

The impact of the prostaglandin D₂ receptor 2 and its downstream effects on the pathophysiology of asthma

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Abstract

Current research suggests that the prostaglandin D₂ (PGD₂) receptor 2 (DP₂) is a principal regulator in the pathophysiology of asthma, because it stimulates and amplifies the inflammatory response in this condition. The DP₂ receptor can be activated by both allergic and nonallergic stimuli, leading to several pro-inflammatory events, including eosinophil activation and migration, release of the type 2 cytokines interleukin (IL)-4, IL-5 and IL-13 from T helper 2 (Th2) cells and innate lymphoid cells type 2 (ILCs), and increased airway smooth muscle mass via recruitment of mesenchymal progenitors to the airway smooth muscle bundle. Activation of the DP₂ receptor pathway has potential downstream effects on asthma pathophysiology, including on airway epithelial cells, mucus hypersecretion, and airway remodelling, and consequently might impact asthma symptoms and exacerbations. Given the broad distribution of DP₂ receptors on immune and structural cells involved in asthma, this receptor is being explored as a novel therapeutic target.

KEYWORDS

asthma, eosinophil, prostaglandin D₂ receptor 2, T helper type 2 cell, type 2 innate lymphoid cell

1 | INTRODUCTION

Asthma is a highly prevalent respiratory condition affecting 358 million people globally,¹ characterized by respiratory symptoms (wheeze, shortness of breath, chest tightness and/or cough) and variable expiratory airflow limitation.² Asthma is usually associated with airway inflammation and airway hyper-responsiveness, resulting in bronchoconstriction upon exposure to specific allergens or nonspecific irritants. Before treatment, most patients with asthma present with chronic inflammation affecting all airways, including the upper respiratory tract and nose, with the medium-sized bronchi being most affected.³

The structural changes (airway remodelling) that take place in the airways of people with asthma include many deleterious processes, for example epithelial damage, goblet cell hyperplasia with mucus hypersecretion, thickening of the basement membrane due to subepithelial fibrosis, increased airway smooth muscle (ASM) mass and increased vascularization in airway walls.³

Two broad key asthma endotypes have been identified, categorized by the degree of T helper type 2 (Th2) cell inflammation present; these are known as “T2-high” and “T2-low” asthma.⁴ “T2-high” asthma is eosinophilic, while “T2-low” asthma consists of a subgroup of patients whose asthma is persistently noneosinophilic, either predominantly neutrophilic or paucigranulocytic.⁵⁻⁷

While asthma is known to the general public as an allergic disease, this may only be true in up to half of cases in adulthood, with the remainder being of nonallergic origin. This underscores the importance of both the allergen and non-allergen-dependent pathways in its pathogenesis.^{8,9} Furthermore, it is now becoming clear that both arms (allergen-dependent and non-allergen-dependent) are involved in ‘T2-high’ (eosinophilic) asthma.⁸ The non-allergen-dependent (innate) pathway is activated by infectious, chemical or physical stimuli acting on the epithelium,⁸ releasing the cytokines interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP) which in turn activate type-2 innate lymphoid cells (ILC2).¹⁰ The

allergen-dependent pathway is induced after sensitization by allergens, resulting in stimulation of antigen-presenting dendritic cells and activation of CD4⁺ Th2 cells.¹¹ Interestingly, TSLP plays a role in allergic sensitization and thus is involved in both allergic- and non-allergic-mediated T2-high asthma.

Evidence is accumulating for a key role for the prostaglandin D₂ (PGD₂) receptor 2 (DP₂) pathway in the pathophysiology of asthma. The DP₂ receptor, one of three PGD₂ receptors, PGD₂ receptor 1, DP₂ and the thromboxane receptor (TP), is a G-protein-coupled receptor (GPCR), previously identified as 'chemoattractant receptor-homologous molecule expressed on Th2 cells' (CRTh2).¹²⁻¹⁴ However, the DP₂ receptor is not only expressed on Th2 cells, but also on many other hematopoietic and structural cells with key roles in asthma pathogenesis, including ILC2, eosinophils, basophils, mast cells, epithelial cells and airway smooth muscle cells. This has led to significant interest in the therapeutic potential of blockage of the DP₂ receptor pathway.¹⁵⁻²² Here we review the impact of DP₂ receptor pathway activation, and the resulting downstream effects on asthma pathogenesis.^{22,23}

