Lack of WASp Unveils Intrinsic Platelet Defects Sustaining Inflammation and Autoimmunity

Authors
Lucia Sereni[1], Maria Carmina Castiello[1], Achille Anselmo[2], Francesco Marangoni[3], Dario Di Silvestre[4], Sara Motta[4], Donato Inverso[1], Roberto Aiolfi[1], Elena Draghici[1], Adrian J. Thrasher[5], Silvia Giliani[6], Alessandro Aiuti[1], Matteo Iannacone[1], Pierluigi Mauri[4], Luigi D. Notarangelo[7], Marita Bosticardo[1], Anna Villa[1]

[1]San Raffaele Hospital, Milano, Italy,[2]Humanitas Hospital, Milano, Italy,[3]Massachusetts General Hospital, Harvard Medical School, Boston, MA,[4]National Research Council (ITB-CNR), Milano, Italy,[5]Institute of Child Health, University College London, London, United Kingdom,[6]Institute of Molecular Medicine "A. Nocivelli", University Hospital "Spedali Civili", Brescia, Italy,[7]Laboratory of Host Defenses, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD

Abstract
Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency characterized by thrombocytopenia, eczema, high susceptibility to develop autoimmune manifestations and malignancies. Although thrombocytopenia is one of the main causes of death, the pathogenesis of platelet (PLT) defect is poorly understood. Here, we evaluated the role of WAS protein (WASp) in PLTs in a new conditional mouse model (CoWas) lacking WASp only in the megakaryocytic (MK) lineage.We observed an increased number of MKs and their progenitors both in CoWas mice and complete $Was^{-/-}$ mice (WKO), as well as normal in vitro PLT production by $Was^{-/-}$ MKs. Upon in vivo depletion of PLTs, WKO and CoWas mice are able to restore PLT count with kinetics comparable to wild-type (WT) mice, suggesting no defect in thrombopoiesis. Of note, WASp-deficient PLTs both in WKO and CoWas mice have a shorter half-life and hyper-activated status before and after ADP stimulation and are more prone to apoptosis. We also found that WKO and CoWas mice develop anti-PLT autoantibodies against $Was^{-/-}$ PLTs in line with different proteomic profile. $Was^{-/-}$ PLTs show decreased metabolic activity, increased ubiquitination pathways and Immunoglobulin content. Moreover, $Was^{-/-}$ PLTs release higher amount of soluble CD40L and are able to induce B-cells activation in vitro culture. Finally, WAS patients show increased CD62P and PAC1 expression at steady state and higher sCD40L plasma levels. The activation profile of human PLTs improves after LV-gene therapy treatment, in all the patients, especially in those with a follow up longer than two years.