International Journal of Biochemistry and Cell Biology 106 (2019) 68–73

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Molecules in focus

The regulatory role of semaphorin 3E in allergic asthma

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ARTICLE INFO

Keywords:
Airway hyperresponsiveness
Airway remodeling
Asthma
Inflammation
PlexinD1
Sema3E

ABSTRACT

Semaphorins were originally discovered as essential mediators involved in regulation of axonal growth during development of the nervous system. Ubiquitously expressed on various organs, they control several cellular functions by regulating essential signaling pathways. Among them, semaphorin3E binds plexinD1 as the primary receptor and mediates regulatory effects on cell migration, proliferation, and angiogenesis considered major physiological and pathological features in health and disease. Recent *in vitro* and *in vivo* experimental evidence demonstrate a key regulator role of semaphorin3E on airway inflammation, hyperresponsivenss and remodeling in allergic asthma. Herein, we aim to provide a broad overview of the biology of semaphorin family and review the recently discovered regulatory role of semaphorin3E in modulating immune cells and structural cells function in the airways. These findings support the concept of semaphorin3E/plexinD1 axis as a therapeutic target in allergic asthma.

1. Introduction

Asthma is the most common chronic lung disease affecting 300 million people worldwide with at least 250,000 deaths annually and a substantial socioeconomic burden (Croisant, 2014). It is highly prevalent in affluent societies, wherein approximately 1 in 10 children and 1 in 12 adults are diagnosed with asthma (Lambrecht and Hammad, 2015). Also, there is a remarkable increase of asthma along with urbanization in developing countries (Croisant, 2014).

Asthma is defined as a chronic inflammatory disease of the conducting airways characterized by bronchial hyper-reactivity, airway wall remodeling, and airway narrowing (Hamid and Tulic, 2009). It is generally characterized by a Th2/Th17-biased response associated with an enhanced recruitment and accumulation of granulocytes into the airways. Moreover, asthmatic airways undergo massive structural alterations manifested by airway smooth muscle (ASM) hyperplasia/hypertrophy, sub-epithelial fibrosis, mucus overproduction, and increased angiogenesis (Hamid and Tulic, 2009).

Despite effective treatment in most of patients, 5–10% of asthmatic patients are refractory to inhaled corticosteroid treatment and therefore require oral administration of corticosteroid and hospitalization (Chung, 2013), thus highlighting the need for better understanding of factors regulating pathological features of asthma.

Recent studies have implicated semaphorins and plexins in many airway diseases including acute lung injury, allergic asthma, and pulmonary fibrosis (Movassagh et al., 2018). These effects are mediated via shaping immune system (Choi et al., 2008) regulation of cell trafficking, and cell to cell interactions (Takamatsu et al., 2010; Morote-Garcia et al., 2012; Choi et al., 2014).

Semaphorins were discovered as axon guidance cues determining the migration pattern of neurons via exerting repulsing or attracting signals during development (Kolodkin et al., 1992). However, it has been shown that expression and function of semaphorins is not restricted to the nervous system. In fact, semaphorins emerge as a large family of versatile mediators present in different organs. They are categorized into eight classes in which class 1 and 2 are specifically found in invertebrates and class V includes the viral ones. Class 3–7 are found only in vertebrates where the secreted semaphorins belong to class 3. Class 4–6 are transmembrane while class 7 members are glycosylphosphatidylinositol (GPI)-linked (Movassagh et al., 2018). Although plexins are the main receptors conveying semaphorin signaling, other proteins could be involved in determination of semaphorin effects as co-receptors or binding partners. In addition, some receptors are shared by different semaphorins, e.g. PlexinD1 can bind semaphorin3E (Sema3E) and Sema4A (Meyer et al., 2016; Pascoe et al., 2015). It should be emphasized that expression, function and the mechanism of action of each semaphorin is highly dependent on the specific context such as cell type, organ/system, and the physiological versus pathological

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https://doi.org/10.1016/j.biocel.2018.11.006
Received 4 July 2018; Received in revised form 6 November 2018; Accepted 12 November 2018
Available online 15 November 2018

Table 1
Semaphorin classification and their receptors.

