EXPLORING THE COMPLEX INTERPLAY BETWEEN PULMONARY FIBROSIS AND THROMBOTIC PATHOLOGY: A NARRATIVE REVIEW

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Abstract

Idiopathic pulmonary fibrosis (IPF) is strongly linked to an elevated risk of thrombotic events and mortality. This review examines the intricate relationship between pulmonary fibrosis and thrombosis, exploring epidemiological data, underlying mechanisms, and therapeutic approaches. A particular focus is placed on the role of extracellular vesicles (EVs) as mediators connecting fibrosis and coagulation. Coagulation factors actively drive fibrosis, while fibrosis induces thrombotic pathways, creating a self-perpetuating cycle. Retrospective studies suggest potential benefits of anticoagulants in IPF; however, prospective trials have faced significant challenges. Emerging therapies, including novel anticoagulants, profibrinolytic agents, and protease-activated receptor (PAR) inhibitors, show promise in preclinical and early clinical studies. EVs are identified as crucial contributors to interstitial lung disease (ILD) pathology, facilitating intercellular communication and promoting both fibrosis and coagulation. EV-based strategies, such as modulation, engineered EVs for drug delivery, and mesenchymal stem cell-derived EVs, hold potential as innovative treatments. Future research should focus on optimizing risk–benefit profiles, identifying predictive biomarkers, and integrating combination approaches targeting fibrotic, thrombotic, and inflammatory pathways. Understanding EVs' role in ILDs could pave the way for targeted interventions and improved outcomes.

Keywords: Idiopathic pulmonary fibrosis, thrombosis, coagulation, anticoagulants, mortality, extracellular vesicles.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a severe interstitial lung disease characterized by progressive lung scarring, ultimately leading to respiratory failure and death. Despite advancements in antifibrotic therapies, IPF continues to have a poor prognosis, with a median survival of 3–5 years post-diagnosis. Evidence indicates that thrombotic events, such as venous thromboembolism (VTE) and acute coronary syndromes (ACS), occur more frequently in IPF patients.

The relationship between fibrosis and thrombosis is bidirectional. Coagulation factors, such as thrombin and factor Xa, stimulate fibroblast activation and collagen deposition, thereby driving fibrosis. Conversely, the fibrotic lung microenvironment activates platelets, impairs fibrinolysis, and induces a hypercoagulable state, creating a feedback loop that accelerates disease progression and increases the risk of fatal thrombotic events. This review explores the epidemiological, mechanistic, and therapeutic connections between pulmonary fibrosis and thrombosis, with a focus on extracellular vesicles as mediators of these pathological processes. It also addresses challenges and opportunities in targeting thrombotic pathways and leveraging EV-based strategies to improve IPF outcomes.

Epidemiological Evidence Linking IPF and Thrombosis

Numerous studies have demonstrated an elevated risk of thrombotic events in IPF patients compared to matched controls. Population-based research has shown increased risks for acute coronary syndromes and deep vein thrombosis in IPF patients, with the highest risk occurring within the first year of diagnosis and persisting over time.

Data suggest a strong association between prothrombotic laboratory abnormalities—such as elevated factor VIII, antithrombin deficiency, and increased D-dimer levels—and the development of IPF. Higher D-dimer levels have also been linked to acute exacerbations of IPF and reduced survival. Autopsy studies further support the role of thrombosis in IPF mortality, with pulmonary thromboembolism identified in a significant subset of patients who experienced acute exacerbations.

A meta-analysis confirms that the risk of venous thromboembolism in IPF patients is approximately double that of the general population. These findings underscore the clinical importance of addressing thrombotic risk in IPF management.

3. Pathogenetic Mechanisms Linking Fibrosis and Thrombosis

The epidemiological link between idiopathic pulmonary fibrosis (IPF) and thrombosis is underpinned by evidence highlighting shared pathogenetic mechanisms. Several coagulation factors act as proteases, traditionally recognized for their role in the coagulation cascade, where they activate downstream proenzymes. Beyond this role, these factors also interact with protease-activated receptors (PARs), integral membrane proteins expressed on various cell types, including platelets and fibroblasts.

PARs consist of both a receptor and a tethered agonist. In their resting state, the N-terminal region masks the agonist sequence, rendering it inactive. Proteolytic cleavage of the N-terminal region by specific proteases exposes the agonist, enabling it to interact with the receptor in an autocrine manner and initiate downstream signaling pathways. PAR-mediated signaling influences numerous physiological and pathological processes, including coagulation, inflammation, pain, and tissue repair.

Thrombin (factor IIa) has been shown to activate PAR-1, driving fibroblast proliferation, procollagen production, and myofibroblast differentiation. Myofibroblasts contribute to the increased extracellular matrix deposition and tissue contractility characteristic of pulmonary fibrosis. Similarly, factor Xa, another critical coagulation protease, activates PAR-1 to promote fibroblast activation and differentiation. Factor Xa also induces fibrosis through PAR-1-independent pathways, such as the release of pro-inflammatory and pro-fibrotic cytokines.

