Metabolic modulation of neurogenesis: Role of glutaminase-2

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Glutamine plays a key role in many metabolic processes. Deamination of glutamine to glutamate is mediated by 2 enzymes: glutaminase 1 and glutaminase 2. While both isoforms are expressed in the nervous system, our understanding of their regulation and function during development and in brain pathophysiology remains incomplete. The work by Velletri et al. published in Cell Cycle provides important insights into regulatory pathways controlling GLS2 expression in the nervous system and GLS2 function in neuronal differentiation (Fig. 1).

First, the authors show that the p53 family member TAp73 promotes transcription of GLS2 during neuronal differentiation of neuroblastoma cells, suggesting an important role of GLS2 in regulating neurogenesis. Indeed, GLS2 overexpression increased neurite outgrowth, whereas GLS2 knockdown had a significant albeit modest inhibitory effect, potentially due to compensatory induction of GLS1. Furthermore, inhibition of GLS activity in primary neurons resulted in impaired neuritogenesis. Notably, modulation of GLS2 expression or activity substantially altered ATP levels in neuroblastoma cells, whereas GSH/GSSG ratio was not affected. It would be interesting to determine whether changes in ATP levels are caused by alterations of electron transport chain activity or glycolysis. In this respect, a previous study by Feng and coworkers implicated GLS2 in regulation of mitochondrial metabolism via generation of glutamate and α-ketoglutarate, thus feeding into the cycle of Krebs.2

In order to gain insights into the role of GLS2 in vivo, Velletri et al. analyzed GLS2 expression in the context of the developing cerebellum. Interestingly, GLS2 transcript significantly increases between postnatal day 0 (P0) and P1, a development stage associated with massive expansion of granule cell progenitor cells. In this regard, it would be important to study whether the GLS increase occurs in proliferating GCPs, postmitotic GCPs, or early born granule neurons. This would guide future experiments aimed at determining whether GLS plays a role not only in differentiating neurons but also in GCP expansion/commitment (Fig. 1).

Despite the clear role of TAp73 in regulation of GLS2 in neuroblastoma cells, GLS2 expression is not affected by p73 loss in the hippocampus and in cultured hippocampal neurons. Although these data tend to exclude a role for p73 in regulation of GLS2 in vivo, it would be important to analyze GLS2 levels at developmental stages preceding the onset of hippocampal phenotypes caused by p73 loss. Furthermore, it would be interesting to analyze expression of p53 family members in different regions of the brain, as the effect of p73 loss could be substantial only in areas where p53 expression is low or absent.

In the last part of this interesting manuscript, the authors perform metabolite profiling of TAp73- and DeltaNp73-deficient cortical neurons in search of potential p73-dependent metabolic alterations. Interestingly, TAp73 loss was accompanied by decreased GABA, without any detectable changes in aspartate and N-acetylaspartylglutamate (NAAG). Conversely, NAAG, its precursor N-acetylaspartate (NAA) and glycine were reduced in DeltaNp73−/− cells, suggesting isoform-specific metabolic functions of p73.

Overall, these findings will certainly initiate fascinating new lines of research aimed at defining the metabolic role of p73 and its isoforms in the nervous system. For instance, an interesting development would be to determine whether a p73 could have unsuspected metabolic role in p53-deficient tumors, especially considering the importance of glutamine metabolism in cancer.

References
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