Intelligent Platelet Inhibitors Are on the Horizon

Meinrad Gawaz

Hemostasis is a tightly regulated physiological sequence of events that maintains vascular integrity and imminent blood loss after vessel injury. Platelets play a critical role in primary hemostasis and in regulation of coagulation. Under physiological conditions, hemostasis and thrombosis are in a fragile equilibrium. Uncontrolled platelet activation leads to intravascular thrombosis and organ failure. In patients with cardiovascular diseases such as coronary artery disease or stroke, antiplatelet therapy has substantially improved morbidity and mortality. To date, several antiplatelet inhibitors, including acetyl salicylic acid, P2Y12 inhibitors, and glycoprotein (GP) IIb-IIIa (integrin αIIbβ3) receptor blockers, are available to prevent or treat arterial thrombosis in affected patients. However, all current antiplatelet drugs inhibit both resting and activated platelets resulting in inhibition of hemostasis. Thus, current antiplatelet therapy is associated with enhanced risk of bleeding. Novel antiplatelet strategies are warranted to control undesired platelet activation without disrupting hemostasis and risking life-threatening bleeding complications.

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In the current issue of Arteriosclerosis, Thrombosis, and Vascular Biology, Topcic et al have developed a temperature-sensitive platelet inhibitor targeting the fibrinogen receptor GP-IIb-IIa. GP-IIb-IIa is required for platelet aggregation. On resting platelets, GP-IIb-IIa is in a low-affinity state that does not allow binding of soluble fibrinogen (Figure). On activation through platelet agonists such as ADP or thrombin, GP-IIb-IIa undergoes a conformational change to a high-affinity state that binds fibrinogen and allows platelet aggregation. Currently available GP-IIb-IIa blockers (eg, abciximab, eptifibatide, tirofiban) bind to the receptor irrespectively of whether it is in a resting or activated state. Recently, Peter’s group has developed a single-chain antibody that selectively blocks the high-affinity GP-IIb-IIa on activated platelets. In contrast to conventional conformation-unspecific blockers, this activation-specific GP-IIb-IIa antagonist preferentially binds to its activated but not to its resting receptor and thus inhibits platelet aggregation without altering platelet adhesion. Therefore, this novel single-chain anti-GP-IIb-IIa antibody inhibits thrombosis in vivo without prolongation of bleeding times in mice.

In the present study, Topcic et al have fused this activation-specific anti-GP-IIb-IIa single-chain antibody (GP-IIb-IIa-single chain fragment C-elasticin-mimetic polypeptide [EMP]) with an EMP derived from a consensus motive of tropoelastin (GP-IIb-IIa-single chain fragment C-EMP). The protein structure of EMP exhibits an inverse temperature transition to a β-sheet structure at temperatures greater than the transition temperature. Topcic et al hypothesized that these characteristics would result in EMP acting as a thermosensitive on/off switch for the single-chain antibody’s antiplatelet properties. The authors convincingly show that their fusion protein single chain fragment C-EMP selectively inhibits platelet function in hypothermia but not at 37°C both in vitro and in vivo. The approach taken by Dr Peter’s group is highly innovative and opens a new area of “intelligent” antiplatelet therapy. In the present article, the authors propose that their molecule might be beneficial for patients who undergo cardiovascular surgery under conditions of medically used hypothermia, which enhances the risk of thromboischemic or thromboembolic complications. In addition, the administration of temperature-sensitive platelet inhibitors may also be of interest in septic patients. Sepsis has been found to be associated with enhanced platelet activation and disturbances of microcirculation due to platelet accumulation. Thus, the use of temperature-sensitive antiplatelet...
drugs might be an attractive strategy to treat microvascular thrombosis and subsequent threatening organ failure in septic patients. In general, the strategy to control drug activity by temperature might provide unique therapeutic opportunities in many areas of medicine.

The advent of biotechnology enabled the design and the development of drugs to improve personalized medical treatment. In the field of antiplatelet therapy, a new age of research has been opened, and novel intelligent platelet inhibitors are on the horizon with greater individual efficacy and a favorable safety profile. Targeting platelet adhesion receptors with activation-specific inhibitors (eg, directed against GPIIb-IIIa)\textsuperscript{2,4} or soluble receptors (eg, collagen receptor GPVI) that allow lesion-specific platelet inhibition at the site of vulnerable plaques without enhancing the risk of bleeding\textsuperscript{7} has the potential to change antiplatelet therapy in the foreseeable future.

**Disclosures**

None.

**References**


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