

Séminaire LBPA

Vendredi 20 octobre 2017 à 11h

Amphi Chemla (Bâtiment IDA)



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Cdc42 : polarization of the megakaryocyte and beyond

Blood platelets are produced by large precursor cells, megakaryocytes (MKs), which extend cytoplasmic protrusions (proplatelets, PPTs) into bone marrow sinusoids. The molecular cues that control MKs polarization and limit transendothelial crossing to PPTs remain unknown.

We have investigated the impact of the actin cytoskeleton dynamics in differentiating MKs. We found that Cdc42 plays a crucial role in driving polarized formation and structuration of the demarcation membrane system (DMS), a complex cytosolic reservoir of membranes for future platelets (1). In parallel, we found that Cdc42 and RhoA act as a regulatory circuit downstream of the MK-specific mechanoreceptor GPIb. Cdc42 (go-signal) and RhoA (stop-signal) are at the centre of a molecular checkpoint that controls transendothelial platelet biogenesis (2). Finally, we demonstrated that in those processes regulated by contacts with the extracellular matrix and cytokines, MKs form different types of podosomes. Contacts to collagen fibers initiated the formation of linear F-actin structures enriched in cortactin that are reminiscent of linear podosomes. While classical punctae podosomes allow digestion of the bone marrow matrix and cellular crossing, linear podosomes appeared as points of contact between collagen fibers and the DMS, suggesting that they might be involved in protrusion elongation. Interestingly, unlike other models, in MKs, only linear podosomes are regulated by Cdc42. Altogether, our findings put F-actin and its regulator Cdc42 at the fore front of platelets production, while it was previously thought that only Tubulin had any effect.

(1) Antkowiak A, Viaud J, Séverin S, Zanoun M, Ceccato L, Chicanne G, Strassel C, Eckly A, Léon C, Gachet C, Payrastre B, Gaits-lacovoni F. Cdc42-dependent F-actin dynamics drives structuration of the demarcation membrane system in megakaryocytes. *J Thromb Haemost.* 2016 Mar 16. 14(6):1268-84. Doi:10.1111/jth.13318.

(2) Dütting S, Gaits-lacovoni F, Stegner D, Popp M, Antkowiak A, van Eeuwijk JMM, Nurden P, Stritt S, Heib T, Aurbach K, Angay O, Cherpokova D, Heinz N, Baig AA, Gorelashvili MG, Gerner F, Heinze KG, Ware J, Krohne G, Ruggeri ZM, Nurden AT, Schulze H, Modlich U, Pleines I, Brakebusch C, Nieswandt B. A Cdc42/RhoA regulatory circuit downstream of glycoprotein Ib guides transendothelial platelet biogenesis, *Nat Commun.* 2017 Jun 15;8:15838. doi: 10.1038/ncomms15838.

Invitée par Jacqueline Cherfils (77 70)