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Xiang Lin[1]

[1]Univ. of Hong Kong

T follicular helper (Tfh) cells play a central role in humoral autoimmunity, including primary Sjögren's syndrome (pSS). However, targeting Tfh cells is challenging in clinical management. Previous studies suggested that inducible T-cell co-stimulator (ICOS) directed Tfh cell motility in engaging bystander B cells, which promoted plasma cell differentiation and antibodies production. Here, we identified a novel function of caveolin-1 (Cav-1) in restraining ICOS expression in Tfh cells and pSS pathogenesis. Cav-1 deficiency significantly promoted human and murine Tfh cell responses, while Cav-1-/- mice exhibited exacerbated disease pathology of experimental SS (ESS). Peroxisome proliferator-activated receptor alpha (PPARa), a downstream transcription factor of Cav-1, rapidly repressed *Icos* transcription upon Tfh polarization, interestingly, independence of lipid metabolism. Phenotypic analyses suggested that Cav-1 and PPARa expressions were decreased in CD4+ T cells from pSS patients and ESS mice. Notably, pharmaceutical activation of PPARa with fenofibrate could suppress human and murine Tfh cells both *in vitro* and *in vivo*, while oral administration of fenofibrate effectively ameliorated ESS pathology in mice with acute or chronic inflammation. These results revealed an unrecognized role of Cav-1/PPARa axis in Tfh cell tolerance and pSS pathogenesis, suggesting PPARa as a promising target in the treatment of humoral autoimmunity.

SESSION: Basic Autoimmunity (AM)