Anti-inflammatory liaisons: T regulatory cells and HDL

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The report in this issue of the Journal of Lipid Research by Rueda et al. shows that the survival and viability of Tregs is improved by incubation with HDL. Previous research over the last 20 years had demonstrated that plasma HDL possessed anti-inflammatory properties (1–4). Much of the early work focused on HDL as a vehicle to carry oxidized lipid products to the liver for catabolism as well as to inhibit the oxidation of LDL. Because HDL was proposed to carry oxidized lipids for excretion, it was also suggested that HDL could go “bad,” or become pro-inflammatory if it was overloaded with oxidized products or if the particles were not removed by catabolism. More recently, another anti-inflammatory aspect of HDL apolipoprotein A-I (apoA-I) was described: apoA-I’s ability to package and remove excess cholesterol from immune cell microdomains, thereby modulating the activity of key signaling pathways (5–8).

Rueda et al. showed that the survival and viability of Tregs is improved by incubation with HDL but not LDL. The report goes on to demonstrate that HDL does not enhance the viability of other types of T cells, including naïve and memory T cells. Mitochondrial respiration was found to increase during incubation with HDL and inhibitors of fatty acid transport reduced respiration and Treg survival, although the specificity of inhibitors is always open to question (9). Treating isolated CD4 Treg cells with scavenger receptor class B, type I (SR-BI) blocking antibody reversed Treg survival promoted by HDL. The authors further showed that incubation of Treg with oleate-loaded albumin increased viability, suggesting that Tregs were primarily employing cholesteryl ester (CE)-derived fatty acids as an energy source. Because Tregs express about twice as much SR-BI as other T cells, it was concluded that HDL-CE sequestered by SR-BI was providing fatty acid used by mitochondria to generate ATP. The reason LDL is not a source of CE fatty acids needs to be explored. However, the authors show that LDL receptor expression is significantly lower in Treg cells compared with naive T cells, suggesting that high levels of SR-BI expression lead to greater uptake of HDL than of LDL.

SR-BI, known as the HDL receptor, a protein that transports cholesteryl ester from HDL into the cell, is located (10–12) on the cell surface predominately in lipid microdomains (13, 14). T cells employ oxidative phosphorylation for most energy needs but use glycolysis during proliferation. Conversion to activated effector T cells is associated with metabolic reprogramming to use glycolytic metabolism whereas fatty acid oxidation promotes Treg development (15, 16). Previous studies have demonstrated that the Treg subpopulation of human peripheral blood mononuclear cells is consistently upregulated by incubation with either short or long chain fatty acids as substrates for oxidative phosphorylation (16, 17).

These studies improve our understanding of inflammation and the interplay among the various factors affecting how Treg cells modulate inflammation. Curiously, the role of metabolism in many processes is often a secondary consideration when planning in vitro studies. Because Tregs modulate the activity and pro-inflammatory behavior of other cells, this research demonstrates the important role of nutrition in modulating the inflammatory response, and suggests that nutrition is an important consideration for in vitro experiments with actively metabolizing cells, and appropriate provision of energy substrates is essential to achieve maximum Treg activity in vivo.

REFERENCES


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