Title: Loss of endothelial barrier integrity in mice with conditional ablation of podocalyxin (Podxl) in endothelial cells

Author: Angélica Horrillo Gracia Porras Matilde S. Ayuso Consuelo González-Manchón

PII: S0171-9335(16)30013-9
DOI: http://dx.doi.org/doi:10.1016/j.ejcb.2016.04.006
Reference: EJCB 50878

To appear in:

Received date: 14-3-2016
Revised date: 26-4-2016
Accepted date: 26-4-2016

Please cite this article as: Horrillo, Angélica, Porras, Gracia, Ayuso, Matilde S., González-Manchón, Consuelo, Loss of endothelial barrier integrity in mice with conditional ablation of podocalyxin (Podxl) in endothelial cells.European Journal of Cell Biology http://dx.doi.org/10.1016/j.ejcb.2016.04.006

Loss of endothelial barrier integrity in mice with conditional ablation of podocalyxin (Podxl) in endothelial cells

Angélica Horrillo[a,b,1], Gracia Porras[a,b], Matilde S. Ayuso[a,b], Consuelo González-Manchón[a,b*]cgmanchon@cib.csic.es

[a]Department of Cellular and Molecular Medicine, Centre of Biological Research-CIB, CSIC, Madrid, Spain

[b]CIBER de Enfermedades Raras (CIBERER), Madrid, Spain

[1]Present address: Unit of Medicine and Experimental Surgery, Hospital Gregorio Marañón, Madrid, Spain

[*]Corresponding author: Department of Cellular and Molecular Medicine, Centro de Investigaciones Biológicas-CIB, CSIC, Calle Ramiro de Maeztu 9, 28040-Madrid, Spain. Tel.: +34918373112-4441; Fax: +34915360432

Abstract

Podocalyxin (Podxl) has an essential role in the development and function of the kidney glomerular filtration barrier. It is also expressed by vascular endothelia but perinatal lethality of *podxl*$^{-/-}$ mice has precluded understanding of its function in adult vascular endothelial cells (ECs). In this work, we show that conditional knockout mice with deletion of Podxl restricted to the vascular endothelium grow normally but most die spontaneously around three months of age. Histological analysis showed a nonspecific inflammatory infiltrate within the vessel wall frequently associated with degenerative changes, and involving vessels of different caliber in one or more organs. Podxl-deficient lung EC cultures exhibit increased permeability to dextran and macrophage transmigration. After thrombin stimulation, ECs lacking Podxl showed delayed recovery of VE-cadherin cell contacts, persistence of F-actin stress fibers, and sustained phosphorylation of the ERM complex and activation of RhoA, suggesting a failure in endothelial barrier stabilization. The results suggest that Podxl has an essential role in the regulation of endothelial permeability by influencing the mechanisms involved in the restoration of endothelial barrier integrity after injury.

Abbreviations: EC, endothelial cell; MLEC, mouse lung endothelial cell; Podxl, podocalyxin; CD34, cluster of differentiation 34; HEV, high endothelial venule; Tie2, tunica intima endothelial kinase 2;