Class	Member	Receptor	(Co)receptor	Reference
1	Sema1a, Sema1b	PlexinA	RTK	(Winberg et al., 1998, 2001)
2	Sema2a, Sema2b	PlexinA-B	Sema1a	(Ayoob et al., 2006; Bates and Whitington, 2007; Hernandez-Fleming et al., 2017; Roh et al., 2016; Wu et al., 2011)
3	Sema3 A-Sema3H	PlexinA1-A4, PlexinD1	Nrp1-2, Chondroitin Sulfate, RTK, VEGFR2, Integrins, L1CAM, NRCAM	(Winberg et al., 1998; Bellon et al., 2010; Bouvree et al., 2012; Brown et al., 2001; Casazza et al., 2010; Castellani et al., 2002; Falk et al., 2005; Franken et al., 2003; Rohm et al., 2000; Taniguchi et al., 2005; Zachary, 2011)
4	Sema4A-Sema4G	PlexinB1-B3, PlexinD1	CD72, CLCP1, ILT-4, NMDAR, RTK, Tim2	(Basile et al., 2005; Burkhardt et al., 2005; Conrotto et al., 2005; Ito et al., 2015; Kumanogoh et al., 2000; Le et al., 2015; Lu et al., 2018; Nagai et al., 2007; Toyofuku et al., 2007; Witherden et al., 2012)
5	Sema5 A-Sema5C	PlexinA3, PlexinB3	Heparan Sulfate, Chondroitin Sulfate, Met	(Artigiani et al., 2004; Kantor et al., 2004; Matsuoka et al., 2011; Saxena et al., 2018)
6	Sema6 A-Sema6E	PlexinA1-A2, PlexinA4	RTK, TREM2	(Katoh and Katoh, 2007; Suto et al., 2007; Takegahara et al., 2006)
7	Sema7 A	PlexinC1	α1β1 Integrin	(Carcea et al., 2014; Inoue et al., 2018)
V	SemaVA-SemaVB	PlexinC1	α1β1 Integrin	(Liu et al., 2010; Myster et al., 2015; Walzer et al., 2005)

CD: Cluster of Differentiation, CLCP1: CUB, LCCL-homology, coagulation factor V/VIII homology domains protein, ILT-4: Immunoglobulin-like transcript 4, L1CAM: Neural Cell Adhesion Molecule L1, Met: Hepatocyte Growth Factor Receptor, NRCAM, neuronal cell adhesion molecule, NMDAR: N-Methyl-D-Aspartate Receptor, Nrp: Neuropilin, RTK: Receptor Tyrosine Kinase, Sema: Semaphorin, Tim2: T-cell immunoglobulin and mucin domain-containing protein 2, TREM: Triggering Receptor Expressed on Myeloid cells, VEGFR2: Vascular Endothelial Growth Factor Receptor 2.

condition. Classification of semaphorin family members and their receptors have been summarized in Table 1.

In this review, we describe the recent advances incriminating Sema3E's role in allergic asthma. We will highlight our novel findings showing a regulating role of this pathway in airway inflammation, airway hyperresponsiveness (AHR) and remodelling.

2. Semaphorin3E

Sema3E is one of the vertebrate secreted class 3 semaphorins. Sema3E plays critical roles in axon path finding and vascular patterning during development. Encoded by the *SEMA3E* gene located on the 7q21.11 chromosomal region in the human genome, full length Sema3E protein contains 775 amino acids (89.2 kDa) (Anon, 2018a). RNA-Seq analysis on normal human tissues has revealed that Sema3E is highly expressed in the brain, urinary bladder, gall bladder, prostate, digestive tract, and lung (Anon, 2018b). Pneumocytes, bronchial epithelial cells, endothelial cells, and macrophages are the main sources of Sema3E expression in the lung (Anon, 2018c). However, Sema3E may undergo differential expression and post-translational modification under pathological conditions. For instance, the full length Sema3E protein has been shown to be cleaved by furin-like enzymes in tumor cells which leads to production of a pro-metastatic invasive isoform (p61) (Christensen et al., 2005).

Besides the non-redundant role of Sema3E in nervous and cardiovascular systems (Gay et al., 2011), it is implicated in negative regulation of the immune system. Sema3E modulates the migration of $CD4^+CD8^+$ T cells in murine thymus via inhibition of CCL25-CCR9 chemokine signaling, which is a critical inducer of thymocyte migration from the cortex into the medulla (Choi et al., 2008), by a dynamic control of β1 integrin adhesion (Choi et al., 2014). In the context of adipose tissue inflammation, Sema3E deficiency is associated with a significant reduction of macrophages and production of pro-inflammatory cytokines without any effect on vascularity in adipose tissue (Shimizu et al., 2013), thus highlighting the context- dependent manner of Sema3E function.

