Platelet-specific deletion of acetyl-CoA carboxylase 1 decreases phospholipid content and impairs platelet functions

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Background: Acetyl-CoA carboxylase (ACC), the first enzyme regulating lipid synthesis, promotes thrombus formation by increasing platelet phospholipid content and thromboxane A2 generation.
Purpose: Our study sought to evaluate whether ACC1 platelet-specific deletion may affect platelet functions by decreasing phospholipid content.
Methods: We generated a new Cre transgenic mouse strain that allows megakaryocyte/platelet specific ACC1 deletion (GpIbCre+/– x ACC1 flx/flx mouse). In vitro, platelet functions were assessed by aggregometry and flow cytometry. In vivo, hemostasis was assessed via the measurement of bleeding time. Lipidomics analysis was carried out on the commercial Lipidyzer platform. Thromboxane A2 secretion was evaluated by ELISA.
Results: As expected, ACC1 deletion was restricted to the megakaryocytic lineage. Hematological parameters in platelet-specific ACC1 knockout mice showed a decrease in platelet count by 30% and an increase in platelet volume by 31%, compared to ACC1 flx/flx platelets. In vitro, platelets from platelet-specific ACC1 knockout mice displayed a decrease in thrombin and CRP-induced platelet aggregation, associated with impaired dense granules secretion. In contrast, ADP-induced platelet aggregation was higher in the absence of ACC1. In vivo, platelet-specific ACC1 knockout mice showed a normal bleeding time. In agreement with our hypothesis, lipidomics analyses showed that ACC1 deletion in platelets was associated with a significant decrease in arachidonic acid-contaning phosphatidylethanolamine plasmalogen, and subsequently with a reduced production of thromboxane A2 upon thrombin or CRP stimulation.
Conclusion: Platelet-specific ACC1 deletion led to a decrease in phospholipid content which, in turn, decreased platelet thromboxane A2 generation, dense granules secretion and aggregation upon thrombin and CRP, but not ADP stimulation. Further studies are needed to elucidate the impact of ADP on platelet functions