

Adrenoreceptors, platelet reactivity and clopidogrel resistance

Yao-Zu Xiang^{1,2}

¹Research Center of Tianjin University of Traditional Chinese Medicine, Tianjin, China; ²Department of Haematology, Imperial College London, Hammersmith Hospital Campus, London, United Kingdom

Platelet activation plays a central role in haemostasis and thrombosis. Antiplatelet therapy is considered to be the 'cornerstone' in the prevention and treatment of thrombotic diseases such as coronary artery disease (CAD), stroke and peripheral arterial disease (PAD). While dual antiplatelet therapy with aspirin and clopidogrel is currently the standard therapy after coronary stent implantation to prevent a life-threatening stent thrombosis, the concept of antiplatelet drug 'resistance' or non-responsiveness has also received increasing attention over recent years, and at least aspirin resistance, clopidogrel resistance and glycoprotein IIb/IIIa (GpIIb-IIIa) inhibitors resistance have been widely reported (1, 2). Therefore, to illuminate the underlying mechanisms of antiplatelet drug resistance such clinical issues are of great importance. In this issue of *Thrombosis and Haemostasis*, Béres et al. (3) identify a potential novel mechanism of clopidogrel resistance, high platelet α -2 adrenergic receptor.

The extent of the platelet aggregation response *in vitro* to adenosine diphosphate (ADP) and the inhibition of vasodilator-stimulated phosphoprotein (VASP) phosphorylation have been used to define clopidogrel resistance in the large majority of studies that have been published so far. The incidence of clopidogrel resistance varied between 5% and 85.8% (4–6), while aspirin resistance was 5.5% ~ 61% (7). The potential mechanisms involved in the variable response to clopidogrel have been fully summarized by De Miguel et al. (8). However, many mechanisms mentioned are still controversial, e.g. polymorphisms of P2Y₁₂ do not seem to play additional roles in modulating the individual response (9, 10). Only 'metabolic activity of the hepatic cytochrome P450' and 'clopidogrel bioavailability' have been well established. Currently, Béres et al. (3) have studied the influence of platelet α -2 adrenoreceptor on increased residual platelet reactivity. Interestingly, their results demonstrate that α -2 adrenergic receptor contributes to high on-treatment platelet reactivity and consequently, to clopidogrel resistance through preserving P2Y₁₂ receptor function.

It is known that human platelets exhibit both adrenergic and dopaminergic receptors that are influenced by different catecholamines. α -2 adrenergic receptors prevail on the platelet mem-

brane; through their stimulation, catecholamines potentiate the effects of other agonists (e.g. ADP) and, at higher concentrations, initiate platelet responses, including aggregation, secretion and arachidonate pathway activation (11). Especially, epinephrine amplifies the response elicited by a number of agonists for platelet aggregation (12). Using five different agonists (ADP, epinephrine, collagen, collagen-related peptide, and ristocetin) and a broad range of agonist concentrations, Yee et al. (13) found that epinephrine was especially reliable and efficient in detecting platelet hyperreactivity, and excellent reproducibility persisted for up to three years. Moreover, platelet hyperreactivity is not limited to epinephrine-mediated aggregation, but can generally be observed with multiple forms of platelet stimulation, and is associated with each major phase of platelet function: From adhesion (increased agglutination in response to low-dose ristocetin) to activation (increased P-selectin expression after granule release) to aggregation (increased aggregation in response to multiple different stimuli) (14). These findings suggest an underlying mechanism that occurs relatively early in the progression of platelet activity (i.e. in proximity to epinephrine's interaction with the α 2A-adrenergic receptor) and that is shared by multiple pathways affecting distinct aspects of platelet function (14).

Through studying 121 stable angina patients on standard dual antiplatelet therapy (75 mg clopidogrel and 100 mg acetylsalicylic acid), Béres et al. (3) also found similar results that patients with high adrenergic activity have significantly increased baseline ADP- and collagen-induced platelet aggregation. In addition, another study demonstrated that platelet α -2 adrenergic receptor plays a significant role in thrombus stabilization (15). Therefore, epinephrine-platelet receptor signal pathway may play a central role in the platelet hyperreactivity relevant for thrombotic disease.

Many platelet agonists function through G-protein-coupled receptors (16). Epinephrine activates the α -2 adrenergic receptor that couples to G_z in platelets, while ADP activates P2Y₁₂ receptor that couples to G_i and P2Y₁ to G_q, respectively (1). Although different in downstream events of the signal transduction pathways, platelet response to both epinephrine and ADP are independent of adenylyl cyclase inhibition which is shared by α -2A adre-

Correspondence to:
Dr. Yao-Zu Xiang
Research Center of Tianjin University of Traditional Chinese Medicine
Nankai District, Anshanxi Road # 312, Tianjin, 300193, China
Tel./Fax: +86 2223051183
E-mail: y.xiang08@imperial.ac.uk

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noceptor and P2Y₁₂ (17). Similar to the P2Y₁₂ receptor, activation of the α -2 adrenoceptor decelerates the deaggregation component shifting the balance toward increased net aggregation (12). Béres et al. (3) found that patients with high α -2 receptor-related platelet reactivity had increased inhibitory capacity of cangrelor, indicat-

ing that in these patients, the functional P2Y₁₂ receptor pool is more preserved. These significant findings may explain how high platelet α -2 adrenergic receptor contributes to clopidogrel resistance. Future studies will be necessary to illuminate the interaction between α -2A adrenoceptor and P2Y₁₂ receptor.

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