Emerging role of the Succinate/SUCNR1 axis in microglial metabolism: from physiology to pathology

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Obesity, characterized by excess adiposity and systemic inflammation, has emerged as a global health concern. Hypothalamic inflammation induced by overnutrition has been implicated in the disruption of neuronal regulatory pathways controlling energy homeostasis. Microglia, as key players in maintaining brain homeostasis and orchestrating immune responses, have gained attention in this context. Recent studies have shed light on the emerging role of succinate/SUCNR1 axis as a signaling pathway involved in energy metabolism and immune regulation both in physiology and pathology. However, the specific interplay between microglia and succinate remains poorly understood. In this study, we newly generated a mouse model with conditional knock-out of SUCNR1 specifically in microglia to investigate the connection between succinate and microglia functionality. Our results revealed that under physiology, mice displayed higher body weight with no significant differences in food intake, but exhibited increased satiety and circulating leptin, along with alterations in the glucose metabolism and increased fat depots. Remarkably, in the context of diet-induced obesity, mice presented diminished weight gain, decreased satiety, lower circulating leptin, and improved glucose metabolism homeostasis. These findings suggest that the absence of SUCNR1 in microglia may disrupt feeding behavior associated to leptin alterations, leading to imbalanced peripheral metabolism in physiological conditions. However, in response to a nutritional challenge, the absence of microglial succinate/SUCNR1 axis appears to confer protection against metabolic derangements. In conclusion, our study provides novel insights into the functional relevance of succinate/SUCNR1 axis in establishing a crosstalk between the brain and the peripheral tissues mediated by microglia.