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# Asthma is not only an airway disease, but also a *vascular* disease

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ABSTRACT

Multiple studies have identified an expansion and morphological dysregulation of the bronchial vascular network in the airways of asthmatics. Increased number, size and density of blood vessels, as well as vascular leakage and plasma engorgement, have been reported in the airways of patients with all grades of asthma from mild to fatal. This neovascularisation is an increasingly commonly reported feature of airway remodelling; however, the pathophysiological impact of the increased vasculature in the bronchial wall and its significance to pulmonary function in asthma are unrecognised at this time. Multiple factors capable of influencing the development and persistence of the vascular network exist within asthmatic airway tissue. These include structural components of the altered extracellular matrix (ECM), imbalance of proteases and their endogenous inhibitors, release of active matrikines and the dysregulated levels of both soluble and matrix sequestered growth factors. This review will explore the features of the asthmatic airway which influence the development and persistence of the increased vascular network, as well as the effect of enhanced tissue perfusion on chronic inflammation and airway dynamics. The response of cells of the airways to the altered vascular profile and the subsequent influence on the features of airway remodelling will also be highlighted. We will explore the failure of current asthma therapeutics in "normalising" this vascular remodelling. Finally, we will summarize the outcomes of recent clinical trials which provide hope that anti-angiogenic therapies may be a potent asthma-resolving class of drugs and provide a new approach to asthma management in the future.



**Contents**



*Abbreviations:* ADAM, A Disintegrin And Metalloprotease Domain; AHR, airway hyperreponsiveness; Ang, angiopoietin; ASM, airway smooth muscle; BALf, bronchoalveolar lavage fluid; bFGF, basic fibroblast growth factor; BM, basement membrane; Col, collagen; CTGF, connective tissue growth factor; CXCL, CXC ligand; CXCR, chemokine receptor; EC, endothelial cell; ECM, extracellular matrix; EPCs, endothelial precursor cells; $FEV_1$, forced expiratory volume in one second; FGF, fibroblast growth factor; FIZZ1, Found in Inflammatory (Z) Zone 1; FN, fibronectin; GAG, glycosaminoglycan; HGF, hepatocyte growth factor; Ig, immunoglobulin; IL-, interleukin; ISS, immunostimulatory sequences of DNA; LTRA, leukotriene receptor antagonist; MMP, matrix metalloproteinase; MT1-MMP, membrane type 1 MMP; OVA, ovalbumin; PDGF, platelet derived growth factor; PlGF, placental growth factor; SDF, stromal cell-derived factor; TGF, transforming growth factor; $T_h$, T helper; TNF, tumour necrosis factor; T-reg, T-regulatory; TSP, thrombospondin; VEGF, Vascular Endothelial Growth Factor; VEGFR, VEGF receptor; vWF, von Willebrand Factor

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## 1. Asthma

Asthma is a chronic inflammatory disorder affecting 300 million individuals worldwide (GINA, 2014). Symptoms of asthma, including episodic airway obstruction, airway hyperresponsiveness (AHR) and reduced lung function, are due to chronic airway inflammation and underlying structural changes to the airway wall (Bosse et al., 2008; Moreno et al., 1986). Features of the remodelled asthmatic airway include airway smooth muscle (ASM) cell hypertrophy (Benayoun et al., 2003) and hyperplasia (Ebina et al., 1990), epithelium metaplasia (Bosse et al., 2008) including epithelial shedding and goblet cell hyperplasia, and altered extracellular matrix (ECM) quantity, composition and distribution, such as the basement membrane, a specialised ECM known to be thickened in asthma (Roche et al., 1989; Wilson & Li, 1997). One feature which is perhaps central to the pathophysiology of this respiratory condition is the reported increased microvascular network of the asthmatic airway wall. Studies suggest an increased blood flow to the airway tissue to promote the chronic influx of inflammatory mediators, abnormal cell growth and proliferation, and thickening of the airway wall, all of which contribute to the pathophysiology of asthma (Bergeron et al., 2010; Ribatti et al., 2009; Zanini et al., 2010).

Surprisingly, the significance of vascular remodelling to this obstructive airways disease has been overlooked, with few literary reports covering this topic. This review aims to identify the significance of the remodelled vasculature network to the progression and severity of asthma, and the initial cause and the multiple factors which may contribute to the persistence of the uncontrolled expanded vascular network in the asthmatic airway.

## 2. Neovascularisation in asthma

### 2.1. Evidence for increased vasculature

The abnormal expansion of the vascular network has been reported in a series of publications which identified increased blood vessel number (Chetta et al., 2003; Grigoras et al., 2012; Hoshino et al., 2001a; Li & Wilson, 1997; Orsida et al., 1999), vessel density (number of vessels/mm$^2$) (Orsida et al., 1999) and percentage vascular area (Kuwano et al., 1993; Li & Wilson, 1997; Orsida et al., 1999; Salvato, 2001; Hoshino et al., 2001a,b,c; Chetta et al., 2003; Hashimoto & Hatanaka, 2005) in the sub-epithelial space (including the lamina propria and submucosa) of asthmatic airways. Asthmatic serum, sputum (Asai et al., 2003; Meyer & Akdis, 2013), bronchoalveolar lavage fluid (BALf) and airway tissue (Hoshino et al., 2001a; Meyer & Akdis, 2013; Tuder & Yun, 2008) contain increased levels of the pro-angiogenic factor Vascular Endothelial Growth Factor (VEGF)-A, compared to non-asthmatic controls. VEGF-A stimulates vascular network expansion, vasodilation and plasma leakage (Yuksel et al., 2013; Zanini et al., 2010). VEGF-A has been studied extensively in the remodelled asthmatic airway. Correlations between VEGF expression and airway vascularity (Chetta et al., 2005; Corrigan et al., 2011; Detoraki et al., 2010; Hoshino et al., 2001a; Lee et al., 2011; Meyer & Akdis, 2013; Tuder & Yun, 2008), disease severity (Hoshino et al., 2001a; Ohta et al., 2002), airflow obstruction (Asai et al., 2003), and a poor lung function (Abdel-Rahman et al., 2006) have been shown in asthmatic individuals.

