CD39 target practice

Debra K. Newman

In this issue of Blood, Hohmann et al describe a new antithrombotic strategy that involves delayed targeting of CD39 to activated platelets, which reduces thrombus size without increasing bleeding.

Thrombosis in the arterial circulation relies heavily on platelet activation and formation of a platelet-rich thrombus. When adequately controlled, this process works well to minimize blood loss from broken blood vessels. However, it becomes pathological when thrombi grow too large for the vessels in which they’ve formed. Pathological thrombi restrict or occlude blood flow to downstream tissues such as the heart, which can result in a heart attack. Antithrombotic drugs have been developed and used successfully to reduce the risk of death associated with acute cardiac events and to prevent their recurrence; however, current Food and Drug Administration–approved antiplatelet drugs are associated with an unacceptably high risk for developing major, and sometimes life-threatening, bleeding. Thus, efforts to identify novel antithrombotic strategies that reduce thrombus size without increasing bleeding risk are justified.

Platelet thrombus formation occurs in a stepwise process, in which activation of the integrin αIIbβ3 and secretion of the soluble agonist adenosine diphosphate (ADP) play important roles (see figure). The first or initiation phase of this process involves formation of a platelet monolayer at the site of vessel injury, which requires adhesion of platelets to activated endothelium or to subendothelial matrix proteins exposed as a consequence of vascular injury. Platelet adhesion is an activating event that results in conversion of the integrin αIIbβ3 from a resting to an active conformation, in which it is competent to bind plasma fibrinogen. In the second phase, circulating platelets bind to immobilized fibrinogen and are thereby recruited into the growing thrombus. In the third phase of the process, platelets recruited to the thrombus by binding to immobilized fibrinogen are activated by soluble agonists released by activated, adherent platelets that form the initial platelet monolayer. Of particular importance is the platelet dense (5) granule constituent, ADP, which binds to two GPCRs, including the Gαq-coupled P2Y1 receptor and the Gai-coupled P2Y12 receptor. GPCR-mediated activation of platelets bound to immobilized fibrinogen initiates the third or perpetuation phase of the thrombus formation process because it results in activation of αIIbβ3, binding of plasma fibrinogen, and recruitment of additional platelets into the growing thrombus. (B) Targeting of soluble CD39 to activated platelets interferes with the perpetuation phase, but not the initiation or accumulation phases, of thrombus formation. Targ-CD39 represents a fusion protein composed of soluble CD39 fused to a single-chain Fv fragment (scFv) of an antibody that is specific for the active conformation of the platelet-specific integrin αIIbβ3. Targeting of CD39 to activated αIIbβ3 ensures that hydrolysis of ADP is delayed until after the first layer of platelets has already been activated and allowed to recruit the second layer of platelets. Consequently, Targ-CD39 interferes only with ADP-mediated activation of recruited platelets, which affects only the perpetuation phase of thrombus formation.
A2 and ADP, which activate recruited platelets on binding to G protein–coupled receptors (GPCRs) on their surfaces. GPCR-mediated activation of recruited platelets enables the third or perpetuation phase of the thrombus formation process because it results in activation of αIIbβ3, binding of plasma fibrinogen, and recruitment of additional platelets into the growing thrombus.

Optimal platelet activation by GPCRs, which contributes importantly to thrombus growth, requires involvement of both Gq- and Gi–coupled receptors. ADP is a particularly potent GPCR agonist because it serves as a ligand for both the Gq-coupled P2Y1 receptor and the Gi-coupled P2Y12 receptor. Existing antithrombotic therapies that interfere with this mechanism of platelet activation include the P2Y12 receptor antagonist, which block ADP binding to the P2Y12 receptor. Physiological mechanisms for regulation of ADP-mediated platelet activation also exist, among which are the activities of ecto-nucleotidases that hydrolyze ADP (and ATP) to AMP and adenosine.

REFERENCES


Comment on Baker et al, page 3147

Multiethnic myeloma

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In this issue of Blood, Baker and colleagues present the first study on genomic differences between multiple myeloma (MM) tumors derived from European Americans (EA) and African Americans (AA).1 They found a lower frequency of IgH translocations in AA compared with EA but otherwise similar genomic profiles.

Myeloma has one of the most striking ethnic disparities in incidence and outcomes in cancer.2 Compared with incidence in EA, both MM and its precursor state, monoclonal gammopathy of undetermined significance (MGUS), are two- to threefold more common in AA. The clinical features of these plasma cell disorders are distinctly different between AA and EA. For example, AA patients with MGUS have lower monoclonal immunoglobulin (Ig) concentrations, a markedly lower frequency of IgM isotype, and a very high frequency (45% in AA compared with 33% in EA) of abnormal serum-free light-chain ratios.3 There is a strong suggestion that AA with MM may have more favorable outcomes than EA. Waxman and colleagues analyzed the National Cancer Institute SEER registries from 1973 to 2005 and demonstrated that the 5-year disease-specific survival for AA was 41.6% compared with 37.4% in EA (P < .001).4 However, in this analysis, AA did not experience the same degree of improvement in survival as EA diagnosed in more recent years. An analysis of the Center for International Bone Marrow Transplant Registry revealed that AA and EA treated uniformly with high-dose therapy and autologous stem cell transplantation have equivalent outcomes.5 The reasons for all of these differences are not clear, but taken together they suggest underlying biological differences between MM tumors in AA and EA patients.

Baker and colleagues sought to answer whether different genomic alterations between AA and EA with MM could account for these clinical observations. Molecular classification systems based on IgH translocations, chromosome content, and gene expression profiling have revealed genomic heterogeneity in MM that is associated with distinct clinical outcomes.6 Given the suggestion of better outcomes for AA compared with EA in clinical studies, a lower frequency of unfavorable genomic features might be expected in AA. They assembled a cohort of AA and EA MM tumors from the Eastern Cooperative Oncology Group trials E3A03 and E9487, the Multiple Myeloma Research Consortium (MMRC) Tissue Bank, and the Mayo Clinic. The available genomic data included IgH translocations by clg–fluorescence in situ

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