2 | PROSTAGLANDINS

Prostaglandins modulate several physiological systems, as well as being involved in a wide range of disease states. They are synthesized sequentially from arachidonic acid by cyclooxygenase-1 and cyclooxygenase-2 and prostaglandin synthase enzymes.²⁴ PGD₂ is synthesized by prostaglandin D synthase enzymes (PGDS).²⁵ Altered levels of hematopoietic PGDS (H-PGDS) may have a role in the pathophysiology of asthma.²⁶

PGD₂ mediates a number of physiological effects in a range of tissues and organs, including inhibition of platelet aggregation,²⁷ and sleep induction.²⁴ PGD₂ is a powerful bronchoconstrictor, in people with and without asthma^{28,29} and induces vasodilation.³⁰ Conversely, PGD₂ can have muscle relaxant and vasoconstrictive properties in other tissues.²⁷ In the airways, PGD₂ also induces mucus secretion,³¹ as well as being an inflammatory mediator.²⁴

3 | DP₂ RECEPTOR PATHWAY ACTIVATION

DP₁, DP₂ and TP receptors mediate the biological effects of PGD₂ (Table 1). All three are rhodopsin-like seven-transmembrane-spanning GPCRs. The DP₁ receptor mediates vasodilatory effects of PGD₂³² and has both inflammatory and anti-inflammatory properties.²⁴ The TP receptor mediates platelet aggregation and vascular and airway smooth muscle constriction.^{24,33} The DP₂ receptor is structurally distinct from DP₁ and TP. The DP₂ receptor is a chemokine receptor, belonging to the chemoattractant receptor branch of the GPCRs.³⁴ As well as PGD₂, several PGD₂-derived metabolites also bind to and activate the DP₂ receptor, including 13,14-dihydro-15-keto-PGD₂, Δ^{12} PGD₂, Δ^{12} PGJ₂, 15-deoxy- $\Delta^{12,14}$ PGD₂, 15-deoxy^{12,14}PGJ₂ and 9 α 11 β PGF₂, suggesting a

TABLE 1 Receptors mediating the biological effects of prostaglandin D₂. The receptors are classified according to the prostanoilid ligand that each binds with greatest affinity

Receptor	Receptor type	Branch	Ligands	Cell/tissue location	Biological role
DP ₁	Rhodopsin-like 7-transmembrane-spanning GPCR	Prostanoid receptor	PGD ₂	Bronchial epithelium ³⁴ Dendritic cells ³⁴	Mediates the vascular effects of PGD ₂ ³² Pro-inflammatory and anti-inflammatory properties ³⁴
DP ₂	Rhodopsin-like 7-transmembrane-spanning GPCR	Chemoattractant receptor	PGD ₂ 13,14-dihydro-15-keto-PGD ₂ , Δ^{12} PGD ₂ , Δ^{12} PGJ ₂ , 15-deoxy- $\Delta^{12,14}$ PGD ₂ , 15-deoxy ^{12,14} PGJ ₂ , 9 α 11 β PGF ₂	CD8 ⁺ T2 cells, Th2 cells, ³⁵ eosinophils, basophils, ³⁶ ILC2s, ³⁷ monocytes ³⁸ mast cells ³⁹ epithelial cells ⁴⁰ airway smooth muscle cells ⁴²	Activation of eosinophils, mast cells, Th2 cells and ILC2s in inflammation. ^{43,47,48,58} Epithelial repair and airway smooth muscle migration ^{40,42}
TP (TP α and TP β isoforms)	Rhodopsin-like 7-transmembrane-spanning GPCR	Prostanoid receptor	TXA ₂ PGD ₂	Platelets, placenta, vascular smooth muscle, brain, small intestine, thymus ²⁴	Vascular and airway smooth muscle constriction ³³ Mediates platelet shape change and aggregation ²⁴

Abbreviations: GPCR: G-protein-coupled receptors; ILC2: innate lymphoid cells type 2; PG: prostaglandin; PGD₂: prostaglandin D₂; PGJ₂: prostaglandin J₂; PGF₂: prostaglandin F₂; DP₁: prostaglandin D₂ receptor 1; DP₂: prostaglandin D₂ receptor 2; Th2: T helper 2; TP: thromboxane receptor; TXA₂: thromboxane A₂.

