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MAPkinaseQuest: novel roadway to $\alpha_{IIb}\beta_3$ activation

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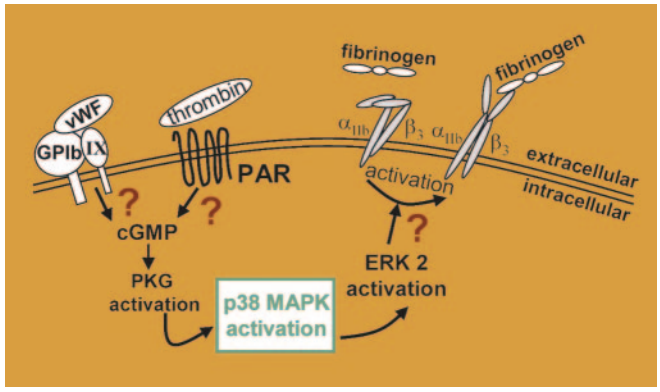
In this issue, Li and colleagues delineate a novel signaling pathway, in which 2 MAPK kinases are shown to regulate the activation of integrin $\alpha_{IIb}\beta_3$ on platelets.



Novel signaling pathway leading to $\alpha_{IIb}\beta_3$ activation. Interaction of VWF or thrombin with their receptors on platelet membrane results in an increase of intracellular cGMP levels, leading to activation of cGMP-dependent protein kinase (PKG). This kinase is upstream of p38 MAPK and ERK2 phosphorylation, which is crucial in $\alpha_{IIb}\beta_3$ activation.

Platelet stimulation begins with the binding of agonists, such as thrombin and von Willebrand factor (VWF) to receptors on the plasma membrane. These interactions transduce a series of intracellular signaling events, collectively referred to as inside-out signaling, which culminate in the conversion of the major platelet integrin, $\alpha_{IIb}\beta_3$, from a quiescent state to an active conformer form capable of binding the soluble ligands. Such activation of $\alpha_{IIb}\beta_3$ is essential for platelet aggregation, an event of critical importance not only in the maintenance of hemostasis but also to the development of myocardial infarction, stroke, and other thrombotic diseases. Thus, the pathways of inside-out signaling and $\alpha_{IIb}\beta_3$ activation have been intensively investigated (reviewed in Shattil and Newman[1]).

Li and colleagues identify a previously unappreciated inside-out signaling pathway. Using pharmacologic and molecular biologic approaches, p38 MAPK is implicated in agonist-stimulated platelet activation. First, 2 inhibitors of p38 MAPK, SB203580 and SB202190, are shown to abrogate platelet aggregation triggered either by VWF interacting with GPIb-IX or by low-dose thrombin or thrombin receptor activating peptides (TRAPs) interacting with PAR1 and PAR 4. Hence, p38 MAPK is involved in platelet activation mediated by 2 major physiologic agonists. Second, VWF-GPIb-IX–mediated activation of $\alpha_{IIb}\beta_3$ in Chinese Hamster Ovary (CHO) cells expressing the platelet receptors is markedly inhibited by cotransfection with a dominant-negative mutant of p38 MAPK. This effect, detected as a significant attenuation of fibrinogen binding to $\alpha_{IIb}\beta_3$, is not due to reduced expression of the integrin or GPIb-IX. If blockade of p38 MAPK activity reduces activation of $\alpha_{IIb}\beta_3$, then VWF and thrombin might trigger phosphorylation of p38 MAPK in platelets. Indeed, the investigators found that both VWF and thrombin stimulated rapid and transient phosphorylation not only of p38 MAPK but also of another MAPK family member, ERK2. Although p38 MAPK and ERK2 are regarded as parallel pathways in many biologic systems,[2] the authors show that p38 MAPK is upstream of ERK2 activation, as p38 MAPK inhibitors and the dominant-negative mutant of p38 MAPK diminished phosphorylation of ERK2. The authors previously reported that engagement of GPIb-IX and PARs increases intracellular cGMP, leading to activation of cGMP-dependent protein kinase (PKG), which, in turn, induces activation of $\alpha_{IIb}\beta_3$ via phosphorylation of ERK2. In the present study, these investigators demonstrate that PKG activation is upstream of VWF- and thrombin-triggered p38 MAPK phosphorylation; this event is completely blocked by specific inhibitors of PKG and is not observed in PKG-knockout mice. Taken together, Li et al have characterized a novel inside-out signaling pathway (see figure) in which physiologic platelet agonists sequentially induce activation of PKG, p38 MAPK, and ERK2, leading to $\alpha_{IIb}\beta_3$ activation. Remaining to be elucidated are the upstream, how agonists trigger PKG activation, and downstream, how ERK2 regulates $\alpha_{IIb}\beta_3$ activation events. Nevertheless, the present study redraws the inside-out signaling map, placing p38 MAPK as a critical mediator of platelet activation and expanding interest in it as a target for protection against cardiovascular diseases.[3] ■

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GATA-1 caught in the AKT

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Stimulation of the PI3-kinase/AKT pathway by the ligand-bound erythropoietin receptor leads to phosphorylation and activation of the transcription factor GATA-1.

Normal erythroid differentiation requires the cytokine erythropoietin (Epo) and its membrane-bound receptor (EpoR). Signals emerging from this receptor are transmitted to the nucleus by a branched network of downstream effectors and ultimately regulate gene transcription. Arguably, the best-studied erythroid transcription factor is the zinc finger protein GATA-1, which regulates all erythroid-specific genes studied to date. GATA-1