ABSTRACT

Atherosclerosis is both a chronic inflammatory disease and lipid deposition disorder characterized by accumulation of lipids, fibrous tissue, and inflammatory cells in the arterial wall. Current atherosclerosis therapy is aimed at lipid targets and focused primarily on reducing plasma cholesterol levels, but has been mildly successful with 60% of risks remaining despite intervention. The link between inflammation and atherosclerosis provides a new avenue for future pharmacologic intervention that may slow the progression of atherosclerosis by targeting inflammation. Clinical and experimental data support the critical role of inflammation in atherosclerosis and suggest that reducing inflammation without affecting lipid levels may reduce the event rate of cardiovascular disease. Yet, no strictly anti-inflammatory drugs are used to treat patients with atherosclerotic diseases. Recently, the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) provided evidence that targeting inflammation by using Canakinumab (IL1-β inhibitor) reduced the rate of cardiovascular events. Therefore, CANTOS scientifically supports the inflammatory hypothesis of atherosclerosis. In this study, we tested this hypothesis using various immunomodulatory approaches. First, we measured the expression of inflammation markers in human atherosclerotic carotid arteries. We demonstrated that inflammatory markers were significantly increased in different location of atherosclerotic lesions compared to normal media and show a positive correlation with miR155. We observed that MiR155 was upregulated in calcification media concomitant with osteogenic genes. We also show that bone marrow TTP deficiency in LDLR$^{-/-}$ mice significantly increased systemic inflammation. Unexpectedly, serum lipid levels and hepatic steatosis were dramatically reduced with

bone marrow TTP deficiency. Increased inflammation and reduced serum lipid offset each other resulting in unchanged atherosclerosis. We also investigated the effect of bone marrow macrophage GP96 deficiency in atherosclerosis to determine the role of TLRs during atherogenesis. Our results show that macrophage GP96 deficiency in bone marrow did not change inflammatory status, serum lipid, nor development of atherosclerosis in LDLR$^{-/-}$ mice. Sparstolonin (SsnB), a selective TLR2/TLR4 inhibitor has known anti-inflammatory effects. We injected mice with super-low dose LPS or LPS plus SsnB. Super-low dose LPS increased serum chemoattractant cytokines, while SsnB treatment reduced these chemokines. However, super-low dose LPS and SsnB administration did not affect atherosclerotic lesions. Atherosclerosis is a complex, multifactorial process, and the interaction between inflammation and atherogenesis is complicated as indicated by our results. Since CANTOS shows that targeting inflammation reduced the rate of cardiovascular events, it opens the field to further investigate the inflammation hypothesis and explore novel therapeutic avenues.