Nonremodeling Properties of Matrix Metalloproteinases
The Platelet Connection

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Matrix metalloproteinases (MMPs) and their endogenous inhibitors, tissue inhibitors of metalloproteinases (TIMPs), play an important role as mediators of tissue remodeling under physiological and pathological conditions.1 Recently, a number of contributions have shown that in addition to chronic remodeling reactions, MMPs are involved in acute biological reactions associated with discrete cell signaling such as regulation of vascular reactivity,2–4 leukocyte activation,5 and platelet function.6–12 The study by Galt and colleagues, published in this issue of Circulation Research, shows that MMP-1, yet another member of the MMP family of enzymes, primes platelets for aggregation.13 They have demonstrated that the outside-in signals delivered by MMP-1 markedly increased the number of protein phosphorylated in platelets. In this respect, MMP-1 acts similar to platelet receptor agonists such as ADP, collagen, and thrombin, which are known to stimulate protein phosphorylation.14 In addition, this work provides further evidence that some biological functions of platelets are regulated by MMPs.

Blood Platelets
Platelets are small (∼2 μm in size) anucleate cell elements that are produced by fragmentation of large mother cell megakaryocytes. Although the process of platelet production (thrombopoiesis) is regulated by thrombopoietin, which controls megakaryocyte proliferation, maturation, and platelet generation, some stages of thrombopoiesis are dependent on the activity of MMP-9.15 Platelets are involved in physiological hemostasis and pathological thrombosis. After accidental or pathological injury, platelets adhere to the damaged portion of the vascular wall initiating an intricate set of reactions that lead via platelet aggregation to the formation of hemostatic plug or occlusive thrombus. Complex platelet metabolic pathways are involved in regulation of platelet function (Figure).

Matrix Metalloproteinases and Platelet Hemostasis
Although collagenolytic activity of platelets was discovered by Chesney et al,16 as early as 1974, the molecular identity of enzymes involved remained unknown until the late 1990s. To date, four MMPs including MMP-1, MMP-2, MMP-3, and MMP-9 have been identified in human platelets.7,8,13 In resting platelets, these enzymes, similar to many cell types, are stored in the latent form. In difference to leukocytes where pro-MMP-2 and pro-MMP-9 are stored in specialized gelatinase granules,17 in platelets, pro-MMP-2 is found in the cytoplasm without an apparent association with α or dense granules.7

Platelet adhesion triggered by von Willebrand factor12 and platelet aggregation by collagen, thrombin and human cancer cells all result in the liberation of both pro-MMP-1 and pro-MMP-2.6,7,10,13 The enzymes translocate to the platelet surface membrane where they appear to colocalize in areas of cell contact with β3 integrins.7,13 The translocation of pro-MMP-1 and pro-MMP-2 to the cell surface is likely to provide stimulus for enzyme activation. Interestingly, pro-MMP-2 may be activated by the classical membrane-type (MT)-MMP/TIMP-2–dependent pathway8 or by a mechanism that does not involve TIMP-2.18 A significant part of MMP-2 may be released or shed to the extracellular compartment.6,7,10 The processes of translocation and release are tightly linked to platelet activation and are downregulated by endogenous inhibitors of platelet aggregation, nitric oxide (NO), and prostacyclin I2 (PGI2).6,10

What is the biological significance of this trafficking of MMPs in platelets? The experiments using molecular and pharmacological inhibitors, as well as recombinant MMP-1 and MMP-2, have shown that these enzymes may prime platelets for adhesion and aggregation.6,11–13 Moreover, MMP-2 is one of the mediators of tumor cell–induced platelet aggregation, the phenomenon that plays a role in the hematogenous dissemination of cancer.10 In contrast, MMP-9, which is expressed in platelets in lower amounts than MMP-1 or MMP-2,13 appears to counteract the platelet-aggregatory effects of MMP-2 and inhibits aggregation,8 whereas MMP-3 is devoid of any effects on aggregation.13 The mechanisms of interactions of MMPs with platelets are still being elucidated. It has been demonstrated that only activated, but not latent, MMP-1 and MMP-2 stimulate platelet function suggesting that a limited proteolysis might underlie the platelet activator actions of these compounds.5,13 The actions of MMP-2 may involve modification of major platelet receptor glycoproteins GP Ibα12 and GP IIb/IIIa11 or their ligands, whereas those of MMP-1 are based upon stimulation of tyrosine phosphorylation and clustering of β3 integrins to focal adhesion points.13 Whether MMP-1 and/or other MMPs modulate tyrosine phosphorylation via interactions with specific platelet receptors remains to be studied. Although the actions of MMPs on platelets may not require...
Overview of major platelet reactions and signaling pathways and how they are thought to relate to MMPs. Receptors are boxed and ligands are circled. ADP indicates adenosine diphosphate; AA, arachidonic acid; AC, adenylate cyclase; cAMP, cyclic AMP; TXA2, thromboxane A2; TP-receptor, thromboxane receptor; PAR, proteinase-activated receptor; PKA, protein kinase A; PKG, protein kinase G; TIMP, tissue inhibitor of metalloproteinases; and vWF, von Willebrand factor.

Over the past few years, MMPs have emerged as a novel class of enzymes, show a low level of selectivity toward individual members of this family. This relative lack of selectivity might be one of the reasons behind the lack of effectiveness of chemical inhibitors in the treatment of cancer.27 It is also important to note that not all pathways of platelet activation are MMP-dependent. For example, platelet aggregation induced by PAR-4 agonist, AYPGKF, is MMP-independent.19 On the other hand, MMP inhibitors may decrease a part of platelet activation that is not sensitive to inhibition with aspirin or ADP antagonists6,10,12 and potentially stabilize the atherosclerotic plaque. Therefore, the concept of selective pharmacological inhibition of MMPs to reduce thrombotic complications of vascular disorders is worth considering.6 Interestingly, PGI2 and NO both decrease activation-induced release of MMP-2.6,10 Moreover, m7E3 (ReoPro, abciximab), a GP IIb/IIIa receptor antagonist, reduced the release of MMPs and attenuated the vascular injury in rats.28 This ability to modulate MMP release from platelets and the vascular wall is likely to contribute to the pharmacological profile of PGI2, NO, and m7E3 as potent antiplatelet agents.

Conclusions

Over the past few years, MMPs have emerged as a novel system that regulates platelet function. Understanding the biological effects of MMPs on the vascular hemostasis and thrombosis may have basic, clinical, and therapeutic significance.

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References


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