Quinolinic acid-mediated activation of striatal parenchymal astrocytes: dynamics of progenitor lineage progression and phenotyping of newly generated neurons

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In the subventricular zone and in the hippocampal dentate gyrus a subpopulation of astrocytes produces neurons throughout life. Recent data demonstrated that parenchymal astrocytes reacting to a lesion are neurogenic ex vivo or can become neurogenic in vivo after overexpression of specific transcription factors.

However, we recently showed that, at chronic stages after Quinolinic Acid (QA)-mediated excitotoxic damage (Nato et al. 2015), subsets of striatal astrocytes undergo a spontaneous activation leading to the generation of new neuroblasts.Thus, astrocyte populations distinct from those subsets serving as neural stem cells can also activate a neurogenic program under specific conditions. During their neurogenic activation, striatal astrocytes upregulate nestin, modulate defined transcriptional programs and give rise to clusters of transit amplifying-like progenitors that in turn generate neuroblasts. By employing lineage tracing in GLAST CRE ERT2 mice we are currently reconstructing the multistep transition of parenchymal striatal astrocytes toward

neurogenesis. Moreover, we are examining the developmental trajectory of neuroblasts and evaluating their heterogeneity. Similar to what occurs in many models of degeneration-induced neurogenesis, newborn neurons fail to express markers of differentiated neurons, and have a transient existence. Nevertheless, they attain complex morphologies and often associate with striatal fiber bundles. They also receive synaptic inputs from spared striatal neurons as well as from cortical and thalamic neurons. These results suggest that newborn neuroblasts do not replace lost striatal neurons but may be involved in transient forms of plasticity or neuroprotection, explaining their transient existence.