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REVIEW ARTICLE

Platelet collagen receptors, signaling and antagonism: Emerging approaches for the prevention of intravascular thrombosis

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Abstract

Collagen, one of the major proteins of sub-endothelial vasculature get exposed following endothelium denudement, is a potent stimulator of platelet adhesion and aggregation. Adhesion of platelets following endothelial injury is the primary event usually associated with uncontrolled platelet activation culminating into intravascular thrombosis, thus needs to be intervened to prevent the pathology related to various peripheral, myocardial and cerebral ischemic episodes. Recent advances in the understanding of collagen mediated platelet adhesion and aggregation have led to the identification of two prominent receptors, glycoprotein Ia/IIa (GPIa/IIa or integrin $\alpha_2\beta_1$) and glycoprotein VI (GPVI) and associated intracellular signaling, which are undoubtedly the new emerging targets for the development of more effective antithrombotic drugs. The optimism for collagen antagonism is based on results obtained so far by the use of monoclonal and polyclonal antibodies, peptide inhibitors, knockouts models and collagen-mimetics in various *in vitro* test systems and animal models. These findings have revealed that collagen receptor inhibition is an attractive and secure strategy for the new drug development to prevent intravascular thrombosis.

Abbreviations: vWF, von Willebrand Factor; ADP, adenosine 5'-diphosphate; TxA_2, thromboxane A_2; CAD, coronary artery disease; PLC, phospholipase C; PP1, protein phosphatase 1; FAK, focal adhesion kinase; PS, phosphotidylserine; CRP, collagen-related peptide; CVX, convulxin; MMP, matrix metalloproteinase; PAR, protease activated receptor; GPVI, glycoprotein VI; COX, cyclooxygenase; SH3, Src homology-3; FcR γ, Fc receptor gamma; SLP-76, SH2 domain-containing Leukocyte Protein of 76 kDa; ERK, extra cellular receptor kinase; JNK, c-Jun N-terminal kinase.

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Contents

Introduction

Collagen, a matrix protein has various structural characteristics with diverse functions. It is a family of proteins consisting of about 28 different types of collagens [1] and is synthesized by a wide variety of cells such as macrophages, smooth muscle cells, endothelial cells, keratinocytes, epithelial cells and fibroblasts [2]. In blood vessels it constitutes about 40% of the total protein [3] which help to maintain vessel wall integrity and elasticity. All types of collagens in the appropriate polymeric form can induce platelet aggregation *in vitro*. Among various collagens, types I, III (fibrillar collagen) and IV (non-fibrillar collagen) are the most platelet reactive and can induce both adhesion as well as aggregation [4] and are present in the vessel wall [2]. Collagen types I and III are exposed to platelets mainly when the injury extends to the deeper layers of vessel wall, the media and adventitia, but in some vessel matrices these collagens are also found in the sub-endothelium [5].

The role of platelets in pathophysiology of intravascular thrombosis is well established and collagen is one of the strong inducers of platelets. GPIa/IIa ($\alpha 2\beta 1$ integrin) and GPVI are the two well established collagen receptors present on platelets [3,6]. Moreover, recent studies have highlighted the importance of these receptors in thrombosis [7–9]. It is thus appropriate to develop novel drugs to prevent collagen mediated thrombosis [10–12]. The present review covers collagen mediated platelet adhesion, activation, aggregation and thrombus formation. Moreover, interplay of collagen receptors and their associated down stream signaling in platelets has also been discussed. Snake venom peptides, natural and synthetic agents, which are collagen receptor antagonists/agonists as well as methodologies to evaluate potential collagen inhibitors have also been included in this review.

Mechanism of collagen mediated platelet adhesion and activation

Endothelial injury leads to platelet adhesion, rolling, tethering, activation, propagation and thrombus formation [13]. Exposure of sub-endothelial collagen fibers and vWF at the sites of vascular injury initiates adherence of a platelet monolayer to build thrombus [14]. The collagen bound vWF interacts with platelets through the GPIb-IX–V complex and the integrin GPIIb/IIIa [15,16]. Platelets differentially interact with the sub-endothelial collagen depending on low or high shear stress [17]. In high shear stress, it interacts with collagen bound vWF through GPIb-IX–V complex and subsequently gets activated by binding to GPVI under flow [18,19]. vWF accelerates the platelet adhesion under flow onto the collagen surface by enhancing platelet aggregation in the platelet-reduced