When neurogenesis goes wrong

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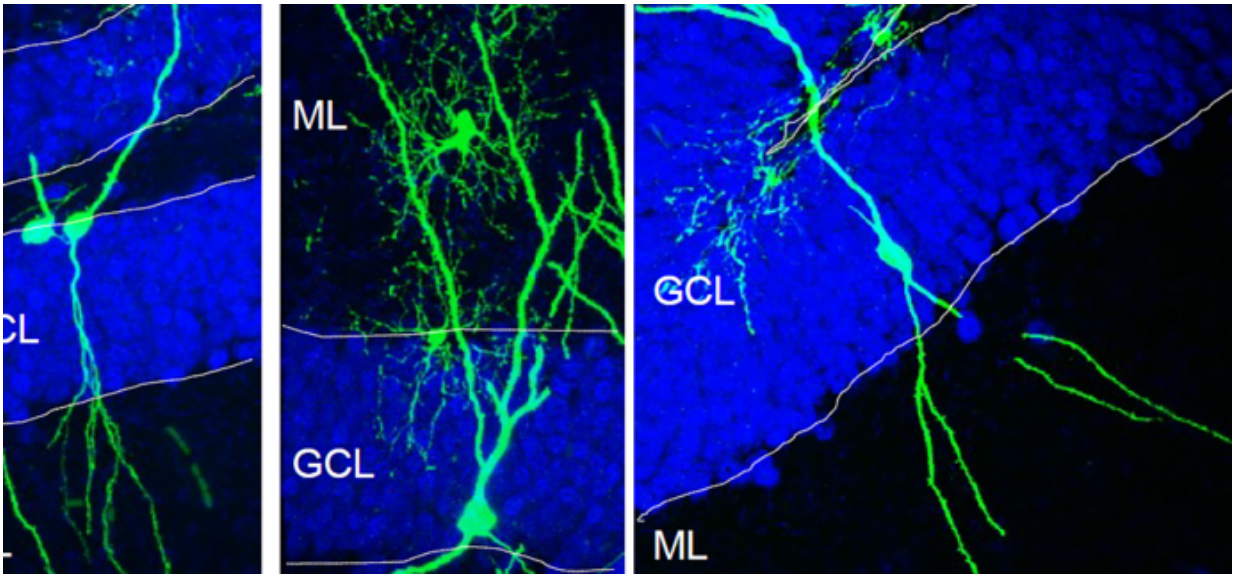

Credit: PLOS

Neurogenesis is a complex biological process by which neurons are generated from neural stem cells and progenitor cells. Indeed, the discovery of a dynamic neurogenesis in the adult brain (in both humans and animals) was a kind of extraordinary revelation. In fact, contrary to common popular belief, neurogenesis continuously occurs in specific regions in the adult brain, such as in the hippocampus and the striatum. Neurogenesis occurs in both physiological and pathological conditions.

In the hippocampus, newly born granule cells (GC) in the subgranular

zone of the dentate gyrus (DG) migrate in the granule cell layer and become functionally integrated into neuronal networks within four to six weeks. Interestingly, recent findings suggest that newborn neurons generated in the context of cerebral ischemia may fail to correctly integrate into pre-existing networks. However, the cellular mechanisms of how ischemic infarcts cause alteration of hippocampal functions are only partially understood.

Memory, neurogenesis and morphological alterations following cerebral stroke

In a recent *PLOS One* article, Woitke and collegues (Jena University Hospital, Germany) hypothesized that increased neurogenesis in the dentate gyrus following stroke may be associated with aberrant neurogenic activity and impaired hippocampus-dependent functions. This might sound somehow counterintuitive, since one would expect that increased neurogenesis may lead to improved cognitive functions. But this is not the case, or at least it does not represent the full and exact picture of what happens.

In fact, it is well known that cerebral stroke stimulates neurogenesis in the adult dentate gyrus, although the functional role of this post-lesion response is mostly unclear. In a physiological context, neurogenesis is strictly regulated and less than 1% of new neurons have aberrant connections in the intact brain. Things may be different following brain damage and insults (strokes, seizures, etc). Using behavioral and viral approaches "we now prove," says Woitke, the leading author of the study, "that aberrant neurogenesis also occurs in the murine hippocampus and is associated with poorer performance in hippocampal-dependent memory tasks following focal infarcts."

In a first attempt, Woitke and colleagues performed the Morris Water

Maze (MWM), a hippocampus-dependent behavioral task routinely used to assess spatial memory functions. Parameters such as latencies ("time to find the platform") and distance ("path lengths") to navigate to the platform were analyzed. As expected, brain ischemic mice generally needed more time to locate the platform, thus suggesting impaired learning and memory functions. In addition, analysis of the adaptive learning strategies in both groups revealed that animals with stroke used a less efficient navigation strategy to find the platform, while hippocampal-dependent strategies were employed more frequently by the control group. When looking at neurogenesis processes the authors observed an increased number of new born neurons in the hippocampus of mice with stroke. Thus, in a second set of experiments, the authors addressed the question of whether the newly generated neurons may have aberrant morphology and location, which in turn may be related to malfunction of hippocampal networks and circuits.

"Using retroviral labeling, we detected a significant number of new GC with atypical morphology and dendritic branching following ischemia," says Silke Keiner, the senior author of the study. In particular, GC displayed an additional dendritic tree extending from the basal pole towards the hilus (a specific subregion of the dentate gyrus) which is considered a typical immature feature of GC neurons. Taken together, ischemia increases the number of newborn neurons but promotes aberrant dendritic branching indicating maladaptive plasticity in the DG.

It is worth mentioning that integrated and functional neurons require dendritic spines. Interestingly, the expression of mature mushroom spines by aberrant newborn cells strongly suggests that these neurons are synaptically integrated, thus being able to influence and alter hippocampal networks.

Conclusions

In general, this study reveals that even a low number of aberrant neurons may severely affect hippocampal functions such as learning and memory. However, the casual link among cellular modifications, neurogenesis and impaired memory functions is far from being fully elucidated. In fact, the analysis of the functional impact of adult neurogenesis in behavioral experiments or cognitive tasks is still quite challenging. As mentioned by the authors, "more studies are needed to clarify whether tailored rehabilitative and therapeutic approaches might counteract aberrant neurogenesis and improve hippocampal-dependent memory performance."

More information: Florus Woitke et al. Adult hippocampal neurogenesis poststroke: More new granule cells but aberrant morphology and impaired spatial memory, *PLOS ONE* (2017). DOI: 10.1371/journal.pone.0183463