Novel pharmacological targets for the inhibition of inflammation and airway remodeling in asthma
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CHAPTER 7

General Discussion
Preface

This thesis is focused on unraveling and targeting reduced corticosteroid sensitivity and airway remodeling, including neuroplasticity, in asthma models. To achieve this, we investigated the role of specific cytokines in inducing airway remodeling and corticosteroid insensitivity. We also evaluated the effects of existing and potential new asthma therapies in dampening airway remodeling and neuroplasticity.

Targeting severe asthma

A key characteristic of asthma is chronic airway inflammation that leads to typical asthma symptoms, such as wheezing, chest tightness, shortness of breath, and cough (1). Despite optimal therapy, some patients with asthma still experience persistent symptoms, which is described as uncontrolled asthma (2). The mainstay of asthma therapy includes inhaled corticosteroids (ICS) which are generally used as controller medications, to target the chronic inflammation, and are nowadays included in combinations with a fast-acting beta-mimetics to focus on alleviating acute bronchoconstriction and preventing exacerbations (1).

Severe asthma is defined as uncontrolled asthma despite treatments with high dose ICS and second controller and/or oral corticosteroids for a minimum 6 months (1–3). Suboptimal therapy in severe asthma patients leads to increased airway hyperresponsiveness (AHR), higher risk of asthma exacerbations, and impaired lung function, which further results in lower quality of life and increased stress-related conditions, such as anxiety and depression (2,4–9). Certain mechanisms of airway inflammation, such as neutrophilic, innate lymphoid cells 2 (ILC2)-related inflammation, and Th17 inflammation, have been associated with severe asthma (4,10–15). Moreover, the pathobiology of severe asthma is also characterized by airway remodeling which can be the consequence of persistent inflammation with several inflammatory mediators acting on structural cells (16–18). Therefore, to unravel severe asthma and target the associated airway inflammation, remodeling as well as reduced ICS sensitivity, increased understanding of these mechanisms and new or improved therapeutic strategies are necessary in severe asthma.

Inflammatory cytokines induce airway remodeling

**The effect of prostaglandin 2 (PGD2) on airway remodeling**

In severe asthma, airway remodeling is a critical pathological feature which encompasses higher extracellular matrix (ECM) deposition, airway smooth muscle (ASM) hyperplasia and hypertrophy, bronchial microvascular remodeling, and goblet cell hyperplasia of the epithelium (19–21). This contributes to the obstruction of airflow and lung function loss (19–21). Type 2 airway inflammation is involved in the development of airway remodeling (22–25). Indeed, antagonism of prostaglandin 2 (PGD2), a type 2 inflammation mediator, has been shown to prevent airway smooth muscle (ASM) migration in vitro, inhibit goblet cell metaplasia in vitro and in vivo, and reduce the ASM mass in asthma patient biopsies (26,27). These results suggested that PGD2 may have direct effects on airway remodeling independent of its inflammatory properties. Features of airway remodeling in asthma, such as goblet cell metaplasia and increased ASM contractile proteins, can be modeled in vitro and in vivo (23–25,28,29). Thus, in chapter 3, we assessed the direct effect of PGD2 in combination with IL-13 on primary human airway epithelial cells (hAECs) differentiation and in allergen-sensitized guinea pig lung slices. Initially, we detected that prostaglandin D2 receptor 2 (DP2) and prostaglandin D2 synthase (PTGDS) genes are expressed in primary hAECs, indicating the potential for response to PGD2 signaling. Next, we found that in differentiated hAECs, PGD2 modestly upregulates MUC5AC expression, and thereby may be involved in goblet cell metaplasia in hAECs. Moreover, there was a trend towards increased MUC5B levels, another goblet cell marker, but no differences were found in ciliated cell markers expression, Tektin and FoxA3, or in the transcription factors related to MUC5AC expression, SPDEF and FoxA3. Goblet cell marker expressions are in inverse correlation with ciliated cell marker expression in this model which is a characteristic of goblet cell hyperplasia (25). Thus, it appears that the effect of PGD2 in driving goblet cell metaplasia may be limited.