3. Sema3E holoreceptor complex and signaling

PlexinD1, the direct binding partner of Sema3E, is dynamically expressed in many embryonic and adult tissues (Gay et al., 2011; Movassagh et al., 2014). PlexinD1 expression is essential for cardiovascular development and mice with genetic deletion of its gene succumb two days postnatal due to cardiovascular defects (Gay et al., 2011). *Sema3e* deficient mice, however, are viable after birth and developmental cardiovascular defects are recapitulated, suggestive of additional PlexinD1 ligand(s) (17). According to RNA-Seq analysis, *PLXND1* is expressed in various tissues such as lung, immune system, placenta, fat tissue, endothelium, spleen, and brain (Anon, 2018d). Human *PLXND1* is located on chromosome 3 (3q22.1) which encodes a 1925 amino acid (212.07 kDa) protein (Anon, 2018e).

Sema3E is recognized as the canonical ligand for PlexinD1, and it does not bind to other plexins which is an exception to the typical pattern of class 3 semaphorin (Gay et al., 2011). In the endothelial cell, Sema3E-PlexinD1 binding is a Neuropilin (Nrp)-independent process which leads to PlexinD1-mediated repulsion (Gay et al., 2011). However, in neuronal cells, Nrp1 and VEGFR2 are the only known co-receptors which could be associated with PlexinD1. In neuronal compartment, gating of Sema3E by these co-receptors is functionally crucial because it switches the repulsive effect of Sema3E-PlexinD1 signaling into an attractive outcome. In fact, Nrp1 expression determines the functional pattern of Sema3E in neuronal cells in axon guidance (Chauvet et al., 2007). As another layer of complexity, the chemo-attraction function of Sema3E is mediated by "PlexinD1/Nrp1/VEGFR2 ternary complex" in which PlexinD1 functions as the ligand-binding partner and VEGFR2 as the signal transducing element; this scenario

does not occur in endothelial cells (Gu et al., 2005; Sakurai et al., 2010).

The intracellular portion of PlexinD1 contains a "Sex and Plexins" SP domain that harbors two highly conserved C1 and C2 regions (Tamagnone et al., 1999) named RasGAP domain because of sequence similarity to a group of Guanosine triphosphatase (GTPase)-Activating *P*roteins (GAPs) and specificity for the R-Ras family of small GTPases (Pasterkamp, 2005; Goel and Mercurio, 2013). The GAP activity of PlexinD1 retracts integrin-mediated cell adhesion to the extracellular matrix (ECM) and downregulates MAPK and PI3K signaling, considered key pathways involved in cell survival, proliferation and migration. Therefore, interaction of Sema3E with ectodomain of PlexinD1 potentially prime the receptor by inducing an intracellular conformational change. Consequently, activated small GTPases (e.g. Rac1, Cdc42 and Rnd), bind to the "Rho GTPase binding domain" or RBD, which leads to disruption of the inhibitory association between the C1 and C2 regions and activation of the GAP (Gay et al., 2011).

Furthermore, in endothelial cells Sema3E treatment decreases the phosphorylation of focal adhesion kinase (FAK), a critical molecule that regulates the turnover of integrin-containing focal adhesions. Rnd1, 2 and 3 have been shown to interact physically with the intracellular domain of PlexinD1 through RBD. These GTPases are required for the activation of in vivo RasGAP activity of PlexinD1. Therefore, they could be considered the potential signaling components mediating the early signaling events upon Sema3E-PlexinD1 interaction regardless of the functional repulsive versus attractive outcome.

Another possibility is that PlexinD1 antagonizes the R-Ras GTPase activity merely via sequestering these enzymes without catalytic intervention (Sakurai et al., 2010). Alteration in cytoskeletal and ECM compartments such as actin polymerization and integrin localization have been demonstrated to be the final targets of semaphorin signaling in various contexts. ADP-ribosylation factor 6 (Arf-6) is another small GTPase by which Sema3E-induced detachment of integrin from ECM is mediated in endothelial cells leading to inhibit angiogenesis (Sakurai et al., 2010). Finally, T-cell activation RhoGTPase activating protein (Tagap) has recently emerged as a specific mediator involved in thymocyte trafficking via direct interaction with the cytoplasmic domain of plexin-D1 (Duke-Cohan et al., 2018). However, the precise mechanism underlying Sema3E effects remains inadequately addressed (Table 2).

