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Review article

The role of platelets in the development and progression of pulmonary arterial hypertension

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ABSTRACT

Pulmonary arterial hypertension is a multifactorial disease characterized by vasoconstriction, vascular remodeling, inflammation and thrombosis. Although an increasing number of research confirmed that pulmonary artery endothelial cells, pulmonary artery smooth muscle cells as well as platelets have a role in the pulmonary arterial hypertension pathogenesis, it is still unclear what integrates these factors. In this paper, we review the evidence that platelets through releasing a large variety of chemokines could actively impact the pulmonary arterial hypertension pathogenesis and development. A recent publication revealed that not only an excess of platelet derived cytokines, but also a deficiency may be associated with pulmonary arterial hypertension development and progression. Hence, a simple platelet blockade may not be a correct action to treat pulmonary arterial hypertension. Our review aims to analyse the interactions between the platelets and different types of cells involved in pulmonary arterial hypertension pathogenesis. This knowledge could help to find novel therapeutic options and improve prognosis in this devastating disease.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive state characterized by proliferative changes in the pulmonary vasculature and subsequent increased pulmonary vascular resistance (PVR), which leads to right-sided heart failure and premature death [1].

The pathogenesis of PAH involves excess vasoconstriction, vascular remodelling, inflammation and *in situ* thrombosis [2–5]. An imbalance between apoptosis and proliferation within the intima, media, and adventitia plays a crucial role in the PAH progression [6]. These pathological mechanisms lead to PVR increase due to narrowing the lumen of small pulmonary arteries.

Platelets are small disc-shaped megakaryocyte cell fragments, which lifespan is about 5–9 days. Platelets store growth factors, cytokines, and vasoactive substances in granules that can be released in a regulated manner upon stimulation (Fig. 1). Alpha granules contain, among others, P-selectin, transforming growth factor β (TGF-β1), platelet-derived growth factor (PDGF), β-thromboglobulin, platelet factor 4, Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES), tumor necrosis factor α (TNFα), interleukin 1α (IL-1α), stromal-derived factor (SDF-1), interleukin 1β (IL-1β), tumor necrosis factor-like weak inducer of apoptosis (TWEAK), fibrinogen and coagulation factors V and XIII [7]. Delta (dense) granules contain serotonin (5-HT), calcium, and ADP/ATP. The activation of platelets, apart from releasing granules, increases the surface expression of various adhesion molecules and receptor (e.g. selectin P, gp IIIa/IIb) as well as the production of thromboxane A2 (TXA2), which in turn activates other platelets and promotes vasoconstriction and local thrombosis (Table 1).

There is growing evidence that inflammation plays an important role in the pathogenesis of PAH. Recent studies have confirmed the role of inflammatory modulators e.g. kynurenine metabolites, interleukin-6 and IL-1β, in the development of PAH [8–10]. Another one of them is the soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK), which belongs to the TNFα superfamily [7,11]. This cytokine is involved in numerous biological responses associated with tissue damage and repair, such as apoptosis, cell growth or angiogenesis [11]. One of the main sources of circulating cytokines e.g. sTWEAK or P-selectin are platelets [7,12]. Microparticles derived from platelets, inflammatory cells, and the endothelium are an increasingly well-recognized signal in a variety of cardiovascular diseases, including thromboembolic events or PAH [13,14].

In this review, we sum up the evidence that platelets are involved in the development of PAH. We describe the thrombotic mechanisms

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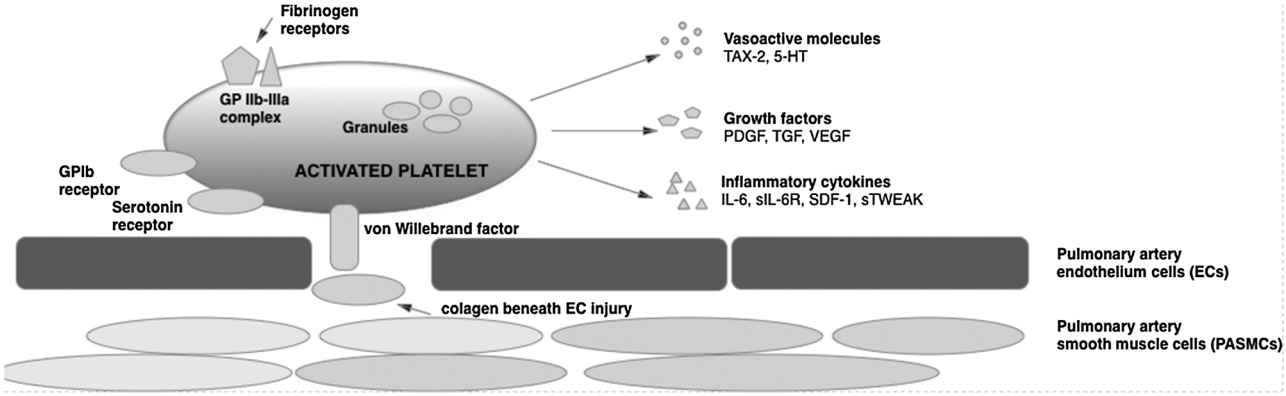

Fig. 1. At the site of pulmonary endothelium injury activated platelets attach to the vascular wall, start to aggregate and release e.g. inflammatory cytokines (e.g. IL-1, IL-6), vasoactive particles (5-HT, TXA-2) and growth (mitogenic) factors (PDGF, VEGF). This leads to pulmonary vasoconstriction, proliferation of smooth muscle cells and finally to pulmonary remodelling.
5-HT - 5-hydroxytryptamine; IL-1 - interleukin 1; IL-6 - interleukin 6; sIL-6R - soluble interleukin 6 receptor; SDF-1 - stromal derived factor 1; PDGF - platelet-derived growth factor; TGF - transforming growth factor; TXA-2 - thromboxane 2; VEGF - vascular endothelial growth factor.

