role in stabilizing the VWF receptor complex GPIb-IX-V by linking GPIbα to the actin cytoskeleton, so why are there increased GPIb-IX-V levels in patient resting platelets, whereas they were decreased in FLNa-null mouse platelets? The answer may lie in the requirement of a coordinated spatiotemporal expression of GPIbα and FLNa for normal intracellular protein trafficking and platelet biogenesis. Consequently FLNa-null MKs are fundamentally different from MKs that potentially degrade FLNa secondary to defective PKA. Is the observed platelet function defect in the patients due to their elevated platelet cAMP levels, known to be inhibitory, or due to altered receptor-cytoskeletal composition and dynamics on platelet stimulation? The finding that mutations in PRKACG cause bleeding and reduced platelet counts provides important insights into normal MK development and platelet function, as well as offering another target gene to interrogate when assessing patients with familial macrothrombocytopenia.

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REFERENCES
laser injury, suggesting that P2X1-dependent activation of neutrophils plays an important role in the formation of the fibrin clot.1 This is a newly appreciated mechanism for ATP in the regulation of fibrin formation, as P2X7 expression on myeloid cells was previously shown to be required for the decroption of TF and release of TF aggregation.2 Conversely, injection of WT neutrophils into injured P2X1−/− mice was not sufficient to reconstitute platelet accumulation into the growing thrombus; rather, P2X1 expression on both platelets and neutrophils is required for full platelet- and fibrin-rich hemostatic plug formation.

Although release of circulating nucleotides ATP and adenosine 5′-diphosphate (ADP; an important platelet agonist) positively regulates generation of the hemostatic plug close to the site of injury, an extra level of regulation is achieved by the metabolism of these extracellular nucleotides with increasing distance from the injured site. Endothelial and plasma ectonucleotidases, chiefly CD39 and CD73, hydrolyze ATP and ADP sequentially to adenosine 5′-monophosphate (AMP) and adenosine, respectively. In contrast to the neutrophil-activating properties of ATP, this study demonstrates that a selective agonist for the A2A adenosine receptor on neutrophils inhibits both neutrophil accumulation at the site of injury and elastase release from the activated neutrophils. This suggests that complete hydrolysis of ATP and ADP through AMP to adenosine may constrain fibrin deposition close to the site of injury by activating neutrophil A2A receptors as concentrations of adenosine (relative to ATP) rise further from the injury site, thereby inhibiting neutrophil elastase release and consequent inhibition of TFPI. Whether in vivo levels of adenosine are consistent with this model is at present unclear; nevertheless, such a mechanism would be consistent with studies that have shown enhanced fibrin deposition in CD39−/− mice.10

In summary, this study demonstrates a novel role for the ionotropic ATP receptor P2X1 on neutrophils in the generation of fibrin at sites of vascular injury through the release of neutrophil elastase (to inactivate TFPI) and confirms a requirement for neutrophil P2X1 to work together with P2X1 on platelets to generate the hemostatic plug (see figure). Because nucleotide: nucleoside ratios are important for regulating both thrombotic and inflammatory events, P2X1 may be an attractive target for the development of antagonists to limit thrombo-inflammatory disease.

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REFERENCES
PMNs deliver first aid to clot

Donna S. Woulfe