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Dietary fatty acids regulate macrophage polarization via epigenetic mechanisms

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Obesity is associated with increased classically activated M1 adipose tissue macrophages (ATMs) and reduced alternatively activated M2 ATMs, which contributes to insulin resistance. Epigenetic mechanisms play important roles in complex diseases including obesity and insulin resistance. We find that the expression of DNA methyltransferase 1 (DNMT1) is significantly induced in macrophages exposed to the saturated fatty acid (SFA) stearic acid and the pro-inflammatory cytokine TNFα, is higher in ATMs isolated from obese mice, but is significantly lower in M2 than in M1 ATMs. Inhibiting DNA methylation pharmacologically by 5-aza-2'-deoxycytidine (5-azadC) or genetically using macrophages from myeloid-specific DNMT1 knockout mice (MD1KO) results in M2 macrophage polarization, evidenced by up-regulation of M2 marker, such as arginase 1 (ARG1), mannose receptor, Dectin-1, programmed cell death 1 ligand 2, interleukin 1 receptor antagonist, interleukin 10, and peroxisome proliferator-activated receptor γ1 (PPARγ1), key regulator of M2 macrophage activation; whereas over-expressing DNMT1 profoundly suppresses interleukin 4-induced ARG1 and PPARγ1 expression. PPARγ1 promoter is enriched with CpG sites. Inhibiting DNA methylation in macrophages by 5-azadC or in MD1KO mice significantly decreases, whereas stearic acid and TNFα significantly increase PPARγ1 promoter DNA methylation. Finally, MD1KO mice have lower adipose tissue inflammation and significantly improved insulin sensitivity without altering body weight. In summary, DNA methylation plays an important role in regulating macrophage polarization. Inhibiting DNA methylation at PPARγ1 promoter promotes M2 macrophage polarization; whereas in obesity, elevated SFAs and pro-inflammatory cytokines enhance PPARγ1 promoter DNA methylation, which contributes to deregulated ATM polarization, inflammation and insulin resistance.

Biography

Bingzhong Xue has completed her Ph.D from University of Tennessee at Knoxville and postdoctoral studies from Beth Israel Deaconess Medical Center/Harvard Medical School. She is currently an Associate Professor at the Department of Biology, Georgia State University. She has published more than 25 papers in reputed journals and serves as one of the review panel members for the American Heart Association and ad hoc reviewer for a number of peer-reviewed journals.