RESISTANCE TO ANTIPLATELET THERAPY

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1 INTRODUCTION

Atherothrombotic complications are the primary causes of cardiovascular mortality and morbidity. The common underlying pathological basis for the development of catastrophic ischemic events during cardiovascular diseases is the occlusive platelet-rich thrombus generation at the site of plaque rupture. Occlusive thrombus development is also responsible for microembolization, which results in microvascular dysfunction following stroke and myocardial infarction. Platelets are not only central to these thrombotic processes ("platelet hypothesis") but also play important roles in atherosclerosis, coagulation, and inflammation (Fig. 1) [1–3]. Therefore, pharmacological agents that suppress platelet function have proven to be beneficial during the acute settings of acute coronary syndrome (ACS) and percutaneous coronary interventions (PCI) where superior platelet inhibition is desired and also during long-term treatment of coronary artery disease, ischemic stroke, and peripheral arterial disease [4]. Since platelets are activated by multiple redundant pathways, simultaneous inhibition of two important secondary agonist pathways [thromboxane A2 by inhibiting cyclooxygenase-1 by aspirin and adenosine 5′-diphosphate (ADP) pathway by inhibiting $P2Y_{12}$ receptor by clopidogrel] is desired. Clinical efficacy of the dual antiplatelet therapy has been demonstrated in large-scale clinical trials. In these clinical trials, a "one size fits all" approach has been adopted without evaluating the platelet response in the individual patient. However, subsequent ex vivo laboratory evaluation of individual antiplatelet response indicated a wide response variability where a substantial number of patients were not receiving the desired benefits with the prescribed dosing regimens. This phenomenon is described as "antiplatelet resistance or nonresponsiveness" [5]. Moreover, continued occurrence of recurrent ischemic events among selected patients with high on-treatment platelet reactivity or among patients exhibiting antiplatelet resistance again highlighted the importance of limitations of uniform dual antiplatelet treatment strategy. Currently, 25 million people in United States use aspirin as an antiplatelet agent to prevent cardiovascular events, whereas, between 1998 and 2004, use of clopidogrel has increased over 7 times whereas the use of clopidogrel with aspirin has increased 16 times in the United States [6]. The "nonresponsiveness or resistance" to antiplatelet therapy is becoming a major concern. Therefore, numerous scientific meetings and hundreds of clinical publications have been focused on this phenomenon. However, the mechanism of antiplatelet resistance, and treatment strategies to address these concerns are still unclear.

2 ROLE OF PLATELETS IN THROMBOTIC EVENTS

Platelets are the smallest blood cells released from megakaryocytes in bone marrow and circulate in blood as disk-shaped anucleate fragments without attaching to the normal vessel wall. They play an important role during normal hemostasis by forming clots at the site of vascular injury to prevent excessive blood loss. In the

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