Atlas of Science
another view on science
http://atlasofscience.org

IL-1 Receptor 8: a novel player in immunothrombosis

In addition to be a key component of blood hemostasis and coagulation, platelets have recently been implicated in thrombotic events associated with immune dysfunctions or inflammation. Platelets participate to innate immune responses and inflammation by releasing a variety of cytokines and chemokines, and by expressing a wide repertoire of functional pattern recognition molecules. Among these, platelets express interleukin-1 receptor (IL-1R) and Toll-like-receptor (TLR) family members, which are involved in platelet activation, platelet-dependent anti-microbial activity and platelet-leukocyte reciprocal activation and immunopathology (Fig. 1).

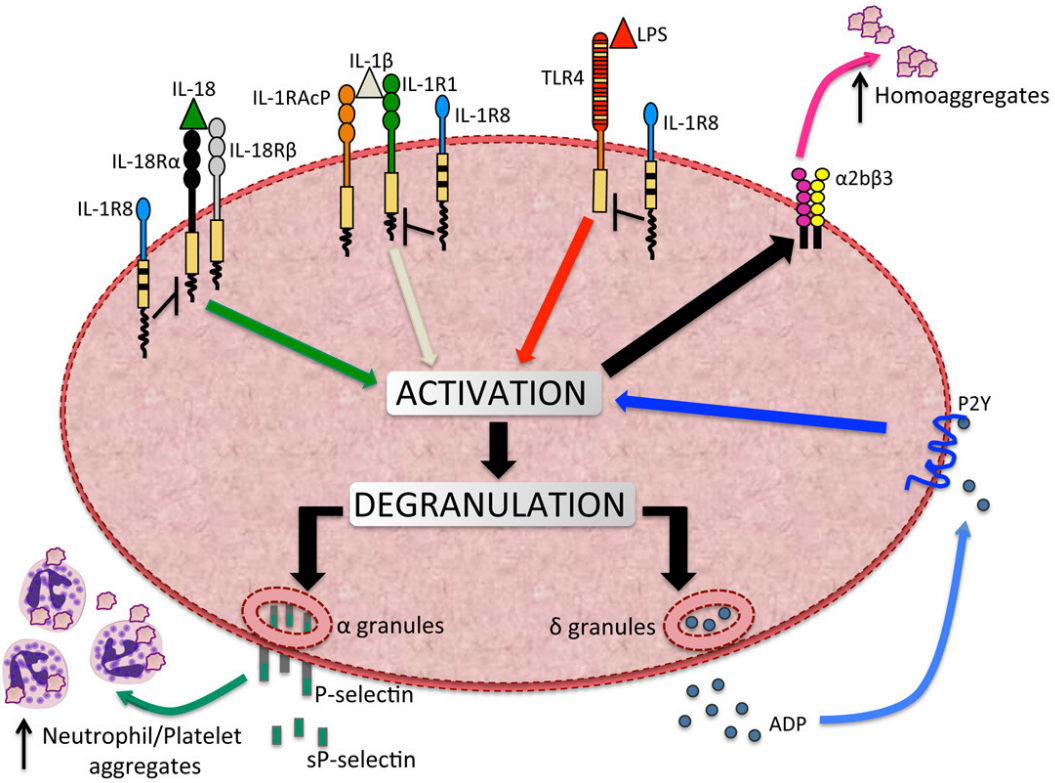

Fig. 1. Expression and function of IL-1R8 in platelets. Pro-inflammatory activation of TLR4, IL-1R1 and IL-18R contributes to platelet α and δ granule release leading to P-selectin surface expression and shedding, and activation of the integrin α2bβ3. These molecules are key actors for the initiation of immunothrombotic events characterized by increased heterotypic (neutrophil-platelet) and homotypic (platelet–platelet) aggregate formations. IL-1R8 emerges as a novel negative regulator of these processes playing relevant roles in immunothrombotic conditions.

Interleukin-1 Receptor 8 (IL-1R8), also known as single Ig IL-1-Related Receptor (SIGIRR) or TIR8, is an anti-inflammatory member of the IL-1R family, which exerts a regulatory role of signalling events downstream of TLRs and IL-1R family members, preventing exacerbated inflammation in different infectious or inflammatory conditions.

We recently reported the first evidence of the expression of IL-1R8 in human and murine platelets and megakaryocytes. The functional role of IL-1R8 in murine platelets was investigated taking advantage of IL-1R8-deficient mice. Despite normal levels of circulating platelets, IL-1R8-deficiency was associated with platelet hyperactivity, together with increased homotypic aggregate formation triggered by pro-thrombotic stimuli (Fig.1). In addition, the lack of IL-1R8 on platelets was associated with increased neutrophil/ platelet aggregate formation in basal conditions and after treatment with lipopolysaccharide (LPS) or IL-1 family members (IL-1 or IL-18) *in vitro* and *in vivo*, indicating that IL-1R8 is a negative regulator of platelet heterotypic aggregation associated with inflammatory conditions and endotoxemia (Fig. 1).

Since IL-1R8 exerts part of its anti-inflammatory function by interfering with IL-1R- and TLR-dependent signalling, we addressed the involvement of these molecules in IL-1R8-deficient platelet reactivity. Interestingly, commensal flora depletion and IL-1R1 deficiency abated platelet hyperactivity and the increased platelet/neutrophil aggregation observed in IL-1R8-deficient mice *in vitro* and *in vivo,* suggesting that microbial TLR ligands as well as IL-1β are involved in platelet hyper activation in IL-1R8-deficient mice. Furthermore, in a mouse model of platelet-dependent thromboembolism, IL-1R8-deficient mice showed an increased frequency of lung blood vessel occlusion by fibrin clots, demonstrating the relevance *in vivo* of the anti-thrombotic activity of IL-1R8.

Finally, it was important to address whether IL-1R8 expression was modified in human pathological conditions associated with platelet dysfunction, in particular in severe systemic inflammatory conditions. Interestingly, in a small cohort of Systemic Inflammatory Response Syndrome (SIRS)/sepsis patients, the expression of platelet IL-1R8 was dramatically abated and negatively correlated with the severity of the condition. In addition, IL-1R8 expression was associated to platelet-derived microparticles, indicating an active shedding of IL-1R8 through microparticle formation during inflammatory conditions. These results suggest that the modulation of IL-1R8 expression in platelets and the following release in microparticles might represent a potential pathogenetic mechanism contributing to platelet dysfunction associated with severe inflammatory conditions.

The results obtained in this study demonstrate that platelets, which have a large repertoire of TLRs and IL-1 receptor family members (IL-1R1 and IL-18Rα, as shown in our study), express high levels of IL-1R8, which is involved in inflammation-related functions of human and murine thrombocytes and plays a novel non-redundant role as regulator of immunothrombosis. Thus, targeting IL-1R8 might represent a promising therapeutic approach in patients with exacerbated innate immune responses and uncontrolled thrombotic events.

Achille Anselmo *and* ***Cecilia Garlanda***
Humanitas Clinical and Research Center, Rozzano, Italy

Publication

Expression and function of IL-1R8 (TIR8/SIGIRR): a regulatory member of the IL-1 receptor family in platelets.

Anselmo A, Riva F, Gentile S, Soldani C, Barbagallo M, Mazzon C, Feruglio F, Polentarutti N, Somma P, Carullo P, Angelini C, Bacci M, Mendolicchio GL, Voza A, Nebuloni M, Mantovani A, Garlanda C

Cardiovasc Res. 2016 Sep