International Journal of Biochemistry and Cell Biology 97 (2018) 108–117

Contents lists available at ScienceDirect

International Journal of Biochemistry and Cell Biology

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

Review article

The fibrogenic actions of the coagulant and plasminogen activation systems in pulmonary fibrosis

Michael Schuliga[a,b,*], Christopher Grainge[b,c], Glen Westall[d], Darryl Knight[a,b,e]

[a] School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, New South Wales, Australia
[b] Priority Research Centre for Healthy Lungs, Hunter Medical Research Institute, New Lambton Heights, New South Wales, Australia
[c] School of Medicine and Public Health, University of Newcastle, Callaghan, New South Wales, Australia
[d] Allergy, Immunology and Respiratory Medicine, Alfred Hospital, Prahran, Victoria, Australia
[e] Department of Anesthesiology, Pharmacology and Therapeutics, University of British Columbia, Canada

ARTICLE INFO

Keywords:
Coagulants
Factor X
Plasmin
Thrombin
Tissue factor
Urokinase plasminogen activator

ABSTRACT

Fibrosis causes irreversible damage to lung structure and function in restrictive lung diseases such as idiopathic pulmonary fibrosis (IPF). Extravascular coagulation involving fibrin formation in the intra-alveolar compartment is postulated to have a pivotal role in the development of pulmonary fibrosis, serving as a provisional matrix for migrating fibroblasts. Furthermore, proteases of the coagulation and plasminogen activation (plasminergic) systems that form and breakdown fibrin respectively directly contribute to pulmonary fibrosis. The coagulants, thrombin and factor Xa (FXa) evoke fibrogenic effects *via* cleavage of the N-terminus of protease-activated receptors (PARs). Whilst the formation and activity of plasmin, the principle plasminergic mediator is suppressed in the airspaces of patients with IPF, localized increases are likely to occur in the lung interstitium. Plasmin-evoked proteolytic activation of factor XII (FXII), matrix metalloproteases (MMPs) and latent, matrix-bound growth factors such as epidermal growth factor (EGF) indirectly implicate plasmin in pulmonary fibrosis. Another plasminergic protease, urokinase plasminogen activator (uPA) is associated with regions of fibrosis in the remodelled lung of IPF patients and elicits fibrogenic activity *via* binding its receptor (uPAR). Plasminogen activator inhibitor-1 (PAI-1) formed in the injured alveolar epithelium also contributes to pulmonary fibrosis in a manner that involves vitronectin binding. This review describes the mechanisms by which components of the two systems primarily involved in fibrin homeostasis contribute to interstitial fibrosis, with a particular focus on IPF. Selectively targeting the receptor-mediated mechanisms of coagulant and plasminergic proteases may limit pulmonary fibrosis, without the bleeding complications associated with conventional anti-coagulant and thrombolytic therapies.

1. Introduction

Pulmonary fibrosis, characterised by the excessive accumulation of fibroblasts and collagen in the lung parenchyma, occurs in a number of restrictive lung diseases including idiopathic pulmonary fibrosis (IPF) (Richeldi et al., 2017). Following lung injury, increased vascular permeability allows the zymogens of blood-circulating hemostatic and plasminergic factors such as factor X (FX) and plasminogen, respectively, to enter damaged parenchymal tissue (McKeown et al., 2009). Once activated, they participate in coagulation or fibrinolysis, processes typically associated with the regulation of blood clotting (Versteeg et al., 2013) (Fig. 1). Intra-alveolar accumulation of fibrin and a heightened thrombotic state are hallmark features of IPF and evidence of extravascular coagulation (Navaratnam et al., 2014). Proteases of the coagulation and plasminergic systems such as thrombin, factor Xa (FXa) and plasmin also exert potent cell-mediated fibrogenic actions that are likely to contribute to the chronic fibrosis of IPF. These actions, such as the activation of protease-activated receptor-1 (PAR-1) on resident lung and infiltrating inflammatory cells are independent of fibrin formation (Schuliga et al., 2017a,b). Plasmin is also involved in the formation of