Disruption of epithelial barrier function is increased in asthmatics and is suggested to be associated with airway inflammation (30–32). This is caused by tight junction proteins defects as well as reduction in adherens and desmosomes reduction (30,33,34). However, we did not find any difference between control and PGD2-exposed differentiating hAECs in a FITC-dextran functional barrier experiment. In line with this, PGD2 also did not affect ZO-1 expression, which is a marker for epithelial tight junctions. This further confirmed that PGD2 has minimal roles in affecting airway epithelial remodeling.

Changes in contractile markers, such as calponin and smooth-muscle MHC (sm-MHC), indicate airway remodeling in ASM and can be evaluated by precision cut lung slices (PCLS) method in guinea pig (28,29). Although PGD2 antagonism resulted in decreased ASM mass in asthmatics’ biopsies as well as prevented ASM migration.
in vitro, it had no effects on ASM proliferation, suggesting a complex mechanism of PGD₁ in ASM remodeling (27). Indeed, we observed that exposure to PGD₁ leads to higher calponin protein expression in allergen-sensitized guinea pig lung slices, without clear effects on sm-MHC, suggesting partial ASM remodeling.

Moreover, recruitment of eosinophils after allergen challenge might not provide additional effects of PGD₁ on ASM remodeling, as we did not observe any differences between saline and ovalbumin challenged animals. In line with this finding, a phase III clinical trials of a PGD₂ antagonist fevipiprant showed that its efficacy in reducing exacerbations and improving lung function, had no correlation with blood eosinophil counts (35). The effect of PGD₁ on airway remodeling is therefore likely independent from eosinophilic inflammation and may be based on other mechanisms, such as a direct effects on the airway structural cells, i.e. airway epithelial and ASM cells (36). The clinical significance of these PGD₁ effects remains to be established.

The effects of IL-17A on airway remodeling
IL-17A is a central pro-inflammatory cytokine in airway diseases and its levels in the sputum, nasal, and bronchial biopsies are higher in asthma and COPD (37–42). The presence of IL-17A in the airway regulates airway epithelial remodeling, with features such as increased epithelial-mesenchymal transition, goblet cell metaplasia, and mucus production (43–47).

It has been suggested that the direct effect of IL-17A on airway epithelial cells might contribute to the pathogenesis of asthma and COPD. However, there is a need to unravel its mechanisms (15). Therefore, elucidating IL-17A pathway mechanisms and functional consequences in airway epithelial cells can be beneficial for targeting Th17-driven airway diseases. Furthermore, air liquid interface (ALI)-cultured primary human airway epithelial cells (hAECs) provides representation of a pseudostratified mucociliary cell culture, rendering it a suitable in vivo model. In chapter 5, the direct roles of IL-17A in airway epithelial cells were measured by using this model during the 14-day differentiation period. First, total RNA sequencing analysis showed that the most differentially expressed genes by IL-17A stimulation are related to Cilia function and development as well as Extracellular matrix organization pathways. Interestingly, a previous study also reported that these pathways are regulated by IL-17A (48). This indicates that indeed, IL-17A might directly affect hAECs differentiation.

In the ciliated cells, the ability to differentiate and proliferate are significantly affected by the development and function of cilia (49–51). Reduced cilia development is known to be related to abnormal cell differentiation (50). To date, limited studies have been done on the role of IL-17A in epithelial cilia development and function. Moreover, IL-17A-induced ciliogenesis inhibition via intraflagellar transport protein 88 (IFT88) activation was reported in keratinocytes (48). Similarly, our data also showed that IFT88 was significantly upregulated by IL-17A stimulation. Moreover, the ciliated cell marker FOXJ1 gene expression was downregulated, suggesting a downregulation of ciliary cells. Since a detailed analysis of cilia function were not included, further investigation of IL-17A functional regulation on ciliated cell development would be an interesting step forward.

