The integrin α\(_{\text{IIb}}\)β\(_{3}\) as an antithrombotic target

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SUMMARY

The objective of this paper is to review briefly the normal physiology of platelet activation which leads to aggregation, to summarize the evidence for the critical role of platelet activation and aggregation in thrombosis, to highlight the key role of the membrane–protein complex glycoprotein IIb/IIIa in this process, and to provide examples of how small molecules can inhibit the aggregatory function of this complex.

INTRODUCTION

When a blood vessel is damaged, either acutely by damage such as wounding or clinical interventions like angioplasty, or more chronically by the pathophysiological processes of atherosclerosis, platelets are activated to adhere to the disrupted surface and to each other. This activation, adherence and aggregation may lead to occlusive thrombus formation in the lumen of the blood vessel, resulting in acute thrombotic syndromes [1–3]. Therefore, prevention of aggregation may be an effective antithrombotic strategy.

PLATELET ACTIVATION, ADHESION AND AGGREGATION

Normal physiology

The final obligatory step in platelet aggregation is the binding of fibrinogen to an activated membrane-bound glycoprotein complex, originally known as glycoprotein (GP) IIb/IIIa, but more recently designated α\(_{\text{IIb}}\)β\(_{3}\) [4–7]. Several processes initiate this final activation of α\(_{\text{IIb}}\)β\(_{3}\). Platelets adhere via unactivated α\(_{\text{IIb}}\)β\(_{3}\) to immobilized fibrinogen or vWF or via GP Ib to vWF and α\(_{\text{IIb}}\)β\(_{3}\) then clusters, leading to release of ADP which subsequently activates the platelets [8,9]. In addition, platelet activators such as thrombin, collagen, epinephrine or ADP are generated and exposed as a consequence of tissue damage [10]. These agonists act to stimulate secretion of additional ADP and serotonin from storage pools within the platelet and stimulate the production of thromboxane A\(_{2}\) by the platelet. Serotonin, ADP and thromboxane A\(_{2}\) act as platelet
activators and recruit additional platelets to the growing thrombus.

During this platelet activation process, \( \alpha_{\text{IIb}} \beta_3 \) undergoes an ill-defined change in the spatial orientation of extracellular domains, resulting in exposure of the occult binding sites for fibrinogen [11–14]. The biochemical processes that underlay the conversion of \( \alpha_{\text{IIb}} \beta_3 \) to the form competent to bind fibrinogen are unknown. However, these conformational changes are paralleled by the exposure of neoeptitopes on the \( \alpha_{\text{IIb}} \beta_3 \) molecule that may be detected with antibodies [15]. The ability of \( \alpha_{\text{IIb}} \beta_3 \) to undergo this conformational change is an intrinsic property of the protein complex, because the activation-dependent epitopes may be induced in solubilized and purified \( \alpha_{\text{IIb}} \beta_3 \) by antibodies and by small molecules [16].

**Activation during disease**

Platelet activation and aggregation have been implicated in the etiology of unstable angina, acute myocardial infarction, in reocclusion following thrombolytic therapy and angioplasty, in transient ischemic attacks and in a variety of other vaso-occlusive disorders [17–21]. In patients with ischemic heart disease, an increase in thromboxane metabolites is observed both in the coronary circulation and in the urine of platelets [17,19].

Antiplatelet therapy, particularly administration of aspirin, has been used in a wide variety of cardiovascular disease states, ranging from the acute thrombotic syndromes of myocardial infarction (MI), unstable angina, stroke, and intermittent claudication to prophylaxis of secondary myocardial infarction or thrombotic cerebrovascular events. It has been evaluated in conjunction with interventional therapy, such as coronary artery or peripheral bypass grafting (CABG/PBG), cardiac valve replacement, and percutaneous transluminal coronary angioplasty (PTCA). The utility of antiplatelet therapy was recently reviewed in a three-part overview of randomized trials of antiplatelet therapy [22,23]. The conclusions from these overviews are that a significant benefit of aspirin is seen in patients with a high risk of occlusive vascular disease, with protection afforded against myocardial infarction, stroke and death. Moreover, antiplatelet agents are beneficial following coronary artery grafts, coronary angioplasty, and implantation of shunts or fistulae [24]. In 214 patients with unstable angina/non-Q-wave myocardial infarction (NQWMI), not prior aspirin users, the combination of aspirin (162.5 mg) and heparin/warfarin (INR 2-3) reduced total ischemic events after 2 weeks (10.5% vs. 27%) and after 14 weeks (13% vs. 25%). This suggests that more aggressive antiplatelet agents might be more effective than aspirin alone [25].

Because there appears to be an intimate involvement of platelet activation and aggregation in these disease processes, and because of the essential role of \( \alpha_{\text{IIb}} \beta_3 \) in platelet aggregation, blockade of the binding of adhesive proteins to this membrane protein is being explored as an antithrombotic mechanism. Both intravenous and oral formulations would be desirable for the acute and chronic management of ischemic syndromes.

**THE STRUCTURE OF GP IIb/IIIa AND ITS ROLE IN HEMOSTASIS**

**Protein structure**

The GP IIb/IIIa complex consists of two subunits which interact noncovalently. GP IIb has two disulfide-linked polypeptide chains (MW = 120000 and 20000) and GP IIIa is a single polypeptide (MW = 95000) [26]. The complex belongs to the integrin superfamily of proteins in the \( \beta_3 \) family (reviewed in Refs. 27 and 28).