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| Overexpression of the platelet P2X1 ion channel in transgenic mice generates a novel prothrombotic phenotypeAbstract number: OC208Oury\* C., Kuijpers† M., Toth-Zsamboki\* E., Bonnefoy\* A., Danloy\* S., Vreys\* I., Feijge‡ M., De Vos§ R., Vermylen§ J., Heemskerk‡ J. W. M., Hoylaerts\* M. F.*‡ Netherlands; §Belgium \*University of Leuven, Belgium; †University of Maastricht, Netherlands;*We have generated transgenic mice overexpressing the human P2X1 ion channel in the megakaryocytic cell lineage. Platelets from transgenic mice exhibited a gain of P2X1 ionotropic activity as determined by more prominent P2X1– mediated Ca2+ influx and platelet shape change. P2X1 overexpression enhanced platelet secretion and aggregation evoked by collagen, convulxin, a GPVI-selective agonist, or the thromboxane A2 mimetic U46619. In contrast, these platelet responses to ADP and thrombin were normal. Perfusing whole blood from transgenic mice over collagen fibers at a shear rate of 1000 s-1 resulted in increased P2X1-dependent aggregate formation and phosphatidylserine exposure. Platelet hyper-reactivity to collagen was correlated with up-regulated extracellular signal-regulated kinase 2 (ERK2) phosphorylation. Accordingly, the MEK1/2 inhibitor U0126 potently inhibited collagen-induced transgenic platelet aggregation both under stirring and over a collagen surface under flow. In a viscometer, shear stress caused potent aggregation of transgenic platelets in conditions where wild-type platelets did not aggregate. In an *in vivo* model of thromboembolism consisting of intravenous injection of a low dose of collagen plus epinephrine, transgenic mice died more readily than wild-type mice. Preinjection of U0126 not only fully protected transgenic mice against thrombosis, but also enhanced the survival of wild-type mice injected with a higher collagen dose. Hence, the platelet P2X1 ion channel plays a role in hemostasis and thrombosis through its participation in collagen-, thromboxane A2 and shear stress-triggered platelet responses. Activation of the ERK2 pathway is instrumental in these processes. |