

TGM2 Is Highly Expressed and Active in Endometriosis Where It Mediates Pro-Fibrotic and Pro-Inflammatory Effects.

Fernando Martinez Estrada,¹ Maik Obendorf,² Stefanie Mesch,² Oliver M Fischer,² Cemsal Bafligil,¹ Manman Guo,¹ Christian Becker,³ Krina Zondervan,³ Catherine Shang,³ Stephen Kennedy,³ Siamon Gordon,⁴ Thomas M Zollner,² Udo Oppermann.¹

¹ University of Oxford, Oxford, United Kingdom; ² Bayer AG, Berlin, Germany; ³ University of Oxford, Oxford, United Kingdom; ⁴ University of Oxford, Oxford, United Kingdom.

INTRODUCTION: Macrophages are abundant in lesions and the peritoneal cavity of endometriosis patients. However macrophage activation profiles are ill defined. M2 or alternative activated macrophages are elicited by Th2 cytokines and support pro-fibrotic networks leading to increased collagen deposition. Transglutaminase 2 is a versatile and robust M2 macrophage marker, able to crosslink extracellular matrix proteins driving deposition in a variety of fibrotic models. Here we investigate TGM2 expression, activity and effects of its inhibition in monocytes, macrophages and lesions in endometriosis patients.

METHODS: Blood, plasma, peritoneal fluid (PF), lesions and eutopic endometrium were collected at the Endometriosis Clinic of the John Radcliffe hospital from informed and consenting donors. Cells were isolated with Ficoll and negative monocyte isolation kits. FACS and Histology on FFPE tissues for TGM2 were performed using the mouse IgG1 Zedira A033 antibody. Enzymatic assays involving cadaverin deposition were from Zedira. 142A Reproductive Sciences Vol. 24, Supplement 1, March 2017 Scientific Abstracts

RESULTS: TGM2 mRNA is higher in monocytes and PF cells in endometriosis patients, compared to patients with peritoneal pain but endometriosis free. FACS staining of peritoneal macrophages confirms increased expression in endometriosis. Soluble protein and activity are higher in the PF of patients. TGM2 protein is also detectable in eutopic and ectopic endometrium where it is highly constrained to the lesion area. Several inhibitors for human and mouse Tgm2 were evaluated, 3 active compounds with diverse action modes, were further investigated in vitro. M1 and M2 macrophage activation assays show that interfering with Tgm2 alters the ability of cells to respond to immune polarizing stimuli. In vivo experiments show that Tgm2 inhibition skews inflammatory responses such as Zymosan induced peritonitis, without affecting pain response. Tgm2 inhibition was monitored by ex vivo analyses of TG activity.

CONCLUSIONS: We conclude that TGM2 is highly expressed and active in endometriosis. Interfering with the enzyme may provide new ways of controlling M2 macrophage dependent inflammation and fibrosis.