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

Keywords: Immune metabolism, inflammation regulation, nerve-immunity, semaphorin, M2 macrophage

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. Kumanogoh and his research group shows 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. The group 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 CX3CR1hi 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.

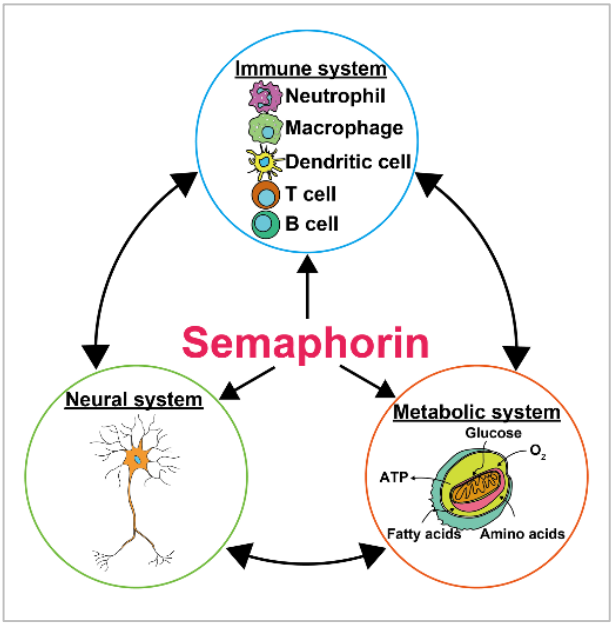


**Fig.1** Integral role of Semaphorin in Neural-Immune-Metabolic system.

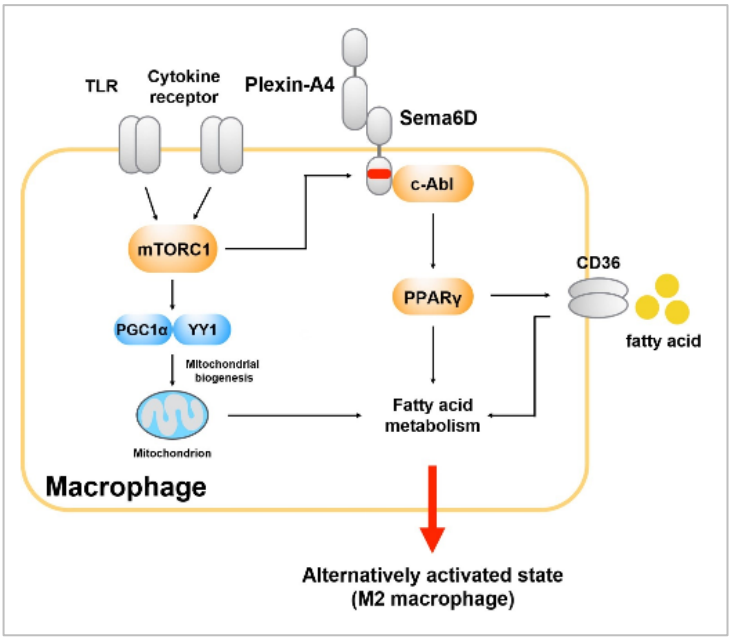


**Fig.2** Semaphorin 6D reverse signaling controls lipid metabolism and anti-inflammatory polarization.

❖ **Article information**

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