Extracellular matrix organization pathways were also observed in IL-17A-induced hAECs differentiation. These include Degradation of extracellular matrix, Collagen formation, and Collagen biosynthesis and modifying enzyme pathways. A study in mice demonstrated that proliferation of Th17 cells causes ECM degradation and matrix metalloproteinase-9 (MMP9) upregulation via STAT3 overactivation, which contributes to parenchymal epithelial remodeling (47). This is in line with our data which showed significant regulations of several MMPs, such as MMP7, MMP13, MMP14, MMP15, and MMP17 gene expressions. Our study demonstrates that the direct IL-17A effects on ECM regulation in airway epithelial might be not correlated with systemic inflammation. Studies in murine and human fibroblasts showed that the IL-17A-induced increased ECM production involves TGF-β activation, NF-κB signaling, and inhibition of JAK2 (45,52,53). Future studies are needed to unravel the mechanisms of IL-17A in airway epithelial molecular regulation.

Studies have suggested a role of IL-17A in shifting airway epithelium into goblet cell hyperplasia and increased mucus production, which are characteristics of several airway diseases, including asthma (44–46,54). Indeed, we observed that IL-17A exposure increased mucus volume production and epithelial goblet cell marker, MUC5AC, protein expression in differentiating hAECs.

A shift towards higher mucus hypersecretory phenotype is further confirmed by the elevated gene expressions of other goblet cell markers MUC5B and SPDEF. Furthermore, our data shows that the most differentially expressed gene by IL-17A in hAECs differentiation is SLCE26A4, which is a known goblet cell hyperplasia inducer in murine airway epithelial cells and human lung mucoepidermoid carcinoma cells (55–57). Similarly, a study in human bronchial epithelial cells also reported that SLCE26A4 is induced by IL-17A (58). Indeed, higher level of SLCE26A4 were observed in endobronchial biopsies (59), lung tissues (56), and serum of asthma patients (60), which were inversely correlated with forced expiratory volume in 1 second (FEV₁)% (60). This indicates the significant role of IL-17A in driving goblet cell hyperplasia which can lead to declined lung function.
One of the most important characteristics in epithelial remodeling is the disruption of epithelial barrier function. Reduced epithelial barrier function has been reported in asthma and is associated with several genetic polymorphisms that lead to increased susceptibility to the environmental factors (61). Moreover, reduced ZO-1 expression and TEER, as well as higher FITC-dextran permeability was observed in the nasal epithelial cells of patients with chronic rhinosinusitis, suggesting a substantial disruption of epithelial barrier function (62). In our data, we observed increased FITC-dextran transmembrane permeability, suggesting epithelial barrier disruption by IL-17A in hAECs.

Future investigation of the underlying mechanism of IL-17A-induced airway epithelial barrier disruption is needed, as it is yet to be unraveled. For example, evaluation of cellular adhesion as well as epithelial tight junction marker dynamics is an interesting next step to explore, since previous studies suggested that repressed gene expression involved in cell adhesion and filaggrin causes tight junction and epidermal barrier disruption in epidermal keratinocytes (63,64).

The IL-17A-induced airway remodeling extends beyond its effects in airway epithelium. In chapter 4, we reviewed the impact of IL-17A in other airway mesenchymal cells, such as fibroblast and airway smooth muscle (ASM) cells (15). Normal human lung fibroblasts express IL-17A receptor, IL-17RA, and proliferate in response to IL-17A (53). Moreover, IL-17A induced α-SMA expression as well as increased ECM deposition (collagen type I and fibronectin) of primary human lung fibroblasts when cultured on soft (polyacrylamide) gels (53). These were executed via inhibition of JAK2 and NF-κB signaling that resulted in this fibrogenic phenotype inhibition (53). Interestingly, the upregulation of collagen-III and fibronectin protein expression by IL-17A was induced in parenchymal fibroblasts and not in bronchial fibroblasts in human (65). This highlights that the different responses to IL-17A in increasing ECM production are determined by fibroblast phenotypes. In line with findings in fibroblasts, human primary ASM cells express IL-17RA, IL-17RC and IL-22R1, which are the Th17-related cytokines receptors (66). Moreover, ASM cells proliferation and migration were promoted upon activation by their corresponding ligands, IL-17A, IL-17F and IL-22, respectively (66, 67). These responses are facilitated by several pathways, as IL-17A and IL-17F effects were prevented by p38 MAPK and ERK 1/2 MAPK inhibitors, and both ERK 1/2 MAPK and NF-xB inhibitors for IL-22 (66,67). This could potentially contribute to ASM mass thickening since they are also shown to decrease apoptosis and promote cell survival (67).

