ICoLA 2019
The 8th International Congress on Lipid &Atherosclerosis(ICoLA)
The 58th Conference of the Korean Society of Lipid & Atherosclerosis
September 5(Thu.) ~ 7(Sat.), 2019, Conrad Hotel Seoul, Republic of Korea

TNF PROMOTES SREBP ACTIVITY AND BINDING TO INFLAMMATORY GENES TO ACTIVATE MACROPHAGES AND LIMIT TISSUE REPAIR

Sung-Ho Park[1] and Lionel Ivashkiv[*2]

[1] *UNIST, Korea*
[2] *Hospital for Special Surgery, USA*

livashkiv@*hss.edu*

Abstract

Cytokine TNF-mediated macrophage polarization is important for inflammatory disease pathogenesis, but the mechanisms regulating polarization are not clear. We performed transcriptomic and epigenomic analysis of the TNF response in primary human macrophages and revealed late phase activation of SREBP2, the master regulator of cholesterol biosynthesis genes. TNF stimulation extended the genomic profile of SREBP2 occupancy to include binding to and activation of inflammatory and interferon response genes independently of its functions in sterol metabolism. Genetic ablation of SREBP function shifted the balance of macrophage polarization from inflammatory to a reparative phenotype in peritonitis and skin wound healing models. Genetic ablation of SREBP activity in myeloid cells or topical pharmacological inhibition of SREBP improved skin wound healing under homeostatic and chronic inflammatory conditions. Our results identify a function and mechanism of action for SREBPs in augmenting TNF-induced macrophage activation and inflammation, and open therapeutic avenues for promoting wound repair.

Keywords

TNF; SREBP2; macrophage polarization; tissue repair; inflammation