Abbreviations: ATII, alveolar epithelial type II; AIIt, annexin A2 heterotetramer; APC, activated protein C; BALF, broncho-alveolar lavage fluid; DAD, diffuse alveolar damage; EGF, epidermal growth factor; ECM, extracellular matrix; FAK, focal adhesion kinase; FV, factor V; FVII, factor VII; FX, factor X; FXa, factor X activated; FXII, factor XII; FDPs, fibrin degradation products; FPR2, formyl-peptide receptor 2; HS, heparan sulfate; IPF, idiopathic pulmonary fibrosis; LRP-1, LDL receptor-related protein 1; MMP, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; PKC, protein kinase C; PAR, protease-activated receptor; TAFI, Thrombin activated fibrinolysis inhibitor; TF, tissue factor; tPA, tissue type-plasminogen activator; TLR-4, toll-like receptor-4; TGF-β, transforming growth factor-β; UIP, usual interstitial pneumonia; uPA, urokinase plasminogen activator; uPAR, uPA receptor

* Corresponding author at: School of Biomedical Sciences and Pharmacy, University of Newcastle, HMRI Building, New Lambton Heights, New South Wales 2305, Australia.
E-mail address: Michael.Schuliga@newcastle.edu.au (M. Schuliga).

https://doi.org/10.1016/j.biocel.2018.02.016
Received 7 November 2017; Received in revised form 16 February 2018; Accepted 19 February 2018
Available online 21 February 2018
1357-2725/

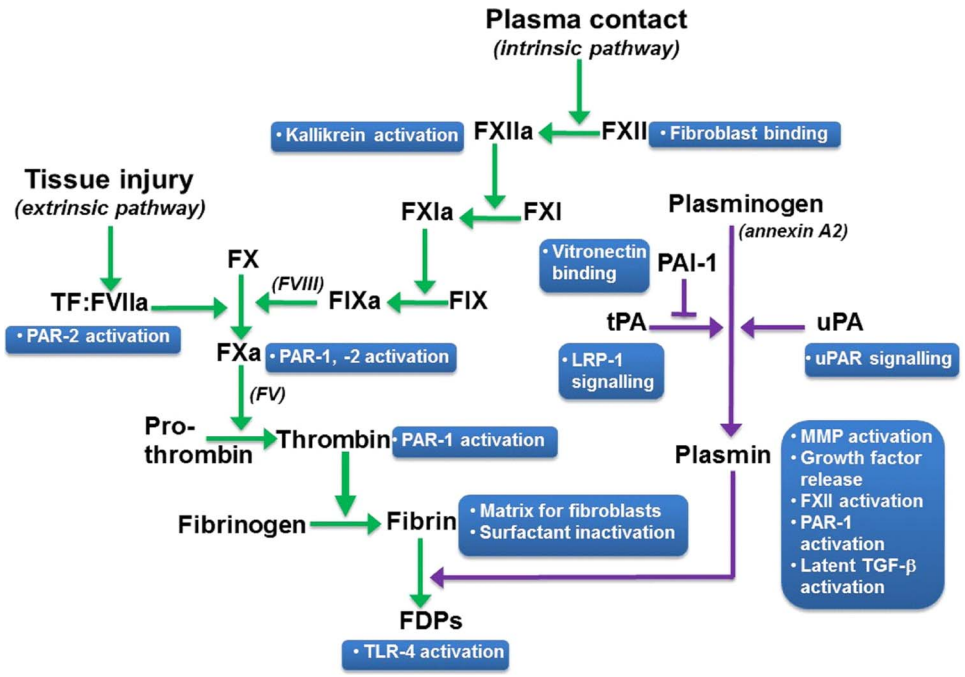

Fig. 1. The involvement of the coagulant and plasminogen activation systems in pulmonary fibrosis. Participants of extravascular coagulation (green pathway) or fibrinolysis (purple pathway) can directly evoke fibrogenic actions by various mechanisms and processes described in detail in the text. **Abbreviations:** FV, factor V; FVII, factor VII; FVIIa, factor VIIa activated; FVIII, factor VIII; FIX, factor IX; FIXa, factor IX activated; FX, factor X; FXa, factor X activated; FXI, factor XI; FXIa, factor XI activated; FXII, factor XII; FXIIa, factor XII activated; FDPs, fibrin degradation products; LRP-1, LDL receptor-related protein 1; MMP, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; PAR, protease-activated receptor; TF, tissue factor; tPA, tissue type-plasminogen activator; TLR-4, toll-like receptor-4; TGF-β, transforming growth factor-β; uPA, urokinase plasminogen activator; and uPAR, uPA receptor.

fibrin degradation products (FDPs) (Millien et al., 2013), activation of matrix metalloproteases (MMPs) and subsequent release of matrix-bound growth factors (transactivation) (Stewart et al., 2013). The proteases which convert plasminogen into plasmin, urokinase- and tissue-type plasminogen activators (uPA and tPA respectively), also directly signal through receptors such as uPAR (Wei et al., 2001) and LDL receptor-related protein 1 (LRP-1) (Hu et al., 2007), involving integrin recruitment to potentially mediate fibrosis.