Asthma therapies effects on airway remodeling and neuroplasticity

The mechanism of bronchial thermoplasty on epithelial fibroblast crosstalk

Despite being a crucial factor in asthma severity, currently there is only one treatment option that specifically inhibits airway remodeling in asthma, namely bronchial thermoplasty (BT) (1,68). Bronchial thermoplasty (BT) is an endoscopic procedure with a localized delivery of radiofrequency waves leading to heating (65⁰C) of the airway tissue (69). The role of BT in targeting airway remodeling is mainly linked with its ability to decrease ASM mass. Moreover, BT reduced type I collagen within the RBM, submucosal nerve density, ASM-associated nerve density, as well as the number of epithelial neuroendocrine cells of asthmatics (70,71). This further resulted in improved clinical outcomes, such as the asthma control test (ACT) scores, the number of exacerbations and emergency department visits at 3 and 12 months after BT (71). These desirable impacts were suggested to be long-lasting, since long term follow up studies of 3 randomized controlled trials pointed out that BT reduces the patient’s asthma exacerbations, emergency department visits and hospitalization up to 5 years after BT treatment (72–74). The significant clinical effects indicate that it is likely that its mode of action goes beyond the originally proposed selective impact on airway smooth muscle.

In chapter 2, we discussed a study by Sun et al. that elucidates the crosstalk between epithelial cells and fibroblasts which might underpin the beneficial effects of BT in patients with severe asthma (75). This study focuses on the role of protein arginine methyltransferase 1 (PRMT1) in fibroblast proliferation leading up to airway remodeling in patients with severe asthma before and after undergoing BT. PRMT1 inhibition leads to reduced proliferation of mouse embryonic fibroblasts (MEFs) and has been suggested to be involved in the pathogenesis of lung diseases, including COPD and asthma (76,77). Bronchoalveolar lavage fluid (BALF) and cultured epithelial supernatants from severe asthma patients showed lowered PRMT1 expression and cell proliferation after undergoing BT. Moreover, they also found upregulation of miR-19a as well as decreased ERK1/2 activity This is of importance as miR-19a is a repressor of ERK1/2 activity and PRMT1 expression (78). Thus, these results show that both BALF and epithelial culture supernatant after BT decreased the proliferation of fibroblasts through a mechanism involving upregulation of miR-19a leading to downregulation of ERK1/2 and PRMT1. Intrigued by such critical changes in fibroblasts, they conducted proteomic analyses on BALF and transcriptomic analysis on epithelial cells to elucidate the secreted factor that initiates between epithelium and fibroblasts. Indeed, it was found that heat shock protein 60 (HSP60) expression was downregulated after BT. HSP60 is a type of protein that is induced after subjecting cells to a stress response such as heat (79). Direct stimulation of lung
fibroblasts with human recombinant HSP60 significantly increased the expression of PRMT1, confirming the crucial role of this intercellular signaling intermediate.

To our knowledge, the first study that demonstrated the impact of BT on PRMT1 expression is the study by Sun et al. [13], and the reduction of PRMT1 might explain the long-lasting effects on epithelial-mesenchymal interactions in response to BT. This inspires potential therapeutic approaches on this signaling pathway, such as inhibition of HSP60 or PRMT1 that could potentially reduce the fibroblasts responses associated with airway remodeling in asthma.