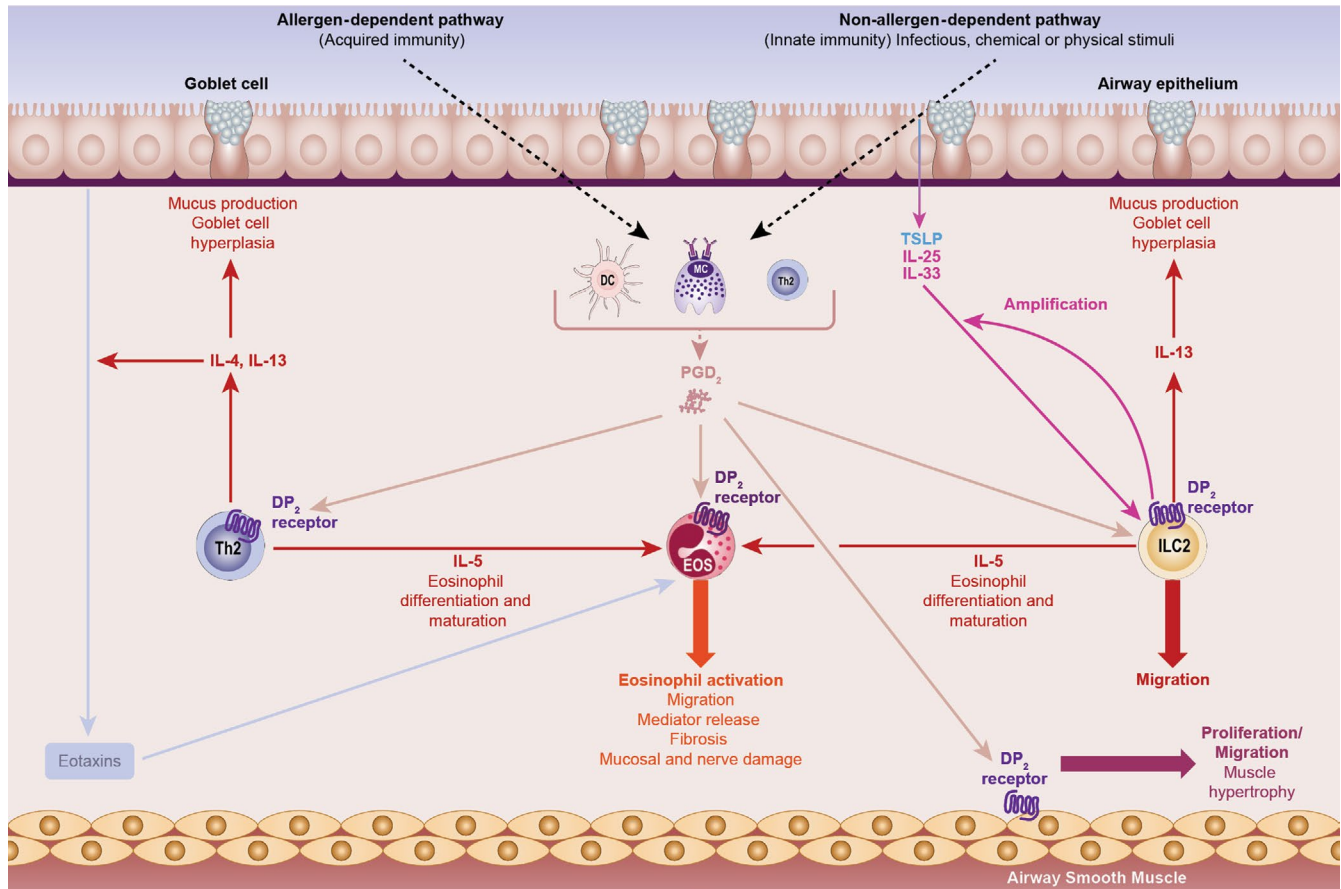


FIGURE 1 The DP₂ receptor pathway and its downstream effects (not to scale). The non-allergen-dependent (innate immunity) pathway is activated by infectious, chemical or physical stimuli causing the epithelium to release the cytokines interleukin (IL)-25, IL-33 and thymic stromal lymphopoietin (TSLP).¹⁰ In allergic (i.e. allergen-sensitized) subjects, exposure to allergens induces the allergen-dependent (adaptive immunity) pathway, stimulating antigen-presenting dendritic cells and activating T helper 2 (Th2) cells.¹¹ Prostaglandin D₂ (PGD₂) is released from antigen-presenting cells, mast cells and to a lesser extent from Th2 cells.^{44–46} Binding of PGD₂ causing DP₂ receptor activation on Th2 cells and ILC2s releases cytokines with further downstream effects on airway epithelial cells. DP₂ receptor activation also leads to ILC2 migration and to amplification of type 2 cytokine production induced by IL-25 or IL-33 from ILC2s,⁴⁸ while binding to airway smooth muscle cells affects cell proliferation and migration, contributing to the increased amount of airway smooth muscle.^{42,47,48} Furthermore, binding of the DP₂ receptor by PGD₂ activates eosinophils indirectly through two pathways: one mediated by IL-5 and a second via eotaxins, mediated by IL-4 and IL-13.^{58,59} Direct eosinophil activation by PGD₂ via DP₂ induces migration of eosinophils, eosinophil shape change, chemokinesis and degranulation.^{12,13} IL: interleukin; TSLP: thymic stromal lymphopoietin; Th2; T helper 2 cells; PGD₂: prostaglandin D₂; ILC2: innate lymphoid cells type 2; DP₂: prostaglandin D₂ receptor 2

broader and more diverse range of ligands for the DP₂ receptor compared with DP₁.³³

The DP₂ receptor shows broad cellular and tissue expression.³³ With regard to inflammatory cells, DP₂ receptors are expressed on the cell surface of CD8⁺ T2 cells, Th2 cells,³⁵ eosinophils and basophils,³⁶ ILC2s³⁷ and monocytes.³⁸ Meanwhile, human mast cells express DP₂ receptors intracellularly.³⁹ The DP₂ receptor is also expressed on structural cells including airway epithelial cells, along with inflammatory cells within the epithelial submucosa, including CD3⁺ T cells and eosinophils.⁴⁰ Patients with asthma have an increased number of T cells expressing the DP₂ receptor within the submucosal compartment compared with those without asthma; accumulation of these T cells is closely associated with severity of asthma.⁴⁰ This may be a result of the known effect of the DP₂ receptor pathway on apoptosis of Th2

