Semaphorin 6D reverse signaling controls macrophage lipid metabolism and anti- inflammatory polarization

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Polarization of macrophages into pro-inflammatory or anti-inflammatory states has distinct metabolic requirements, with mechanistic target of rapamycin (mTOR) kinase signaling playing a critical role. However, it remains unclear how mTOR regulates metabolic status to promote polarization of these cells. Here we show that an mTOR–Semaphorin 6D (Sema6D)–Peroxisome proliferator receptor γ (PPARγ) axis plays critical roles in macrophage polarization. Inhibition of mTOR or loss of Sema6D blocked anti-inflammatory macrophage polarization, concomitant with severe impairments in PPARγ expression, uptake of fatty acids, and lipid metabolic reprogramming. Macrophage expression of the receptor Plexin-A4 is responsible for Sema6D-mediated anti-inflammatory polarization. We found that a tyrosine kinase, c-Abl, which associates with the cytoplasmic region of Sema6D, is required for PPARγ expression. Furthermore, Sema6D is important for generation of intestinal resident CX3CR1^{hi} macrophages and prevents development of colitis. Collectively, these findings highlight crucial roles for Sema6D reverse signaling in macrophage polarization, coupling immunity, and metabolism via PPARγ.