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Disabled-2 is Required for Efficient Haemostasis and Platelet Activation by Thrombin in Mouse

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Backgrounds:

The essential role of platelet activation in haemostasis and thrombotic disease focuses attention on unveiling the underlying intracellular signals of platelet activation. Disabled-2 (Dab2) has been implicated in platelet aggregation and in the control of clotting responses. Nevertheless, there is not yet any *in vivo* study to provide a direct evidence for the role of Dab2 in haemostasis and thrombosis.

Materials and Methods:

In this study, megakaryocyte/platelet lineage-restricted Dab2 knockout ($Dab2^{-/-}$) mice were generated by using the PF4-Cre transgenic system. Bleeding time and thrombus formation assays was performed to explore Dab2 function in primary haemostasis and thrombosis. Further, platelet aggregation, spreading, clot retraction, integrin αIIbβ3 activation assays and platelet signaling protein activation were analyzed to delineate the intrinsic properties of Dab2 platelets.

Results:

$Dab2^{-/-}$ mice appeared normal in size and platelet production but bleeding time was prolonged and thrombus formation was impaired. Analyses of the intrinsic properties of $Dab2^{-/-}$ platelets revealed a decrease in fibrinogen content and selective defects in platelet aggregation, spreading on immobilized fibrinogen, and clot retraction in response to low concentrations of thrombin. Investigation of the role of Dab2 in thrombin signaling showed decreased thrombin-induced Akt-Ser473 and mTOR-Ser2448 phosphorylations and integrin αIIbβ3 activation in $Dab2^{-/-}$ platelets. In contrast, basal expression of CD41 and thrombin receptors (PAR3 and PAR4) and thrombin-induced CD62P expression and PDK1-Ser241 phosphorylation were not affected.

Conclusion:

These data indicate that Dab2 is a key regulator of haemostasis and thrombosis by playing a selective role in cytoskeleton reorganization and mTORC2-Akt-mTORC1 pathway underlying thrombin-stimulated signaling.