ADULT NEURAL PROGENITOR CELLS AS NEW TOOL TO STUDY HYPOTHALAMIC NEUROGENESIS

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Introduction: Adult neurogenesis (aNG) represents a key form of neuroplasticity. In the adult mamm,alian brain, well-characterized neurogenic niches are the subventricular zone (SVZ) of the lateral ventricles and in the subgranular zone (SGZ) of the dentate gyrus. Recently, adult hypothalamus (Hyt), a central regulator of metabolism and energy balance, has emerged as a region in which new neurons are constitutively generated from proliferating neural progenitor cells (NPC). At present aHytNG is suggested to have an active role in the regulation of metabolic homeostasis in response to long-lasting environmental changes, including diet. As an example, overfeeding conditions lead to an increase of free fatty acids (FFA), which may exert toxic effects (lipotoxicity) on several tissues/organs, including brain. Here, lipotoxicity may contribute to the onset of central metabolic hormone resistance, a critical neural mechanism for the development of several metabolic disorders, including type 2diabetes and obesity. Research on aHytNG has just begun but there are several obstacles that slow down all researches on this topic, among all, the fact that aHytNG rate is much lower than in SVZ or SGZ. The use a cellular model to study aHytNG, could be a useful strategy to overcome these obstacles, but to date there is no in vitro model available. Thus, taking advantage of our expertise in the study of aNG, we established and phenotypically characterized aHytNPC primary cultures.

Material and methods: Cells were isolated from hypothalami of 3-mo old C57BL/6male mice. To phenotypically characterize aHytNPC, immunocytochemistry coupled with image-based High Content Analysis (HCA) were performed. By HCA, we are able to acquire functional and morphological information from collections of individual cells simultaneously. The multiparametric nature of HCA is particularly well-suited to study heterogeneous systems such as primary NPC cultures, where different cellular subtypes coexist and may respond differently to perturbations.

Results: In our hands, these cells showed self-renewal capability, as demonstrated by the neurosphere assay. Moreover, we proved their undifferentiated state, since they express bona fide NPC markers, such as SOX2and nestin. These cells are also multipotent, due their ability to differentiate toward neuronal and glial lineages, hence, we demonstrated that they actually are aHytNPC. Furthermore, when exposed to FFA-enriched environment, viability and self-renewal capability of aHytNPC were impaired, in a concentration-dependent manner.

Discussion and conclusions: Here for the first time, we provide a cellular model suitable to investigate aHytNG in vitro. Currently, we are pharmacologically characterizing aHytNPC in order to identify molecules, both endogenous signals and drugs, able to positively or negatively modulate their properties. Understanding the mechanisms underlying aHytNPC regulation would potentially contribute to increase our knowledge on the role of aHytNG and on the pathophysiology of metabolic disorders