Background: Atherosclerosis causes more death than any other pathophysiological process. It has a well-established inflammatory macrophage (Mφ)-mediated component which can be stoked by uncontrolled diabetes. However, there are also protective, regulatory Mφ processes that can help quell atherosclerosis. Lipoprotein Lipase (LPL) on the Mφ surface can hydrolyze circulating triglyceride-rich lipoproteins into glycerol and free fatty acids to provide a non-glucose energy source. We hypothesized that regulatory Mφs have high LPL activity, which would promote fatty acid metabolism to drive inflammation-resolving functions, and that this LPL activity is inversely related to ambient glucose.

Method and Results: Mφs were cultured and differentiated from bone marrow harvested from wild-type mice aged 9-16 weeks. Two weeks after harvest, these Mφs were polarized with (1) interferon-γ and lipopolysaccharide to stimulate classically-activated, inflammatory Mφs or (2) interleukin-4 to stimulate alternatively-activated, regulatory Mφs. The resulting phenotypes were validated by canonical transcript markers (Tnfa/Nos2 for inflammatory Mφs and Ym1/Arg1 for regulatory Mφs) and cell surface markers (CD68 and CD206, respectively). Using a triglyceride analog that fluoresces when cleaved by LPL, we found that regulatory Mφs have far greater LPL activity than inflammatory macrophages at baseline (33 ± 2 vs 1 ± 0.2 a.u., p < 0.001, n=8). By varying glucose concentration during the polarization, this effect was most pronounced at normal, physiological concentrations of glucose (5 mM, ~90 mg/dL) and blunted at a high-glucose concentration that can be found in uncontrolled diabetes (25 mM). Each experiment was repeated across multiple batches of Mφs (n=4) and from multiple mice (n=15), male and female.

Conclusion: Taken together, our findings support a model in which regulatory Mφs are programmed to utilize LPL to drive the inflammation-resolving phenotype and that this process works best at low, physiologic glucose concentrations. Future translational work will investigate whether a lack of LPL-mediated regulatory Mφ function is a reason why patients with uncontrolled diabetes have higher atherosclerotic burden and plaque instability.

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