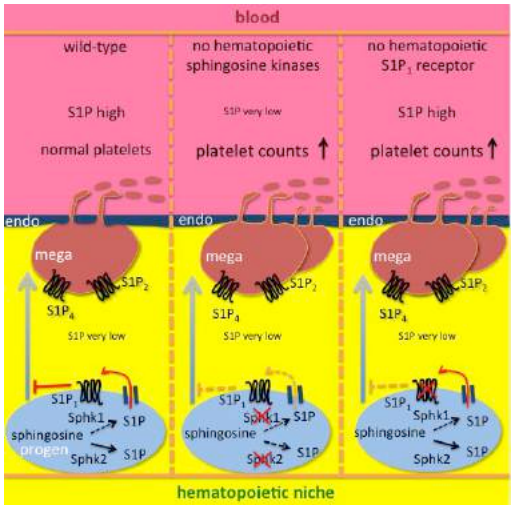
S1P receptor-1 mediated sensing of the vascular S1P gradient is dispensable for platelet formation.

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Abstract:

Sphingosine-1-phosphate receptor-1 ($S1P_1$, encoded by *S1pr1*) has been reported to be indispensable for guiding proplatelet extensions into bone marrow sinusoids along the S1P gradient, and to play further roles in proplatelet fragmentation and platelet aggregation. Yet clinical use of S1P pathway modulators including fingolimod has not been associated with thrombocytopenia, bleeding, or thrombosis. To address this apparent paradox, we revisited the role of S1P in murine platelet biology. Surprisingly, S1P gradient ablation achieved by genetically impairing encoding sphingosine kinases 1&2) or S1P degradation in interstitial fluids (by global deletion of *Sgpl1*, encoding S1P lyase) did not induce thrombocytopenia. Hematopoietic S1P deficiency was instead associated with a significant increase in peripheral blood platelet counts that was also observed with hematopoietic *S1pr1* deletion. Pan-hematopoietic $S1P_1$ deficiency was further associated with a decrease in erythrocytes as well as a non-significant increase in megakaryocytes in bone marrow and spleen. In contrast, megakaryocyte-selective *S1pr1* deletion did not impact platelet counts, and $S1P_1$ expression and signaling were both undetectable in mature murine megakaryocytes in situ. Concordantly, neither genetic deficiency nor pharmacological modulation of S1P1 had any impact on the activation and spreading of murine platelets.
Our results are in line with clinical observations and argue that $S1P_1$ is dispensable for platelet production and activation in mice. Instead, $S1P_1$ acts as a net inhibitor of platelet production, possibly by promoting the differentiation of common megakaryocyte-erythrocyte progenitors toward the erythroid fate.



Recent Publication:

Niazi H, Zoghdani N, Couty L, Leuci A, Nitzsche A, Allende ML, Mariko B, Ishaq R, Aslan Y, Becker PH, Gazit SL, Poirault-Chassac S, Decouture B, Baudrie V, De Candia E, Kono M, Benarab A, Gaussem P, Tharaux PL, Chun J, Provot S, Debili N, Therond P, Proia RL, Bachelot-Loza C, Camerer E: Murine thrombopoiesis is not facilitated by blood S1P sensing, but suppressed by S1P signaling in the hematopoietic niche. *In print at Blood Advances*



Biography:

Hira Niazi is a third year graduate student in the Camerer laboratory (Team 8, INSERM U970 / Paris Cardiovascular Research center - PARCC). She received a grant from the Higher Education Commission of Pakistan through a competitive exam (GAT) to obtain Masters and PhD in France.

Her interests lie in the regulation of cell trafficking by the sphingosine-1-phosphate (S1P) gradient. She is using immunohistochemistry, flow cytometry and other techniques to assess how the presence, viability and distribution of megakaryocytes, lymphocytes, hematopoietic stem cells and myeloid cells are impacted by the absence of S1P and its receptors in different cellular compartments under homeostasis. In her future work, she will be applying this knowledge to pathological conditions with a reported imbalance of S1P distribution such as Gaucher's disease and Sickle cell disease, in order to study the role of S1P imbalance in disease progression and investigate potential S1P directed therapeutic interventions.

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