**Budesonide effects on airway neuroplasticity in a murine chronic asthma model**

As the mainstay therapy in asthma of all severity, inhaled corticosteroids (ICS) are primarily targeted at airway inflammation and, secondly, at airway remodeling in asthma (1,80). Budesonide, a widely used corticosteroid in asthma treatment, is known to be involved in changes in a wide range of structural cells in the airway, including epithelial cells, fibroblasts, ASM cells, and vascular endothelial cells, thus contributing to the pathologic features of airway remodeling (80). A recently discovered feature of the remodeled asthmatic airway is the occurrence of airway neuroplasticity (4,81,82). Neuroplasticity is defined as changes of structure, function, and connection of the nervous system in response to stimuli (83). Currently, little is known about the corticosteroids regulatory effects in the airway nervous system. It has been reported that nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) protein levels in serum were elevated in asthma patients without ICS treatment compared to asthmatics with ICS treatment (84). Moreover, dexamethasone, a potent synthetic corticosteroid, downregulated nerve growth factor (NGF) expression in eosinophils from peripheral blood of asthma and allergic rhinitis patients (85). However, the subsequent changes in airway neuroplasticity are unknown.

The role of corticosteroids in neuroplasticity has long been researched in central nervous system (CNS) diseases. For example, dexamethasone regulates BDNF expression and neuroplasticity in several areas of the central nervous system (CNS) which might contribute to CNS diseases' pathologies, such as depression, epilepsy, Alzheimer’s, Huntington’s, and Parkinson’s diseases (86–88). Given these potential effects in the CNS, it is compelling to further evaluate the role of corticosteroids in airway neuroplasticity, which might be one of its mechanisms in targeting airway remodeling.

In Chapter 6, we studied the effects of inhaled budesonide in allergen-induced neuroplasticity in a murine chronic asthma model. Previously, this model has been shown to increase expression of the neuronal growth factor BDNF, the pan-neuronal marker PGP9.5, and neurofilament expression around the airways as well as increased responsiveness to methacholine, suggesting a higher airway innervation that contributes to AHR (82). In our study, we investigated 2 timings of inhaled budesonide administration: starting together with ovalbumin challenges (preventive) and 3 weeks after the start of ovalbumin challenges (therapeutic). Inhaled budesonide dampened ovalbumin-induced βIII-tubulin increase, a marker of neuronal growth, when administered preventively, but not therapeutically. Interestingly, its anti-inflammatory properties are preserved in both administrations, as seen in its consistent ability to prevent eosinophil infiltration into the airways. This indicates the ability of corticosteroids in inhibiting allergen-induced neuroplasticity, but not in reversing once it has been established.

Eosinophil activation lowers neurons’ activating threshold and promotes neural growth, giving rise to increased nerve growth and activity (89). However, once the neural growth took place, further reduction of eosinophil activation might not result in its reversal. Studies in allergen-sensitized guinea pigs demonstrated that preventive administration of dexamethasone inhibits neuronal-derived eosinophil protein adhesion (intercellular adhesion molecule 1; ICAM-1) expression, airway reactivity, and M2 receptor dysregulation (90,91). This might explain our observation that the anti-neuroplasticity effects of inhaled budesonide are exclusive as preventive use.

**Reduced corticosteroid sensitivity in asthma**

**IL-17A reduced corticosteroid sensitivity**

Corticosteroid insensitivity is an important issue, as there is currently no substitute for the role of corticosteroids in the management of asthma (Chapter 1). All types of cells in the lung express glucocorticoid receptors (GR), suggesting its wide range of effects (92,93). Thus, elucidating the mechanisms of reduced corticosteroid insensitivity is a critical step to prevent or even reverse this phenomenon. Chapter 4 reviewed the role of IL-17 in corticosteroid insensitivity in asthma. An IL-17-high gene signature was associated with poor response to ICS therapy in FEV1%-predicted—over-30-months change in COPD patients (94). Reduced corticosteroid sensitivity has been studied in several cell types, including inflammatory and structural cells. Dexamethasone, a potent corticosteroid, failed to induce Th2/Th17 cell deaths in bronchoalveolar lavage (BAL) from IL-17 high-asthmatics (95). Furthermore, in human ASM cells, synergistic stimulation of IL-17A and dexamethasone induced CSF3 gene expression, which consequently increased neutrophilic inflammation in the airway (96).
IL-17A pretreatment reduced budesonide’s ability to prevent TNF-α-induced IL-8 production in human airway epithelial cells experiment in vitro (97). In addition, GRβ levels are increased after IL-17A/F stimulation in airway epithelial cells from asthmatics (98). This indicates the direct contribution of IL-17 in reducing ICS sensitivity in airway epithelial cells. However, the functional consequences of these mechanisms in airway epithelium have not been examined yet. Thus, in chapter 5 we investigated the interactions of dexamethasone, a potent corticosteroid, and IL-17A on primary hAEC differentiation. During the differentiation period, we subjected the cells to IL-17A, dexamethasone, or their combination.