2. Idiopathic pulmonary fibrosis (IPF)

IPF is a devastating and progressive disease characterised by an inexorable decline in lung function (Ahluwalia et al., 2014). Patients with IPF experience shortness of breath, exercise limitation, and a dry non-productive cough, all of which progressively worsen until death ensues (Smith et al., 2013; Wuyts et al., 2014). The median survival of patients with IPF is comparable to many cancers, being 2–5 years from diagnosis, whereas the incidence of IPF is variably reported as 3–9 people per 100,000, with prevalence and mortality increasing with age (Rubenfeld et al., 2005; Cheifetz, 2016; Cochi et al., 2016). Prevailing views on IPF focus on the fibrosis arising from persistent micro injuries to the alveolar epithelium and an aberrant wound repair response (Selman et al., 2004). The resulting fibrosis usually emanates from the basal sub-pleural regions of the lung and with time spreads caudally to all parts of the lung, causing irreversible damage to parenchymal tissue and function (Ryu et al., 2014). Morphologically, the 'patchwork' pattern of fibrosis in IPF, histologically described as an usual interstitial pneumonia (UIP) pattern, comprises interstitial thickening, the existence of fibroblast foci and honeycombing cystic remodelling (Rabeyrin et al., 2015). Acute exacerbations of IPF (AE-IPF), which may be triggered by infection, general anaesthesia or most commonly have no identifiable cause, induce a rapid deterioration in lung function; AE-IPF have a mortality of approximately 50%. Patients with AE-IPF exhibit a 'diffuse alveolar damage' (DAD) pathological pattern which is superimposed on that of UIP, and often involves previous unaffected regions of lung (Papiris et al., 2010; Bhatti et al., 2013). Features of DAD include spatially uniform alveolar damage, hyaline membranes comprising fibrin accumulation along the alveolar wall, lung haemorrhage and fibrosis in the inter- and intra-alveolar spaces (Meduri and Eltorky 2015). There are no current therapies proven to be of benefit in AE-IPF, though two recently FDA-approved therapies for IPF, pirfenidone and nintedanib, are the first to show efficacy in reducing the rate of decline in lung function and to increase survival from the disease in general (King et al., 2014; Richeldi et al., 2014). Whilst, the actions of pirfenidone and nintedanib are modest and come with considerable side effects, they have provided incontrovertible evidence that the natural history of IPF can be favourably modified.

The current accepted paradigm of IPF pathogenesis is that the disease arises from a dysfunctional wound-repair response to injury of the alveolar epithelium; inadequate re-epithelialisation triggers a cascade of events leading to pathological remodelling, rather than wound resolution and tissue restitution (Richeldi et al., 2017). Increased alveolar epithelial type II (ATII) cell apoptosis has an important role in the development of pathological fibrosis in IPF (Plataki et al., 2005). Apoptotic ATII cells impede the regeneration of the damaged alveolar epithelium, as they are the progenitors of the air-blood barrier forming type I alveolar epithelial cell (Hagimoto et al., 1997; Lee et al., 2004; Budinger et al., 2006; Sisson et al., 2010). Mutations in the genes of surfactant proteins expressed specifically in ATII cells that lead to incorrect protein folding and endoplasmic reticulum (ER) stress, a trigger of apoptosis, occur in a subset of patients with IPF (Armanios et al., 2007). Following lung injury, epithelial, endothelial and fibroblast cells normally undergo migration and/or proliferation in a coordinated process to repair the damaged tissue. However, in IPF, this process becomes excessive and dysregulated, leading to the accumulation of fibroblasts and abnormalities of the extracellular matrix (ECM) (Fixman et al., 2007). Lung fibroblasts, by the synthesis and deposition of collagen I and III and other ECM components including fibronectin and hyaluronic acid, expand the volume of the ECM in the lung interstitium and airspaces (Redington 2000). Aside from important biomechanical contributions in tissue remodelling, lung fibroblasts produce an array of inflammatory and fibrogenic mediators which also contribute to fibrosis (Alkhouri et al., 2014).

3. Extravascular coagulation in IPF

Population-based case-control studies show a strong association between IPF and measures of pro-coagulant activity, with a heightened thrombotic state resulting in the accumulation of fibrin in the alveolar airspaces (Noble et al., 2012; Navaratnam et al., 2014; Kim et al.,