

iTAP/FRMD8 is required for ADAM17-mediated functions in inflammatory diseases

Marina Badenes^{1,2,3,4}, Emma Burbridge^{4,5}, Ioanna Oikonomidi⁴, Érika de Carvalho⁴, Abdulbasit Amin⁴, Pedro Faísca^{1,2,4}, Pedro M. Domingos⁶, Colin Adrain^{4,5}

¹ I-MVET (Research in Veterinary Medicine), Faculty of Veterinary Medicine, Lusófona University - Lisbon University Center, Lisbon, Portugal

² CECAV (Veterinary and Animal Research Center), Faculty of Veterinary Medicine, Lusófona University - Lisbon University Center, Lisbon, Portugal

³ IPLUSO (Superior School of Health, Protection and Animal Welfare, Polytechnic Institute of Lusophony), Lisbon, Portugal

⁴ GIMM (Gulbenkian Institute for Molecular Medicine), Portugal

⁵ Patrick G Johnston Centre for Cancer Research, Queen's University, Belfast, N. Ireland

⁶ ITQB (Instituto de Tecnologia Química e Biológica António Xavier), Universidade Nova de Lisboa, Oeiras, Portugal

Introduction: The metalloprotease ADAM17 (also called TACE) plays fundamental roles during development and promotes homeostasis and multiple inflammatory diseases by shedding key signalling molecules from the cell surface. ADAM17 exists within an assemblage, the "shedase complex," containing a rhomboid pseudoprotease (iRhom1 or iRhom2). The FERM domain-containing protein iTAP/Frmd8 is an iRhom-binding protein that prevents the precocious shunting of ADAM17 and iRhom2 to lysosomes and their consequent degradation.

Objectives: The purpose of this study was to determine the impact of iTAP/Frmd8 loss on inflammatory Adam17-associated phenotypes in mice.

Materials and Methods: We challenged controls *versus* iTAP/Frmd8 global KO to inflammatory models of disease associated to ADAM17 pathway, specifically sepsis and colitis. We also performed studies on mouse iTAP/Frmd8 global KO derived inflammatory cells.

Results: We found that iTAP/Frmd8 KO mice exhibit defects in inflammatory and intestinal epithelial barrier repair functions associated with Adam17 loss, but not the collateral defects associated to ADAM17 deletion.

Conclusions: This work shows that pharmacological intervention at the level of iTAP/Frmd8 may be beneficial to target ADAM17 activity to treat chronic inflammatory diseases.

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