It is not well understood how the abnormal vascular expansion fits into the development and progression of asthma and at what stage the vascular changes occur or become important. A correlation between asthma severity and neovascularisation has been shown, with severe asthmatics having the highest percentage of vascularity, followed by moderate and finally mild asthmatics (Salvato, 2001). This correlation is further emphasised by studies showing severe and moderate asthmatics to have an increase in both vessel number as well as percentage vascular area in the medium airways (Hashimoto & Hatanaka, 2005; Salvato, 2001), a pattern which is also seen in fatal asthmatics compared with non-fatal asthmatics (Carroll et al., 1997; Kuwano et al., 1993). In addition to this, there are also suggestions of the presence of replicating endothelial cells in the vessels in asthma (Wilson, 2002; Wilson & Bamford, 2001).

Some studies have found correlations between lung function (forced expiratory volume in one second ($FEV_1$)) and AHR with airway vascularity (Grigoras et al., 2012; Hoshino et al., 2001a; Orsida et al., 1999). In contrast, others fail to show any correlation of vascular properties with disease severity (Chetta et al., 2003), however this could be due to low sample size and the pooling of mild and moderate asthmatics into a single group to compare against severe asthmatics. The reporting of correlations could be dependent on the method by which the vascular expansion was quantified. Orsida et al. demonstrated a correlation between $FEV_1$ and AHR with vessel density, however no correlation was seen with percentage vascular area (Orsida et al., 1999).

Pooling of serum-derived mediators has been reported in the asthmatic airway (Bosse et al., 2008), and is a result of vasodilation, vessel permeability (Wilson, 2000), and oedema reported in the asthmatic airway (Baluk et al., 2005; Bosse et al., 2008; Salvato, 2001; Wilson, 2000), possibly due to the chronic state of inflammation (Mauser et al., 2013; Paredi & Barnes, 2009) or the presence of new and leaky vessels. Plasma engorgement is a feature of immature vessels and vascular hyperpermeability, which are phenomena consistent with inflammatory disorders (Detmar et al., 1994; Fava et al., 1994). Pooling of plasma in the airway tissue is thought to contribute to airway thickening and airway obstruction as discussed later in this review.

Despite contradicting reports regarding the relationship between vascularity and disease severity, whether phenotype or progression, literature from other fields (cancer (Gacche & Meshram, 2013), and rheumatoid arthritis (Thairu et al., 2011)) demonstrates that an abnormal vascular network disrupts tissue homeostasis. In the asthmatic airway, the increased vascularity may be underlying the persistent state of airway inflammation, abnormal cell behaviour and decreased lung function.

### 2.2. Evidence for neovascularisation contributing to asthma pathophysiology

#### 2.2.1. Inflammation

Normal airway vasculature is important as a means of inflammatory cell trafficking to the lumen and epithelium, a direct barrier from the outside environment, as well as regulating air temperature and humidity as air enters and leaves the lungs. Increased vasculature in the airway facilitates a continuous influx of mast cells, neutrophils, eosinophils, and inflammatory mediators (McLeish et al., 1986). This is permissive of the persistent, chronic inflammation of the asthmatic airway and pooling of these mediators in the airway tissue leads to tissue pathology, contributing to the autoimmune nature of asthma (Widdicombe, 1992).

Many pro-inflammatory mediators such as histamine (Chediak et al., 1991), bradykinin (Laitinen et al., 1987), fibroblast growth factor (FGF) (Presta et al., 2005), hepatocyte growth factor (HGF) (Nakamura & Mizuno, 2010), platelet derived growth factor (PDGF) (Oikawa et al., 1994) and angiogenin (Gao & Xu, 2008), also possess pro-angiogenic properties when in a chronic inflammatory environment such as the asthmatic airway (Orsida et al., 1999), and could cause dilation of bronchial blood vessels (Chediak et al., 1991).

#### 2.2.2. Increased metabolic demand of the tissue

The uncontrolled influx of nutrients and stimulating growth factors (although essential for tissue growth, repair and homeostasis) are capable of causing abnormal tissue growth and facilitate abnormal cell behaviours and hyperactivity. In addition to enabling the chronic state of inflammation of the airways, the continuous supply of nutrients promotes ASM cell hypertrophy, fibroblast hyperactivity, increased deposition of ECM proteins and fibrosis, epithelial and mucous cell hyperplasia and hypersecretion, which leads to the persistence of the structural changes of the remodelled asthmatic airway (Aikawa et al., 1992; Benayoun et al., 2003; Widdicombe, 1993; Zanini et al., 2010). It has been suggested many times throughout the literature that the structural changes contribute to the development of persistent AHR (James et al.,

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