therapeutic windows for pathway modulation without compromising epithelial regeneration. Rigorous preclinical validation of Notch-targeted biologics (eg, selective γ-secretase inhibitors, DLL4-neutralizing antibodies) combined with controlled clinical trials are essential to systematically characterize the risk-benefit ratio and translational feasibility of this strategy.

Highlights

What are the main findings?

- The Notch signaling pathway has a pivotal role in regulating the balance between Th1 and Th2 cells, which is crucial in controlling the immune response in asthma.
- Interfering with the Notch pathway leads to a reduction in airway inflammation and remodeling, two major contributors to asthma pathology.

What is the implication of the main finding?

- The ability to manipulate the Notch signaling pathway offers a potential new avenue for the development of targeted asthma treatments that address the underlying immune imbalances.
- These findings lay the groundwork for future clinical research and trials to evaluate the safety and efficacy of Notch pathway modulators in the treatment of asthma, potentially leading to innovative therapeutic options.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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