Animal studies support these findings. Mice lacking PAR-1 exhibit significantly reduced collagen accumulation following bleomycin exposure compared to wild-type controls. Moreover, pharmacological inhibition of PAR-1 using the pepducin P1pal-12 protects mice from bleomycin-induced pulmonary fibrosis. These studies highlight the critical role of coagulation factors and PAR signaling in the interplay between fibrosis and thrombosis.

4. Extracellular Vesicles: Bridging Fibrosis and Coagulation in Interstitial Lung Diseases

Extracellular vesicles (EVs) have emerged as significant mediators in the intricate pathophysiology of interstitial lung diseases (ILDs), including idiopathic pulmonary fibrosis (IPF). These nano-sized, membrane-bound structures facilitate intercellular communication and play key roles in disease progression, particularly in fibrosis and coagulation.

EVs are lipid bilayer-enclosed structures released by cells into the extracellular environment and can be broadly categorized into three types based on their size and biogenesis: **exosomes** (30–150 nm), **microvesicles** (100–1000 nm), and **apoptotic bodies** (1–5 μm). Exosomes are generated within the endosomal system and released upon fusion of multivesicular bodies with the plasma membrane. Microvesicles, also called ectosomes, form through outward budding and fission of the plasma membrane, while apoptotic bodies are shed as blebs from dying cells.

In ILDs, EVs are found in various biological fluids, including bronchoalveolar lavage fluid (BALF), blood, and sputum. Their composition and cargo reflect their cellular origin and the pathological state of the lung microenvironment. EVs can transport a diverse array of bioactive molecules, such as proteins, lipids, and nucleic acids (e.g., mRNA, miRNA, and other non-coding RNAs), which can influence the behavior of recipient cells.

Advanced techniques such as nanoparticle tracking analysis, flow cytometry, and proteomics have been employed to characterize EVs in ILDs. These studies reveal that EVs in patients with lung diseases carry distinct molecular cargo compared to those from healthy individuals. For example, sputum exosomes from IPF patients exhibit unique microRNA (miRNA) profiles, including elevated levels of miR-142-3p and miR-33a-5p, which are associated with fibrotic pathways.

MicroRNAs, small non-coding RNA molecules, regulate gene expression post-transcriptionally and play crucial roles in disease pathogenesis. The altered miRNA profiles in IPF-derived EVs suggest their involvement in fibrosis progression and their potential utility as biomarkers for disease diagnosis and monitoring. EVs thus represent a promising avenue for understanding the interplay between fibrosis and coagulation in ILDs, with potential implications for developing novel therapeutic strategies.

Conclusions

The complex interplay between pulmonary fibrosis and thrombotic pathology represents a critical frontier in understanding interstitial lung diseases (ILDs), particularly idiopathic pulmonary fibrosis (IPF). This review underscores the bidirectional nature of this relationship, where coagulation factors drive fibrotic processes, and the fibrotic lung environment activates thrombotic pathways. This self-reinforcing cycle contributes to disease progression and highlights the importance of addressing both aspects for effective disease management.

The strong epidemiological evidence linking IPF with an increased risk of thrombotic events, combined with emerging insights into the underlying molecular mechanisms, underscores the need for clinicians to be vigilant about thrombotic complications in these patients. While initial attempts at therapeutic anticoagulation have faced challenges, advancements in understanding specific coagulation pathways suggest that more targeted therapeutic approaches could provide better outcomes.

A particularly promising area of research lies in the role of extracellular vesicles (EVs), which serve as both biomarkers and active participants in fibrotic and thrombotic processes. EVs carry bioactive molecules, including procoagulant and profibrotic factors, and facilitate intercellular communication, making them critical contributors to disease progression and attractive targets for novel therapies.

Several priorities emerge for advancing the field. Developing sophisticated biomarker panels that incorporate EV-based markers could enhance disease monitoring and risk assessment. Exploring targeted therapies aimed at specific coagulation pathways, rather than broad-spectrum anticoagulation, may improve the risk–benefit balance. Additionally, EV-based therapeutic approaches, such as modulating endogenous EVs or utilizing engineered EVs for drug delivery, represent a promising avenue for innovation in IPF treatment.

As we further unravel the intricate relationship between coagulation and fibrosis, it is clear that successful management of IPF will require integrated strategies addressing both processes. The dual role of EVs as biomarkers and therapeutic targets offers exciting opportunities to develop such comprehensive approaches. Future research should focus on clinical studies evaluating combination therapies and deepening our understanding of EV biology in ILDs, paving the way for improved outcomes in patients with IPF.

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