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EXPERIMENTAL ARTHRITIS

iRHOM2—a new potential therapeutic target for inflammatory arthritis

TNF-α convertase (TACE) is an essential regulator of TNF activity and, as such, has been considered as a potential therapeutic target for rheumatoid arthritis (RA). However, as TACE is not only required for the shedding of soluble TNF from cells, but also for activating epidermal growth factor receptor (EGFR) signalling (important for maintenance of skin and intestinal integrity), concerns over adverse effects resulting from blocking EGFR activation have hampered this approach. iRHOM2 regulates the activity of TACE and, according to a paper now published in *The Journal of Clinical Investigation*, is critical for the development of inflammatory arthritis in mice and could represent a new drug target for RA.

"We knew, through a collaboration with Tak Mak and David McIlwain at the University of Toronto, and Thorsten Maretzky at the Hospital for Special Surgery, NY, that mice lacking iRhom2 do not release TNF from myeloid cells because TACE maturation is blocked in the absence of iRhom2; the mice had no spontaneous pathologies. These findings were published in *Science* last year," explain Carl Blobel and Jane Salmon, the lead researchers on the current paper.

> "Mice lacking iRhom2 expression ... were protected against serum transfer arthritis..."

The authors furthered these findings here by studying the expression and function of iRHOM2 in cells from patients with RA, and by investigating the role of the iRhom2/TACE pathway in the K/BxN inflammatory arthritis mouse model.

"We show that iRHOM2 is upregulated in synovial macrophages from RA patients, and moreover, that downregulation of iRHOM2 in human macrophages by siRNA treatment blocks production of active TACE and release of TNF," say Blobel and Salmon. Mice lacking iRhom2 expression (*Rhbdf2*$^{-/-}$ mice) and mice lacking TACE expression in myeloid cells (*Taceflox/flox/LysM-Cre* mice) were protected against serum transfer arthritis, developing reduced synovitis and cartilage erosion than control mice, and notably, they were protected to a similar extent as *Tnfa*$^{-/-}$ mice.

"A particularly promising aspect of targeting iRHOM2 is the opportunity to inactivate TACE and block TNF release only from specific cells—those that contribute to joint damage. Thus it could offer safety and efficacy advantages over current anti-TNF treatments," conclude Blobel and Salmon.

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Original article Issuree, P. D. *et al*. iRHOM2 is a critical pathogenic mediator of inflammatory arthritis. *J. Clin. Invest.* doi:10.1172/JCI66168