cells.⁴¹ Additionally, ASM cells from patients with asthma express the DP₂ receptor.⁴²

PGD₂ binds to the DP₂ receptor as part of both the allergen-dependent (acquired) and non-allergen-dependent (innate) immune response (Figure 1). In subjects with asthma, PGD₂ is released primarily from mast cells,⁴³ but is also released in lower concentrations from Th2 cells⁴⁴ and antigen-presenting dendritic cells,⁴⁵ following stimulation of either the allergen-dependent or the non-allergen-dependent pathways.⁴⁶ Binding of the DP₂ receptor by PGD₂ on Th2 cells leads to the release of type 2 cytokines, notably IL-4, IL-5 and IL-13.⁴⁷ The DP₂ receptor also mediates the ILC2 response to PGD₂, resulting in the migration of these cells to sites of inflammation and release of the same cytokines (IL-5, and IL-13 and to a lesser extent, IL-4).⁴⁸ Release of IL-13 from ILC2s in response to DP₂ receptor activation is upregulated in the presence of IL-25

and IL-33 released from the airway epithelium.⁴⁹ In addition, DP₂ receptor activation in combination with either IL-25 or IL-33 has a synergistic effect on cytokine production from ILC2s (Figure 1).⁴⁸ Recent research shows that autocrine control, within ILC2s, may be a mechanism by which DP₂ receptor activation has a local immunomodulatory role beyond the major PGD₂ release from mast cells.⁵⁰

Subsequent to their release, IL-4, IL-5 and IL-13 have numerous effects on the cells and tissues of the inflammatory pathways in asthma. Meanwhile, these inflammatory cytokines are involved in several other inflammatory conditions beyond asthma. IL-4 and IL-13 have an important role in the pathogenesis of chronic sinusitis with nasal polyps and atopic dermatitis.⁵¹ IL-5 is implicated in allergic rhinitis,⁵² atopic dermatitis,⁵³ idiopathic pulmonary fibrosis, Churg-Strauss syndrome (eosinophilic granulomatosis and polyangiitis),⁵⁴ eosinophilic oesophagitis⁵⁵ and hypereosinophilic syndrome.⁵⁶

