Vittoria Infantino et al., Immunol Case Rep 2019, Volume 3

CITRATE EXPORT PATHWAY AND UPREGULATION OF SLC25A1 AND ACLY GENES IN ENDOTOXIN/CYTOKINE-INDUCED MACROPHAGES

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In response to proinflammatory triggers, macrophages undergo metabolic shift to support the bioenergetic and biosynthetic requirements of the cell. Metabolite level changes are largely due to a rewiring of the Krebs cycle following immune cell stimulation. Activated macrophages show an altered Krebs cycle, one consequence of which is the accumulation of citrate. In this context most of citrate is diverted from Krebs cycle and channelled into the "citrate export pathway" consisting in the increase of the export of citrate into cytosol by the mitochondrial citrate carrier (CIC)-encoded by the SLC25A1 gene-followed by its cleavage into acetyl-CoA and oxaloacetate by ATP citrate lyase (ACLY). Citrate export is a consequence of SLC25A1 and ACLY genes upregulation in LPS as well as in TNFα and IFNγ activated macrophages. Remarkably, TNFα and LPS exert their effect via NF-kB sites located in SLC25A1 and ACLY gene promoters. STAT1 is responsible for IFNγ-induced SLC25A1 and ACLY upregulation, as demonstrated by its binding to STAT responsive elements in both gene promoters. What is the fate of exported citrate? Citrate-derived acetyl-CoA is used to synthesize PGE2 and oxaloacetate to produce NADPH needed for NO and ROS. SLC25A1 and ACLY gene silencing or inhibition of CIC or ACLY by different synthetic and natural molecules results in reduction of NO, ROS and PGE2 levels suggesting that the citrate pathway can be a new target to be addressed in inflammation.

BIOGRAPHY

Vittoria Infantino has completed her PhD in Cell Biochemistry and Pharmacology in 2005 studying the transcriptional regulation of the human mitochondrial carrier genes. Further she focused on the mitochondrial carrier gene regulation mechanisms as Post-Doc in the laboratory of Prof. Iacobazzi, Bari. She moved to University of Basilicata in 2008 where she is now Research Scientist in Cellular Biology. Currently, her research is focused on the "Relationship between gene regulation and metabolism in physiological and pathological conditions, with particular interest in cancer and inflammatory diseases". To deepen these topics, she performed a stay at the Trinity College Dublin-Biomedical Science Institute- School of Biochemistry-laboratory of Professor Luke O'Neill. She has 36 publications in peer reviewed international journals with H-index 19 and has been serving as an Editorial Board Member to reputed Journals.

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