First, we confirmed previously reported IL-17A gene signature upregulation in our model (94). ALI-cultured hAECs showed increased expression of IL-17A gene signature when exposed to IL-17A, and these were not altered by the presence of dexamethasone. Consistently, the protein expression of several IL-17A inducible genes were measured by ELISA and showed similar patterns. Furthermore, the top 10 most regulated genes by IL-17A were also not inhibited by dexamethasone. For these genes, an IL-17A gene signature Z-score was calculated for each group and showed no difference between IL-17A with and without dexamethasone. Moreover, most of the genes which were at least 1.5-fold regulated by IL-17A stimulation were less inhibited. This gene expression analysis suggested that dexamethasone had minimal effects on IL-17A-induced gene expressions. In addition, the expression of two canonical corticosteroid genes, HSD11B2 and FKBP5, were prevented almost completely by IL-17A. This confirms the lack of dexamethasone effect in this model and indicates that IL-17A inhibits dexamethasone signaling.

Next, we evaluated the functional consequences of the decreased sensitivity of dexamethasone in IL-17A-induced hAECs differentiation. We previously discussed that IL-17A stimulated goblet cell metaplasia and increased mucus production as well as disrupted the epithelial barrier. Interestingly, although the increased goblet cell metaplasia and mucus production were not inhibited, the epithelial barrier disruption by IL-17A was restored by dexamethasone. Genetic analysis exploration suggested the involvement of pathways related with cilia function and development. Therefore, IL-17A and dexamethasone functional interaction on ciliated cell development and its association with improved barrier integrity would be of interest to investigate further.

Clinical implications and conclusions
In most patients, asthma is well controlled with optimized standard treatment which includes ICS. Nevertheless, a number of patients still experience uncontrolled asthma despite optimal treatment consisting of high dose ICS and second controller and/or systemic corticosteroids for a minimum of 6 months (1–3). Recent advances in research have uncovered types of inflammation with distinct biological markers that possibly drive the characteristics severe asthma, and further give rise to airway remodeling and reduced corticosteroids sensitivity. Our studies in this thesis describe findings that might help unravel the pathological features of severe asthma, such as:

- Bronchial thermoplasty (BT) treatment causes downregulation of HSP60-PRMT1 signaling pathway, which results in sustained effects on epithelial-mesenchymal interactions (Chapter 2).
- Prostaglandin 2 (PGD2) has modest direct effects on airway smooth muscle remodeling and epithelial cell function, which is independent from its effect on eosinophilic inflammation (Chapter 3).
- Interleukin 17A (IL-17A) increases airway remodeling in structural cells, such as ASM cells, fibroblasts, and epithelial cells (Chapter 4 and Chapter 5). IL-17A exposure during primary human airway epithelial cells (hAECs) differentiation induces goblet cell metaplasia, including mucus production, and epithelial barrier disruption (Chapter 5).
- Corticosteroids restore epithelial barrier disruption as induced by IL-17A, whereas inflammatory responses and mucus production in response to IL-17A were insensitive to corticosteroids (Chapter 5).
- Preventive treatment with inhaled budesonide has a protective effect against neuroplasticity that correlates with its anti-inflammatory properties. However, budesonide does not reverse established neuroplasticity (Chapter 6).

Collectively, these findings provide additional novel mechanisms which can support our efforts to target severe asthma characteristics and improve treatment strategies.
Chapter 7 - General discussion

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