Table 1
Major substances in pulmonary arterial hypertension pathophysiology released by activated platelets.

Group	Substance	Effect
Vasoactive substances	5-HT, Thromboxane A2	Increase vasoconstriction and impair the endothelial-smooth muscle cells (SMC) cross talk.
Mitogenic & growth factors	PDGF	Contributes to a higher proliferation rate of SMCs and fibroblasts.
	TGF-β1	Pulmonary smooth muscle cells over-proliferation leading to vascular remodelling.
	Insulin-like growth factor 1	
	VEGF	
	Epidermal growth factor	
	Thrombospondin 1	
Inflammatory cytokines	TNF-α, IL-1 α, IL-1β, IL-6	Exaggerate inflammatory response in ECs contributing to endothelial dysfunction.
	P-selectin	Promotes platelet aggregation and leukocyte migration to the injured site of endothelium.
	TWEAK	Modulates inflammatory processes and tissue healing.
	CXCL12 (SDF-1)	Localised in alpha granules, facilitates migration and differentiation of CD34 progenitor phenotype.
	sIL-6R	Binds to circulating IL-6 and associates with gp130, activating cells that express only gp130 on surface.

5-HT - 5-hydroxytryptamine; IL - interleukin; sIL-6R - soluble interleukin 6 receptor; SDF-1 - stromal derived factor 1; PDGF - platelet-derived growth factor; SDF - stromal derived factor; TGF - transforming growth factor; TNF - tumor necrosis factor; TWEAK - tumor necrosis factor-like weak inducer of apoptosis; VEGF - vascular endothelial growth factor.

through which platelets may be associated with this disease. The review is focused on molecules released by platelets during the inflammatory processes occurring in pulmonary arteries in PAH.

2. Review

2.1. Involvement of platelets in thrombotic processes in PAH

Thrombotic lesions are common pathological findings in PAH. Small vessel arteriopathy due to thromboembolic changes was found upon autopsy in 57% of PAH patients in a study from 1984 and for many years, thrombosis was considered a crucial factor in PAH pathogenesis [15]. The co-existence of pulmonary arteriopathy with recanalized thrombi in patients who did not have pulmonary thromboembolic disease cemented a role for thrombosis in the PAH pathogenesis. Some studies reported high frequencies (20%, 30%, and 56%) of thrombotic lesions in the histopathological classification of hypertensive pulmonary vascular disease [16–18]. Its role is still not fully elucidated. One theory was based on the fact that activation of coagulation contributes to the pathogenesis of PAH through luminal narrowing (both from the fibrin clot itself and related vascular remodelling, likely driven by proteases, tissue factor, factor Xa and thrombin). An alternate view is that thrombotic arteriopathy is only a bystander (epiphenomenon) of pulmonary vascular remodeling [19,20].

Tissue factor (TF) that together with von Willebrand Factor (vWF) during endothelial injury initiate coagulation cascade and platelet aggregation, could play an important role in thrombosis in situ occurring in PAH. In physiological conditions, TF is expressed at low levels in the pulmonary vessel wall, but it is increased in the vascular lesions in PAH patients [21]. PAH patients have also higher levels of circulating vWF, what is related to worse outcome [22]. Furthermore, endothelial cells (ECs) with higher expression of TF release more prothrombotic microparticles [23]. Enhanced platelet activation and coagulation cascade abnormalities (e.g. alterations of serotonin (5-HT), thromboxane (TXA2) or NO levels) overlap in PAH-related thrombosis [24].

Non-injured ECs by releasing nitric oxide (NO) and PGI2 - two important inhibitors of platelet aggregation - diminish thrombosis and through the synthesis and release of the profibrinolytic tissue plasminogen activator (t-PA) activate the fibrinolytic cascade. On the other hand, injured or activated ECs could produce the antifibrinolytic plasminogen activator inhibitor-1 (PAI-1) and enhance unfavourable prothrombotic processes [25,26]. TF exposure in injured ECs starts the coagulation process through complex formation with Factor VIIa, which in turn catalyses the activation of Factor X. They produce and release the vWF that attracts and activates platelets, as well as, thromboxane that contracts pulmonary smooth muscle cells (SMCs) and enhances platelets aggregation [19]. Platelets, by releasing various cytokines, affect SMCs and fibroblasts, simultaneously influencing inflammatory processes. Cytokines and chemokines recruit various inflammatory cells (T cells, B cells, macrophages, dendritic cells, mast cells) and these cells contribute to further release of chemokines, cytokines and growth factors, which in turn promote EC proliferation, migration and resistance to apoptosis, contributing to vascular remodeling and finally to arterial narrowing [6,14,27]. One of the chemokines potentially