4. Sema3E and PlexinD1 expression in asthma

We have recently demonstrated that Sema3E is highly expressed in bronchial biopsies obtained from healthy subjects. Interestingly, along with disease progression from mild, to moderate, to severe forms, Sema3E immunoreactivity diminished with a significant difference between healthy and severe asthmatic subjects. In addition, the bronchoalveolar lavage fluid (BALF) level of Sema3E secretion is significantly reduced in severe allergic asthmatic patients compared to healthy subjects, and inversely correlated to forced expiratory volume in 1s. Along the same line, primary human bronchial epithelial cells isolated from severe asthmatics displayed a downregulation of Sema3E mRNA and protein levels (Movassagh et al., 2017a). In addition, surface expression of Sema3E high-affinity receptor, PlexinD1, is reduced in human ASM cells from allergic asthmatic patients (Movassagh et al., 2014) suggesting that expression of Sema3E-PlexinD1 regulatory axis is impaired in asthma.

In line with our findings in human is a signficant reduction of Sema3E expression in the mouse airways after either acute or chronic challenge with house dust mite (HDM) (Movassagh et al., 2017b, c). Collectively, our data from both human studies and *in vivo* models indicates that Sema3E expression is decreased in asthmatic conditions and suggests not only a crucial role of this chemorepellent in regulating asthmatic phenotype, but also suggests a role as a potential biomarker to stratify the severity of the disease. Accordingly, further studies are warranted to investigate whether Sema3E is differentially expressed in glucocorticoid-resistant versus sensitive asthmatic patients, and to assess Sema3E levels before and after therapy.

5. Sema3E as a regulator of airway remodeling

Airway remodeling is a key feature of asthma and plays an important role in disease progression (Hamid and Tulic, 2009). Structural changes in the asthmatic bronchial wall include epithelial shedding and goblet cell hyperplasia, sub-epithelial fibrosis, enhanced thickness of smooth muscle layer, and angiogenesis (Fajt and Wenzel, 2015).

We showed that Sema3E significantly reduces growth factor induced human ASM cell proliferation and migration (Fig. 1). This inhibitory effect of Sema3E was associated with suppression of F-actin polymerization, Rac1 GTPase activity, ERK1/2 and Akt signaling (Movassagh et al., 2014). In concert with these findings, *the in vivo* model of allergic asthma demonstrated that acute or chronic intranasal HDM exposure induces higher mucus overproduction and collagen deposition in the airways of Sema3E-deficient mice compared to the control littermates. Interestingly, enhanced overexpression of the genes involved in production of mucus and collagen (*Col3* and *Muc5a*) was observed in both naïve and upon HDM-challenged *Sema3e*$^{-/-}$ mice compared to WT littermates (Movassagh et al., 2017d). Conversely, treatment with exogenous Sema3E-Fc significantly reduced mucus overproduction and collagen deposition (Movassagh et al., 2017b) and airway angiogenesis (unpublished data) in HDM mouse model of asthma. Altogether, these findings support the notion that Sema3E could modulate airway remodeling (Fig. 1).

6. Sema3E as a major mediator in regulation of allergic airway inflammation and hyperresponsiveness

6.1. Sema3E/PlexinD1 axis and lung DC subsets

Dendritic cells (DCs) are the most potent antigen presenting cell found in the lung, mainly located in the conducting airways of the epithelium (van Helden and Lambrecht, 2013). Depending on their maturation and activation states, DCs acquire specific ability to effectively induce immunological tolerance or to stimulate functionally

Table 2
Summary of signaling components mediating Sema3E effects on various cell types.

Binding receptor	Co-receptors	Small GTPases	Key signaling pathways	Cytoskeleton	ECM
PlexinD1(6,23,79)	Nrp1 (22) VEGFR2 (47)	R-Ras (24) RhoA (28) Rac1 (19,37,80,81) Rap1 (82) Cdc42 (83) Rnd2 (84) Arf-6 (24) Tagap (28)	MAPK/ERK (19,85,86) PI3K/Akt (19,85) FAK (24,87)	F-actin (19,81)	b1-integrin (24)

Arf6: ADP-ribosylation factor 6 (Sakurai et al., 2010), Tagap: T-cell activation RhoGTPase activating protein (Duke-Cohan et al., 2018).

