IJAE
Vol. 118, n. 2 (Supplement): 165, 2013
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Thrombotic events in models GATA-1 low myelofibrosis characterized by altered localization of P-selectin during megakaryocyte development

L. Sancillo[1], M. Zingariello[1,2], E. Zetterberg[3], M. Verrucci[4] , D. Bosco[5], A.R. Migliaccio[4,6] and R.A. Rana[1]

[1] Dept.of Medicine and Ag.Sci., Section of Human Morphology, University of study "G.d'Annnunzio", Chieti-Pescara, Italy
[2] CBM,Faculty of Medicine,Rome, Italy
[3] Dept. of Hematology, University Hospital, Copenhagen, Denmark
[4] Hematology,Oncology and Mol.Med.and Animal Welfare, ISS, Rome, Italy
[5] GMCN, Chieti, Italy
[6] Mount Sinai School of Medicine, NY,USA

Patients with primary myelofibrosis (PMF) have increased risk for bleeding and thrombosis. It is debated whether propensity to thrombosis is due to increased numbers of platelet microparticles and/or to pathological platelet-neutrophil interactions.This interactions are mediated by P-selectin and even though the megakaryocytes(Mk)of MF patients express normal levels of P-selectin,it remains abnormally localized to the DMS rather than being assembled into the a-granules in platelets.Mice carrying the hypomorphic Gata1low mutation express the same Mk abnormalities presented by PMF patients,including abnormal P-selectin localization to the DMS and develop with age myelofibrosis,that closely resembles human PMF.The aim of this study was to determine whether Gata1low mice would develop thrombosis with age and,in this case,the role played by P-selectin in the development of the trait.To this aim,Gata1low mice were crossed with P-sel^{null} mice according to standard genetic protocols and Gata1^{low}P-sel^{WT},Gata1l^{ow}P-sel^{null} and Gata1^{WT}P-sel^{null} or Gata1^{WT}P-sel^{WT} littermates obtained.Platelet count,hematocrit as well as platelet microparticle levels were determined on all the different mutants.It was shown that platelet counts are reduced in Gata1^{low} mice.Moreover,platelet microparticles are reduced in Gata1low mice and P-selectin positive platelet microparticles were not found.The presence of thrombosis was determined by immunohistological staining of organs.Gata1low mice with or without the P-selectin null trait had a prolonged bleeding time and thrombosis was seen adult and old Gata1^{low} mice,but the Gata1^{low}/P-sel^{null} mice were rescued.Thus,presence of the P-selectin null trait rescued Gata1^{low} mice from the thrombotic phenotype,but did not change level of platelet microparticles.All these data indicate that abnormal localization of P-selectin,induced by the Gata1^{low} mutation,and thus, increased pathological interactions with leucocytes,is responsible for the increased presence of thrombosis seen in these mice.

Key words
Myelofibrosis, Megakaryocytes, P-Selectin.