Eosinophils are important inflammatory effector cells in type 2 asthma. They are mainly synthesized in the bone marrow from eosinophil progenitor cells, in response to allergic stimuli in the airways.⁵⁷ These induced eosinophils (iEos)⁸ are released into the blood stream from the bone marrow, mediated mostly by IL-5.⁵⁷ Eosinophils are activated by binding of the DP₂ receptor by PGD₂,⁵⁸ through two pathways: one mediated by IL-5, and a second via eotaxins driven by IL-4 and IL-13⁵⁹ (Figure 1). Eosinophil activation induces migration of eosinophils,¹³ shape change, chemokinesis and degranulation.¹² The migration of eosinophils from the blood stream to the bronchial mucosa is mediated by endothelial adhesion molecules such as vascular cell adhesion molecule-1 (VCAM-1) and P selectin, whose expression is facilitated by IL-4 interacting with tumour necrosis factor (TNF)- α .^{60,61}

Initial study in mice indicates that a second group of eosinophils, known as resident eosinophils (rEos), may be present in the lung parenchyma,⁵⁷ potentially part of a wider group of homeostatic eosinophils resident in other tissues.⁶² These findings need to be confirmed by further research, including in humans.

4 | THE IMPORTANCE OF THE DP₂ RECEPTOR PATHWAY

The DP₂ receptor pathway amplifies the inflammatory reaction, by enhancing and increasing the immune response. This amplification is illustrated in studies of PGD₂ and other inflammatory mediators, including a second group of arachidonic acid derivatives, cysteinyl leukotrienes (cysLTs), in Th2 cells and ILC2s.^{48,63,64}

In Th2 cells, cysLTs acting alone are weak inducers of the type 2 cytokine IL-13, compared with induction via the DP₂ receptor pathway with PGD₂. However, the cysLT leukotriene E₄ (LTE₄) acting together with PGD₂ results in an amplified response in induction of all three cytokines, IL-4, IL-5 and IL-13.⁶⁴

Stimulation of the DP₂ receptor pathway with PGD₂ has a 4.5 times greater effect than IL-33 on ILC2 migration, although there is no additive effect of these mediators in combination.⁴⁸ Similarly, in terms of cytokine production, PGD₂ induces the production of IL-4, IL-5 and IL-13 from ILC2 more strongly than IL-25 and IL-33.

Importantly, PGD₂ has a synergistic effect on type 2 cytokine production induced by IL-25 or IL-33 (Figure 1).

The combination of PGD₂ and LTE₄ has an additive effect on ILC2 migration, in contrast to when LTE₄ is combined with either of the cytokines IL-25, IL-33 or TSLP, where no additive effect is seen.⁶³ Furthermore, PGD₂ and LTE₄ in combination have a synergistic effect on the production of some ILC2-derived cytokines (IL-4, IL-8, granulocyte-macrophage colony-stimulating factor, macrophage-stimulating factor and amphiregulin) and an additive effect on other type 2 cytokines (IL-5 and IL-13). The accumulation of evidence from these *in vitro* studies suggests a central role for the DP₂ receptor pathway, not only in the stimulation of the inflammatory response, but also in the amplification of the response to other inflammatory mediators, including cysLTs, IL-25 and IL-33.

5 | DOWNSTREAM EFFECTS OF DP₂ RECEPTOR ACTIVATION AND CLINICAL CONSEQUENCES

The central role of DP₂ receptor activation in the inflammatory cascade leads to numerous downstream effects on cells and tissues involved in the pathophysiology of asthma with biological consequences, including effects on airway epithelial cells, airway remodelling through subepithelial fibrosis, effects on ASM and mucus hypersecretion (Figure 1). The pivotal role of DP₂ receptor pathway activation suggests a role in asthma exacerbations.⁶⁵⁻⁶⁷

5.1 | Airway epithelial cells

Airway epithelial cells express multiple inflammatory proteins and release cytokines, chemokines and lipid mediators in response to various stimuli.³ Biopsy specimens show that people with asthma have reduced numbers of DP₂ receptor-positive epithelial cells compared with those without asthma and that this reduction is associated with the severity of asthma.⁴⁰ A potential effect of stimulation of the DP₂ receptor pathway on the airway epithelium is through the recruitment and activation of eosinophils, which causes damage to the airway mucosa and associated nerves through release of granule-associated basic proteins, and also through the release of reactive oxygen species, which cause injury to mucosal cells.⁶⁸

