CaN-NFAT controls immunometabolic reprogramming of human monocytes and contributes to immunoparalysis in sepsis

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Energy metabolism of monocytes in steady-state relies on fatty acid oxidation, while exposure to environmental stimuli as invading pathogens or pathogen-originated ligands is followed by monocyte activation leads to a metabolic switch, represented by increased glycolysis linked with anabolic processes. This immunometabolic switch ensures the gain of required amount of energy and intermediate metabolites for defensive processes, vital for host protection. Metabolic processes are altered in many pathologies including sepsis progression.

The immunometabolic status and its subsequent transformations are regulated by various signaling pathways (e.g. mTOR or HIF-1a). Calcineurin (CaN) – NFAT signaling pathway has well established role in the context of immune response and inflammation, nevertheless its role in the regulation of metabolism is not defined. CaN-NFAT is activated by various exogenous and endogenous ligands via pattern recognition receptors. Similar activation signal is leading to rewiring of immunometabolic status in monocytes. We targeted CaN-NFAT of activated monocytes by immunosuppressives – Cyclosporin A and Tacrolimus, and focused on the alterations in monocyte metabolism.

Interestingly our data suggests, not yet described direct link between CaN-NFAT axis and the regulation of immunometabolism. We have observed significant changes in glycolytic activity measured by Seahorse, which were confirmed by metabolomics. These changes may affect also effector defensive functions of immune cells. We observed changes in functionality of monocytes induced by immunosuppressive treatment and show significant decrease in ROS production. This might lead to the impairment of important immune-protective function of myeloid cells as monocytes use ROS for killing of phagocyted pathogens. We also found several parallels in patients with septic shock.

In summary, we showed a novel aspect of the CaN-NFAT in the monocyte metabolism and their effector functions, indicating possible role of this signaling pathway in increased susceptibility of immunoparalyzed patients to various secondary infections.