**P2X1 ion channel is critical for vascular integrity in inflammation**

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**Introduction:**

In addition to their role in hemostasis and thrombosis, platelets play a key role in inflammation by supporting leukocyte extravasation and maintaining vascular integrity in inflamed tissue. In mice, thrombocytopenia provokes bleeding that is limited to the site of inflammation. In humans, in the absence of injury, some patients show spontaneous bleeding while others do not bleed despite equally low platelet counts. Though the mechanisms controlling vascular integrity are not fully understood, it has been reported that, in thrombocytopenic mice, neutrophils are responsible for inflammation-associated haemorrhage. The platelet ATP-gated P2X1 ion channel has been involved in arterial thrombosis and may represent an attractive target for antiplatelet therapy since P2X1-deficient mice do not show prolonged bleeding time. Recently, we have shown that this ion channel also regulates neutrophil function.

**Purpose:** To investigate whether P2X1 ion channels contribute to maintain vascular integrity in acute inflammatory conditions.

**Methods:** We used P2X1-deficient mice in two models of acute inflammation. Acute colitis was induced by oral administration of dextran sodium sulfate (DSS). Disease activity index (DAI) was determined to assess colitis severity (diarrhea, bleeding, weight loss). Differential counts of leukocytes and platelets, hematocrit and hemoglobin levels were measured. Crosstalk between platelets, neutrophils and endothelium was evaluated using laser-induced injury of arteriolar endothelia in cremaster muscle. Accumulation of platelets, neutrophils and fibrin generation were recorded in real-time by intravital microscopy. Lung inflammation was induced by intratracheal instillation of LPS from P. aeruginosa. Platelets were depleted by injection of an anti-GPIb antibody. Bronchoalveolar lavage fluids (BALF) were collected 6 hours later to measure hemoglobin levels and leukocyte counts.

**Results:** In the model of acute colitis, P2X1-deficient mice displayed higher intestinal blood loss as compared to control animals, resulting in anemia. This was associated with increased colon infiltration by myeloperoxidase-expressing myeloid cells and more severe intestinal crypt erosion. In the thrombo-inflammatory model of cremaster muscle microcirculation, DSS-treated P2X1-deficient mice showed a strong increase of neutrophil accumulation at the site of arteriolar wall injury whereas platelet recruitment in the growing thrombi was severely impaired. In the acute lung inflammatory model, thrombocytopenic P2X1-deficient mice presented more lung haemorrhage than control mice. The numbers of neutrophils in BALF were also augmented.

**Conclusion:** P2X1 deficiency exacerbates bleeding in inflamed intestine and airway, possibly due to increased accumulation of neutrophils in tissues combined with impaired platelet aggregate formation. Hence, P2X1 ion channel is critical for vascular integrity in acute inflammation.