Mucus hypersecretion in asthma occurs as a result of increased numbers of goblet cells in the airway epithelium and increased size of the submucosal glands,³ which are mediated by elements of the DP₂ receptor pathway. Mucus production is stimulated by IL-13 (and/or IL-4) secreted from Th2 cells and ILC2, either by acting directly on mucus-secreting goblet cells or indirectly through mediators activated in the lung.⁶⁹ Furthermore, IL-13 released from Th2 and ILC2 induces goblet cell hyperplasia.⁷⁰ In a mouse model of chronic airway inflammation, a DP₂ receptor antagonist caused a reduction in goblet cell hyperplasia and mucus production, as well as inhibiting airway eosinophilia.⁷¹

5.2 | Airway remodelling

Airway remodelling in asthma results in persistent airflow limitation, a decrease in lung function, and airway hyper-responsiveness.⁷² The structural changes involved in airway remodelling include subepithelial fibrosis (increased collagen content of the subepithelial tissue just beneath the basement membrane), increased ASM mass and increased blood vessels in airway walls.³

Fibrosis in the airway tissue may be a downstream effect of eosinophil proliferation. Specifically, transforming growth factor (TGF)- β derived from activated eosinophils might be involved in fibrosis of the airways of people with asthma.⁷³ Further evidence for the role of eosinophils in airway remodelling comes from a study in which treatment with an anti-IL-5 antibody decreased the number of eosinophils in the airways and reduced airway remodelling in mild-to-moderate asthma, represented by reduced deposition of eosinophil-derived extracellular matrix proteins and decreased numbers of myofibroblasts.^{68,74} However, the clinical implications of this are yet to be confirmed.

Airway smooth muscle in people with asthma shows both proliferation (hyperplasia) and growth (hypertrophy).³ Infiltration of the ASM by mast cells releasing PGD₂ has subsequent effects on the inflammatory cascade through binding of the DP₂ receptor on eosinophils and ASM cells. In a mouse model of chronic asthma, eosinophil-deficient mice had significantly less ASM hyperplasia than wild-type mice, which was associated with decreased TGF- β -positive cells, mostly eosinophils.⁵⁵

In addition to the effect of PGD₂ on eosinophils, DP₂ receptor activation on the surface of ASM cells is likely to be involved in the promotion of ASM cell migration and to contribute to increased ASM mass in asthma.⁴² Moreover, DP₂ receptor antagonism reduces ASM cell migration and filamentous actin (microfilament) content in ASM cells.⁴² This may also be linked to airway hyper-responsiveness, which involves excessive contraction of ASM cells, uncoupling of airway contraction, thickening of the airway wall and effects on sensory nerves.³

In summary, the clinical implications of DP₂ receptor pathway activation are likely to be related to the resulting downstream effects on the airways. These include effects on inflammatory cells and direct effects of DP₂ receptor activation on structural cells such as epithelial cells and ASM cells. Eosinophil degranulation causes damage to the airway mucosa and nerves, and affects airway remodelling through effects on fibrosis, as well as influencing ASM cell hyperplasia. ASM cells are also affected directly by DP₂ receptor activation, resulting in cell migration and increased ASM mass. Mucus hypersecretion is induced by DP₂ receptor pathway activation through IL-4 and IL-13 released from Th2 and ILC2, as well as the induction of goblet cell hyperplasia through IL-13.

DP₂ receptor pathway activation may also influence asthma exacerbations. Severe exacerbations are associated with upper respiratory tract viral infections and exposure to allergens,⁶⁶ or both synergistically.⁶⁵ Activation of the DP₂ receptor pathway is involved in both the allergen-dependent and non-allergen-dependent immune

pathways, suggesting that activation of this pathway is likely to have an effect on asthma exacerbations. For example, the DP₂ receptor pathway is induced by viral RNA resulting in an increase in eosinophil accumulation; therefore, the allergic response may be amplified through the presence of viral RNA.⁶⁷

6 | EFFECTS OF DP₂ RECEPTOR BLOCKAGE ON ASTHMA

Limitations of the current treatment options for asthma have led to the investigation of the potential of DP₂ receptor antagonism as a therapeutic option. Given the multiple downstream effects discussed above, the DP₂ receptor pathway appears to be a desirable target for investigation. There are currently several drugs in development targeting this pathway with varying degrees of success.^{22,23}

