Lentiviral gene therapy corrects platelet phenotype and function in patients with Wiskott-Aldrich syndrome

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Abstract

BACKGROUND:
Thrombocytopenia is a serious issue for all patients with classical Wiskott-Aldrich syndrome (WAS) and X-linked thrombocytopenia (XLT) because it causes severe and life-threatening bleeding. Lentiviral gene therapy (GT) for WAS has shown promising results in terms of immune reconstitution. However, despite the reduced severity and frequency of bleeding events, platelet counts remain low in GT-treated patients.
OBJECTIVE:
We carefully investigated platelet defects in terms of phenotype and function in untreated patients with WAS and assessed the effect of GT treatment on platelet dysfunction.

METHODS:
We analyzed a cohort of 20 patients with WAS/XLT, 15 of them receiving GT. Platelet phenotype and function were analyzed by using electron microscopy, flow cytometry, and an aggregation assay. Platelet protein composition was assessed before and after GT by means of proteomic profile analysis.

RESULTS:
We show that platelets from untreated patients with WAS have reduced size, abnormal ultrastructure, and a hyperactivated phenotype at steady state, whereas activation and aggregation responses to agonists are decreased. GT restores platelet size and function early after treatment and reduces the hyperactivated phenotype proportionally to WAS protein expression and length of follow-up.

CONCLUSIONS:
Our study highlights the coexistence of morphologic and multiple functional defects in platelets lacking WAS protein and demonstrates that GT normalizes the platelet proteomic profile with consequent restoration of platelet ultrastructure and phenotype, which might explain the observed reduction of bleeding episodes after GT. These results are instrumental also from the perspective of a future clinical trial in patients with XLT only presenting with microthrombocytopenia.

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KEYWORDS:
Wiskott-Aldrich syndrome; X-linked thrombocytopenia; gene therapy; platelets