Macrophage glutaminolysis, the Good, the Bad and the Umami

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Abstract

•Macrophage plasticity and adaptability to local environmental cues rely on a rapid metabolic rewiring. Glutaminase (GLS) converts glutamine to glutamate to fuel anabolic processes and support redox and epigenetic reactions. Here, we identify a key role for GLS in macrophage effector functions. Loss of GLS1 diminished alternative macrophage polarization and reduced efferocytosis. This was not associated with canonical glutamate dehydrogenase (GLUD1)-dependent conversion of glutamate into α-ketoglutarate in the mitochondria to fuel the tricarboxylic acid cycle or classical mTor-dependent metabolic reprogramming. Gls1 deficient macrophages rather refocused cellular metabolism to a high redox state and a low transamination-dependent mitochondrial efficiency. Targeted deletion of GLS1 in myeloid cells resulted in failure of apoptotic cell uptake leading to accelerated atherosclerosis. Our findings position glutaminase-dependent metabolic reprogramming as a critical process that enables continued clearance of ACs by macrophages to avoid the pathologic consequences of defective efferocytosis in vivo.

Keywords

Hematometabolism, cardiometabolic diseases, atherosclerosis