A study of 79 patients with inadequately controlled asthma with the dual antagonist of human D-prostanoid and DP₂ receptors, AMG 853, showed no effect on asthma control or on any of the secondary endpoints.⁷⁵

The DP₂ receptor antagonist OC000459 was investigated in a study of 132 steroid-free patients with moderate persistent asthma. This study met its primary endpoint of a significant difference in FEV₁ for the per protocol population, but not for the full analysis population. Quality of life and night-time symptoms improved significantly for both populations, but not sputum eosinophil counts.⁷⁶ In a second study of 16 patients, OC000459 showed significant reduction in the late asthma response, but not the early asthma response compared with placebo. A significant reduction in sputum eosinophil counts and difference in eosinophil shape change was also seen compared with placebo.⁷⁷

Fevipirant, the most advanced of the DP₂ receptor antagonists in development, is an orally delivered, highly selective, reversible DP₂ receptor antagonist.⁷⁸ Pharmacological studies have shown that fevipirant is a competitive inhibitor of DP₂ receptor-mediated responses involved in asthma.⁷⁹ Furthermore, fevipirant has a short time to peak plasma concentration, has a long half-life, does not interact with food and is excreted through multiple pathways reducing the risk of drug-drug interactions and pharmacogenetic or ethnic variability.^{78,80}

In Phase II clinical trials, fevipirant had a positive effect on lung function in patients with asthma, as well as improving control and quality of life.^{15,16,18} In a study of 61 patients with persistent eosinophilic asthma, those treated with fevipirant had a 3.5 times greater reduction in eosinophilic airway inflammation (the primary outcome) than those treated with placebo.¹⁸ There is preliminary evidence to suggest that fevipirant has a healing effect on the airway epithelium,¹⁸ as well as reducing ASM mass in people with asthma.⁴² All studies to date show a favourable safety and tolerability profile for fevipirant.

A worldwide Phase III programme of fevipirant is currently under way which may help to further our understanding of the

benefits of DP₂ receptor antagonism on clinical outcomes in patients with asthma.

The effects of these drugs on the DP₂ receptor pathway may not be limited to asthma. DP₂ receptor expression is seen in mast cells and fibroblasts in nasal polyp tissue, on T cells in the nasal mucosa of patients with allergic rhinitis and in Th2 cells in patients with atopic dermatitis, indicating that there may also be potential for positive effects of DP₂ receptor antagonism in other organs and conditions.^{39,81,82} Data also suggest a potential role for antagonism of the DP₂ receptor pathway in reducing eosinophilic inflammation in patients with COPD, but not on clinical outcomes to date.⁸³ Further investigation is required to determine potential clinical effect in COPD.

7 | CONCLUSION

Activation of the DP₂ receptor pathway through both the allergen-dependent and non-allergen-dependent pathways elicits multiple downstream effects. These are mediated by the release of important inflammatory mediators including the type 2 cytokines IL-4, IL-5 and IL-13, as well as the activation of eosinophils, one of the key effector cells in type 2 asthma that are associated with an increased risk of exacerbations. Activation of the DP₂ receptor may have direct effects on the airway epithelium and on increasing ASM mass. The role of DP₂ receptor binding by PGD₂ as both an inducer and amplifier of inflammatory pathways is becoming increasingly clear. Activation of the pathway has numerous downstream effects and biological consequences, including on airway epithelium and smooth muscle, airway remodelling, mucus hypersecretion and possibly exacerbations. The broad range of expression of the DP₂ receptor on hematopoietic and structural cells involved in the pathogenesis of asthma and the encouraging initial clinical trials of the DP₂ receptor antagonist, fevipiprant, support the view that DP₂ receptor antagonism is an attractive therapeutic target for asthma.

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Professor Brightling reports grants and personal fees from Astra Zeneca/ MedImmune, grants and personal fees from Chiesi, grants and personal fees from Glaxo Smith Kline, grants and personal fees from Novartis, personal fees from Sanofi/ Regeneron, personal fees from Teva, grants and personal fees from Mologics, grants and personal fees from 4DPharma, grants and personal fees from Roche/Genentech, grants and personal fees from Gossamer, outside the submitted work. Professor Brusselle reports personal fees from Astra Zeneca, personal

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