Role of SLC7A5 in metabolic reprogramming of human monocyte/macrophage immune responses

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Abstract

Amino acids (AAs) are necessary nutrients which act not only as building blocks in protein synthesis, but also in crucial anabolic cellular signaling pathways. It has been demonstrated that SLC7A5 is a critical transporter that mediates uptake of several essential amino acids (EAAs) in highly proliferative tumors and activated T cells. However, the dynamics and relevance of SLC7A5 activity in monocytes/macrophages is still poorly understood. We provide evidence that SLC7A5-mediated leucine influx contributes to proinflammatory cytokine production via mTORC1-induced glycolytic reprograming in activated human monocytes/macrophages. Moreover, expression of SLC7A5 is significantly elevated in monocytes derived from patients with rheumatoid arthritis (RA), a chronic inflammatory disease, and was also markedly induced by LPS stimulation of both monocytes and macrophages from healthy individuals. Further, pharmacological blockade or silencing of SLC7A5 led to a significant reduction of IL-1β downstream of leucine-mediated mTORC1 activation. Inhibition of SLC7A5-mediated leucine influx was linked to downregulation of glycolytic metabolism as evidenced by the decreased extracellular acidification rate (ECAR), suggesting a regulatory role for this molecule in glycolytic reprograming. Furthermore, the expression of SLC7A5 on circulating monocytes from RA patients positively correlated with clinical parameters, suggesting that SLC7A5-mediated AA influx is related to inflammatory conditions.

Keywords: Monocyte, Macrophage, Leucine, mTORC1, Glycolysis, Rheumatoid arthritis (RA), IL-1β