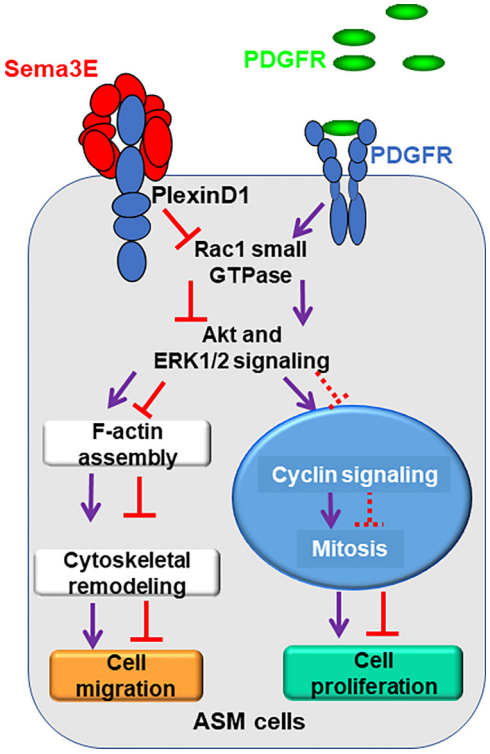

Fig. 1. Sema3E inhibitory effect on airway remodeling in allergic asthma. Binding of sema3E to PlexinD1 in ASM cells induced an array of events leading to inhibition of migration and proliferation, considered key factors in airway remodeling. Signaling cross-talk between PlexinD1 and PDGFR reduced growth factor-mediated proliferation and migration which was associated with decreased activation of Rac1, Akt and ERK1/2 as well as reduced assembly of actin filaments. F-actin: Filamentous actin, PDGF: Platelet-derived Growth Factor, PDGFR: Platelet-derived Growth Factor Receptor.

distinct T cell subsets (Th1, Th2, or Th17). In the lung, five lung DC subsets have been defined. Subsets include conventional DC (cDCs), monocyte-derived DCs (Mo-DCs) and plasmacytoid DC (pDCs) (van Helden and Lambrecht, 2013). The cDCs could be further divided into $CD11b^+$ and $CD11b^-$ where the latter express langerin and CD103 (Guilliams et al., 2014). $CD11b^+$CD103- cDC (cDC2) are endowed with the ability to prime effector CD4 Th cells in both homeostatic and asthmatic conditions whereas $CD103^+$ CD11b– cDC (cDC1) play a crucial role in the development of tolerogenic protective response upon allergen inhalation. cDCs and Mo-DCs contribute to HDM-induced airway inflammation, with lung $CD11b^+$ cDC2s being necessary and sufficient to induce allergic sensitization. DCs functional behaviour is dictated by many local factors including the presence of semaphorin 3 family members (Curreli et al., 2016).

Our recent data showed that Sema3E deficiency led to enhanced airway inflammation in mice which was heightened upon HDM allergen encounter (Movassagh et al., 2017b, c; Movassagh et al., 2017d). Specifically, *Sema3e* deficiency results in a high number of $CD11b^+$ cDC in the lung at baseline and upon HDM challenge, associated with enhanced eosinophilia and neutrophilia, AHR, and efficient Th2 and Th17 cytokine response (Movassagh et al., 2017b, d). Conversely, Sema3E treatment reduced significantly HDM-induced airway and lung neutrophilia and eosinophilia, and AHR (Movassagh et al., 2017b, e), events that were associated with a reduced number of lung $CD11b^+$ dendritic cells. These data suggest an important role of Sema3E mediated DC function in driving exaggerated neutrophilic and eosinophilic inflammatory response, considered one of the critical characteristics observed in severe asthma (Hamid and Tulic, 2009).

6.2. Role of Sema3E in regulation of neutrophil functions

Neutrophil-rich airway inflammation is a common feature of severe refractory asthma. Although allergic asthma is classically believed to be dominated by type 2 immune response, in almost half of the patients there is a low- or non- type 2 phenotype especially in severe forms (Fajt and Wenzel, 2015). A growing body of evidence illustrates that semaphorins and their receptors are involved in regulation of neutrophil functions. For instance, recent studies reveal a crucial role for Sema7 A-PlexinC1 axis in promoting neutrophil migration in acute lung injury and hypoxia models (Morote-Garcia et al., 2012; Granja et al., 2014). On the other hand, Sema3C therapeutic effect on lung injury is mediated by decreased lung neutrophil influx, and silencing its expression leads to a significant increase in neutrophil activity (Vadivel et al., 2013).We have addressed the regulatory role of Sema3E in the regulation of pulmonary neutrophil recruitment *in vivo* using HDM mouse model of allergic asthma. Intranasal HDM challenge induced an enhanced pulmonary accumulation of neutrophils in *Sema3e*$^{-/-}$ mice, whereas *in vivo* Sema3E treatment decreased HDM-induced neutrophil recruitment. Interestingly, increased pulmonary neutrophilia was observed in naïve *Sema3e*$^{-/-}$ mice suggesting a regulatory role of this pathway in maintaining pulmonary neutrophil homeostasis. Furthermore, human neutrophils showed a constitutive expression of Sema3E high-affinity receptor, PlexinD1; and Sema3E inhibited chemokine -induced migration via suppression of GTPase activity and F-actin assembly (Movassagh et al., 2017e).

