INTERLEUKIN 17 RECEPTOR D (IL-17RD) REDUCES INCIDENCE OF COLLAGEN INDUCED ARTHRITIS

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Background: IL-17RD is a member of the IL-17 receptor family. In contrast to the other IL-17 receptors, IL-17RA, -RB, -RC and -RE, little is known about the ligand and function of IL-17RD. Recently, IL-17RD has been described to negatively regulate a selection of IL-17A responsive genes. IL-17RD is therefore proposed to limit IL-17A signalling.

Objectives: In this study we examined IL-17RD expression in multiple cell types and its role in the development of collagen induced arthritis.

Methods: Human synovial fibroblasts from Rheumatoid Arthritis (RA) patients were stimulated with tumour necrosis factor α (TNFα), interleukin 1β (IL-1β) or IL-17A for multiple time points. IL-17RD expression levels were measured via qPCR. Collagen induced arthritis (CIA) was induced in IL-17RD knockout mice and wildtype littermates. At days 1 and 21, mice were immunised intradermally with chicken collagen type II in complete Freund’s adjuvant (CFA). Mice were scored 3 times a week for clinical disease defined as swollen joints with a maximum score of 8. Due to ethical reasons, mice were removed from the experiments when they reached a score of 6. CD4+ memory T cells, CD8+ memory T cells, CD19+ B cells and monocytes were isolated from WT spleens and analysed for IL-17RD expression. Blood neutrophil migration assays were performed in vitro using WT and IL-17RD deficient (IL-17RD KO) mouse synovial fibroblasts.

Results: Human synovial fibroblasts from RA patients have baseline expression of IL-17RD. Upon stimulation with TNFα a significant downregulation of IL-17RD expression was measured from 24 hours onwards. IL17 stimulation had a similar effect as TNFα on IL-17RD expression. Lack of IL-17RD did not result in differences in CIA severity, but the incidence of CIA was reduced. IL-17RD is mainly expressed in synovial fibroblasts. IL-17RD KO synovial fibroblasts attract less neutrophils likely by lower production of neutrophil attractants.

Conclusions: An inflammatory environment causes synovial fibroblasts to down-regulate IL-17RD expression. Lack of IL-17RD reduces the incidence CIA, which is an IL-17-driven model. The decrease in CIA incidence is likely explained via the reduced attraction of neutrophils to the site of inflammation.

Disclosure of Interest: None declared


MONOCYTE DOWNREGULATION OF MITOCONDRIAL TRANSCLOCATOR PROTEIN MAY BE A CONTRIBUTORY MECHANISM TO INFLAMMATION IN RA


Background: The translocator protein is an 18 kDa mitochondrial transporter, involved in cholesterol efflux in macrophages. Recent work demonstrates that macrophages engineered to over-express TSPO, exhibit increased cholesterol efflux, and reduced ability to form a pro-inflammatory (M1) phenotype, with significant reduction in the ability to produce TNF-α. Additionally, there is growing data to demonstrate a difference in TSPO expression in monocytes in those with inflammatory diseases compared with healthy, as exemplified by studies of multiple sclerosis, suggesting a role for TSPO in the generation of inflammation.

Objectives: In this study, we investigate the expression of TSPO in healthy and RA peripheral blood monocytes, and in monocyte derived macrophages (MDM); differentiated to an M1 (pro-inflammatory), and M2 (reparative) phenotype.

Methods: Using positive magnetic-activated cell sorting, we use peripheral blood mononuclear cells from 24 RA patients with active disease (as determined by clinical examination, and DAS28 CRP score), and 24 healthy controls, to isolate peripheral blood monocyte mRNA and protein, to ascertain any differences in TSPO expression in healthy and RA peripheral blood monocytes, and in monocyte derived macrophages (MDM), differentiated to an M1 (pro-inflammatory), and M2 (reparative) phenotype.

Results: Our findings indicate that both healthy and RA peripheral blood monocyte derived macrophages (M) exhibit a statistically significant downregulation of TSPO at mRNA and protein level, when activated to a pro-inflammatory (M1) macrophage phenotype, with no change in TSPO expression in MDM activated to a reparative (M2) phenotype. Our mRNA data also suggests that M1 macrophages from both healthy and RA donors, exhibit a significant reduction in expression of key cell components promoting cholesterol efflux in macrophages, including CYP27A1, and ABCA1. Our data additionally demonstrates a significant reduction in expression of TSPO between healthy and RA monocytes, at both mRNA and protein level (mean fold change TSPO mRNA of 1.00 for healthy monocytes, and 0.47±0.24, p<0.001 for RA monocytes and mean TSPO optical densitometry of 1.01±0.10 for healthy monocytes and 0.85±0.02 p<0.05 for RA monocytes relative to β-actin).

Conclusions: Our findings indicate that pro-inflammatory activation of both healthy and RA monocyte-derived macrophages downregulates TSPO, and is also associated with reduction in key components of the cholesterol efflux pathway, in line with pre-existing studies of TSPO silencing and over-expression in human macrophages. Furthermore, we demonstrate that RA peripheral blood monocytes themselves may have a predisposition to a pro-inflammatory phenotype through downregulation of TSPO expression, which could indicate an as yet uninvestigated cellular mechanism contributing to synovial inflammation in RA.

REFERENCES: