PLATELET ACTIVATION AND CAROTID ARTERIAL ATHEROTHROMBOSIS

Kenneth Kun-yu Wu

Introduction

Blood platelets play a major role in atherosclerosis and thrombosis [1]. They are critical for the pathogenesis of human carotid atherosclerosis, thromboembolism, and thrombotic stroke. A key event in all these processes is platelet activation by matrix proteins notably collagen and by inducers at the arterial damage site. Platelet activation results in drastic changes which include the following key events: 1) membrane phospholipid changes facilitating coagulation reaction and thrombin generation; 2) conformation changes in glycoprotein IIb-IIIa rendering it functionally active for fibrinogen binding and platelet aggregation; 3) activation of arachidonic acid metabolism with the synthesis and release of thromboxane A2 (TXA2); and 4) intracellular changes leading to release of biologically active compounds from dense-granule (ADP, serotonin) and alpha-granules. Alpha-granular products comprise growth factors, coagulation factors, β-thromboglobulin (β-TG), platelet factor 4 (PF-4), and P-selectin.

ADP, thrombin, and TXA2 recruit new platelets and amplify platelet activation and aggregation. TXA2 and serotonin are vasoconstrictive agents and are important in ischemia. P-selectin is secreted on to the platelet membrane and maybe involved in platelet-neutrophil interaction. Growth factors such as platelet-derived growth factors play a key part in smooth muscle cell migration and proliferation. Hence, platelet activation leads to platelet aggregation and causes or contributes to vasoconstriction, internal hyperplasia, atherosclerosis, and thrombosis.

Platelet activation generally occurs on and at the vicinity of damaged arterial wall. However, clinical studies provide evidence to indicate that platelet aggregates and activated platelets are detectable in circulating blood of patients with various arterial atherothrombotic disorders [1,2]. Methods used to determine platelet activation in patients evolve from platelet aggregation and platelet aggregate ratios developed in the 1970s to βTG, PF-4, and TXB2 (urinary 2,3-dinor-TXb2 ) in the 1980s and platelet surface markers by flow cytometry in the 1990s (Table 1). Despite the use of diverse techniques over a more than 20-year span, the results are consistent and certain conclusions may be reached: 1) patients with myocardial infarction (MI) or thrombotic stroke are more prone to have platelet aggregates and activated platelets in circulating blood than healthy subjects and 2) platelet preparations obtained from patients with MI or stroke are more reactive in vitro in response to...
mechanical stirring ("spontaneous" platelet aggregation), chemical stimulation, or shear stress.

Table 1. Laboratory Assays for Platelet Activation and Aggregation

| 1970s          | Platelet aggregation
|                | Spontaneous aggregation
|                | Induced aggregation
|                | "Circulating" platelet aggregates
|                | Platelet α-granule releasates
|                | β-thromboglobulin
|                | Platelet factor 4
| 1980s          | Thromboxane B₂ and metabolites
|                | Serum TXB₂
|                | Urine 2,3-dinor-TXB₂
|                | Plasma or urine 11-dehydro-TXB₂
| 1980s-90s      | Activated platelet membrane markers by flow cytometry
|                | Conformational active glycoprotein IIb-IIIₐ
|                | P-selectin (GMP-140, or PADGM)
|                | Platelet aggregates by flow cytometry
|                | Sizing of platelet aggregates by flow cytometry using GPIb MoAb
|                | Platelet-neutrophil aggregates
|                | Dual label with P-selectin and GPIb Ab’s

We previously reported spontaneous platelet aggregation in patients with stroke and demonstrated by a formalin fixation method a corresponding increase of circulating platelet aggregates in these patients [3-5]. It has recently been shown in a prospective study that post-MI patients who exhibited persistent positive spontaneous platelet aggregation increased risk for recurrent MI and MI-related mortality by several fold [6].

We have recently shown by flow cytometry the persistent presence of activated platelets and platelet-neutrophil aggregates in patients with atherothrombotic stroke but not