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POSTER ABSTRACTS

301.VASCULATURE, ENDOTHELIUM, THROMBOSIS AND PLATELETS: BASIC AND TRANSLATIONAL

Platelets from Ehlers-Danlos Syndrome Patients Exhibit Reduced GPVI Levels and Impaired Integrin αIIbβ3 inside-out Signaling

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Background: Patients with Ehlers-Danlos syndrome (EDS) have a high susceptibility to bleeding. Easy bruising is included as a criterion for the classification of multiple types of EDS. Although the association between EDS and the tendency to bleed has been acknowledged for a long time, a definitive understanding of the underlying mechanisms contributing to bleeding diathesis in EDS patients is still lacking.
Objective: To characterize platelet function in a cohort of EDS patients and a murine EDS model.
Methods: A cohort of 53 patients with hypermobile (49%), classical (26%), classical-like (21%), or vascular (4%) types of EDS and a group of 53 healthy control subjects matched by age and gender were included in the study in accordance with the University of Iowa Institutional Review Board-approved protocol. The International Society of Thrombosis and Haemostasis bleeding assessment tool (ISTH-BAT) was used to assess the bleeding tendency in study participants. Because a single mutation in hypermobile type is currently unknown, we used *Col5a 1* $^{+/-}$ mice as a murine model of the classical type of EDS. The function of human and mouse platelets was evaluated using standardized agonist-induced *in vitro* assays.
Results: The mean ISTH-BAT score was 0.1 in healthy controls and 9.2 in EDS patients ($P < 0.001$). An abnormal ISTH-BAT score was observed in 33 out of 53 (62%) EDS patients and 0 of 53 healthy controls ($P < 0.001$). Platelets from EDS patients exhibited reduced aggregation and αIIbβ3 activation (with normal αIIbβ3 surface exposure) in response to stimulation with collagen, collagen-related peptide, or thrombin receptor activator peptide-6, compared to healthy controls. Platelet secretion of dense and α-granules and surface phosphatidylserine exposure were comparable between EDS and healthy subjects. Evaluation of collagen receptors on the surface of resting platelets showed a mild deficiency of GPVI in EDS patients compared to healthy controls ($P < 0.001$), while the integrin α2 levels were similar in both groups ($P = 0.152$). Analysis of GPVI signaling revealed downregulation of Syk (Y525/526), PLCγ2 (Y1217), and talin (S425) phosphorylation in EDS patients ($P < 0.05$ vs. healthy controls), suggesting a defect in collagen-induced integrin αIIbβ3 inside-out signaling. Consistent with our observations in EDS patients, *Col5a1* $^{+/-}$ mice demonstrated a bleeding tendency characterized by prolonged tail-bleeding time ($P < 0.05$ vs. wild-type control). Platelet function testing showed that *Col5a 1* $^{+/-}$ mouse platelets recapitulated the abnormalities detected in human EDS platelets.
Conclusions: Our data corroborate the observation that EDS patients exhibit a high risk of hemorrhagic complications.EDS platelets are characterized by reduced baseline GPVI expression that was associated with decreased agonist-induced platelet aggregation, αIIbβ3 activation, and impaired collagen-induced integrin αIIbβ3 inside-out signaling.

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