7. Conclusion

Given its diverse roles in many biological processes, it is not surprising that Sema3E/PlexinD1 axis plays an important role in the key events modulating airway inflammation, remodeling, and AHR in allergic asthma (Fig. 2). Several unanswered questions warrant further investigation including which isoform of Sema3E is produced in asthmatic airways; and whether it correlates with disease severity or therapeutic outcomes. Future research should also evaluate the role of Sema3E in mouse models other than HDM, e.g. cockroach, to ascertain if its effect is independent of type of allergen. We still do not know the precise role of Sema3E in modulating: eosinophil function or migration; the expression of epithelial innate-derived cytokines (IL-25, IL-33 and TSLP); and epithelial-mesenchymal transition in asthmatic airways. Furthermore, considering the enhanced IgE production in *Sema3e* deficient mouse model (Movassagh et al., 2017d), studies on B cells can address whether Sema3E regulates IgE class switching. Also, the full range of molecular signaling mediated by Sema3E is still poorly understood and is likely to yield unexpected finding in the future. Taken together, Sema3E/PlexinD1 pathway provides a fascinating example that warrants more research to enhance our understanding of asthma pathogenesis.

Author contributions

H.M. contributed to literature review analysis and preparation of the manuscript. L.K. and L.S contributed to literature review analysis and preparation of the manuscript A.S.G. analyzed literature data and prepared the manuscript. All authors revised and approved the final version of the manuscript.

Competing interests

The authors have declared that no conflict of interest exists.

Acknowledgments

This work was supported by the Canadian Institutes of Health Research grant (MOP # 115115), National Sciences and Engineering

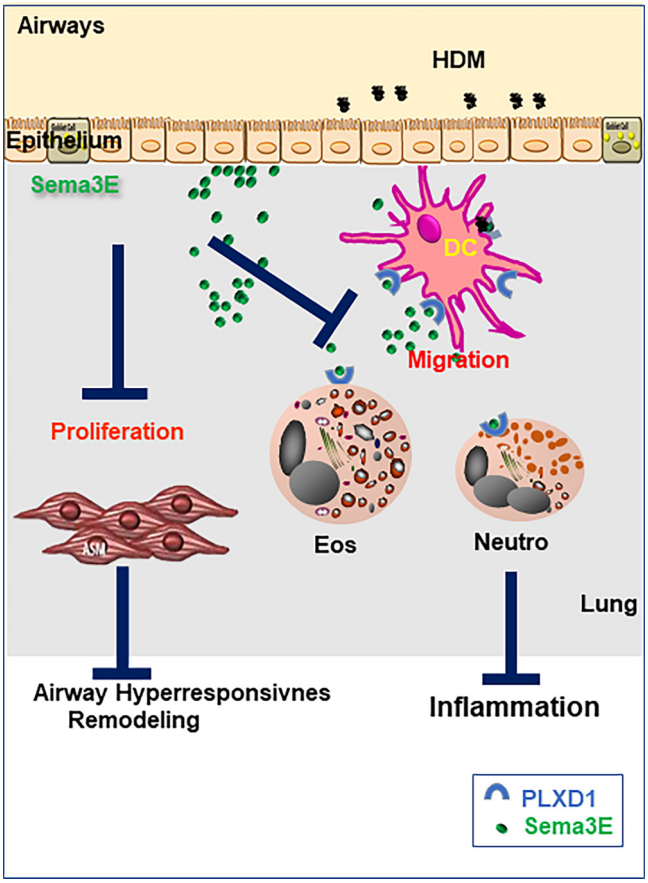

Fig. 2. Sema3E mode of action on airway inflammation and AHR in allergic asthma. Epithelial cell derived Sema3E targets pulmonary DC function, neutrophil and eosinophils recruitment and migration; and ASM cells proliferation and or migration leads to dampening of airway inflammation, AHR, and remodeling. HDM: house dust mite.

Research Council grant (RG PIN/386289) and Children Hospital Research Foundation grant to A. S. G.

H. M. was supported by Research Manitoba-Children's Hospital Research Institute of Manitoba Studentship.

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