

● PERSPECTIVE

Do new neurons contribute to functional reorganization after brain damage?

The finding that adult neurogenesis occurs constitutively in the brain was a breakthrough in neuroscience and soon gained attention as a possible mechanism for neurorepair after brain damage. In a recent study we show that the dentate gyrus (DG) reorganizes anatomically over time after damage, while new neurons undergo maturation and activate in response to a contextual fear memory recall (Aguilar-Arredondo and Zepeda, 2018). These findings provide new evidence on the possible role of neurogenesis in cognitive recovery after brain injury.

The potential of the brain to change continuously, in particular as a consequence of damage, is a focus of attention for neurobiologists. Pioneer studies in the 1980's first showed that cortical representations were not fixed. Furthermore, it was shown that functional deficits triggered by cortical lesions could be resolved over time resulting in functional reorganization. These observations built on the idea that the brain was plastic, meaning that neuronal cells could change their properties after suffering damage, providing a mean for neurorepair. Nowadays, it has been well established that after damage, surviving neurons modify the balance in its excitatory/inhibitory communication and also undergo axonal and dendritic sprouting, both of which have been suggested to contribute to reorganization. Also, the release of molecules such as trophic factors as well as revascularization and activation of a number of signalling pathways have been shown to contribute to reorganization ultimately facilitating the recovery of functions (for a review, see Wieloch and Nikolic, 2006).

In terms of neurorepair, the above-mentioned mechanisms were the main considered to underlie functional recovery until the late 1990s and beginning of the 2000, when a new form of constitutive brain plasticity became widely accepted to occur: adult neurogenesis. For some time, adult neurogenesis in mammals was not a topic of study, in part because of the experimental constraints that posed working with autoradiography, the standard technique used to analyse cell proliferation. The use of the analogue of thymidine BrdU to label new cells *via* immunohistochemistry together with the use of retroviral particles and the use of conditional animals opened the possibility to study adult neurogenesis for many labs. Since then, several important questions have emerged in relation to the potential functions of new neurons and the associated mechanisms that regulate their production and integration into pre-established neuronal networks.

The evidence in mice and more recently in humans showing that different types of brain damage trigger an exacerbated neu-

rogenic response in the subgranular zone (SGZ) of the dentate gyrus of the hippocampus and the subventricular zone (SVZ) at the walls of the lateral ventricles raised the hypothesis that new neurons born in response to damage contributed to the structural and functional reorganization of the brain (Liu et al., 1998; Arvidsson et al., 2002; Jin et al., 2006). Since then, different research groups have evaluated if new cells born in response to damage: 1) survive and achieve maturation; 2) migrate towards the area of lesion; 3) show anatomical integration (*i.e.*, by establishing axonal connections with the target region); 4) show synaptic integration and; 5) display synaptic activation.

Ultimately, behavioural studies have aimed at providing a causal link between neurogenesis and functional recovery. In a recent work we show that after a focal lesion to the DG, new neurons born in response to damage survive for at least 30 days and activate in response to a DG-mediated cognitive demand, but not in response to a DG-independent task (Aguilar-Arredondo and Zepeda, 2018). Activation of new neurons occurred in response to retrieval of a contextual fear memory, but not in response to spatial exploration. Along activation, long-term potentiation, which is impaired at 10 days after damage, recovers by 30 days post-injury (Zepeda et al., 2013). The finding that new neurons born after damage become mature while specifically activating in response to contextual fear retrieval, suggests that they achieve to incorporate synaptically into the DG circuit and support the recovery of a cognitive function.

Up to now, there is experimental evidence showing that new neurons are produced from 1 and until 16 weeks after middle cerebral artery occlusion showing that continuous SVZ exacerbated neurogenesis after damage is not acute nor transient (Thored et al., 2006). Beyond survival, it has also been shown that new neurons in the DG achieve maturation and send axonal projections to CA3 as evidenced from fluoro-gold tracing studies (Sun et al., 2007). Neurons born after cortical injury develop electrophysiological properties similar to those of neurons born under physiological conditions and respond to electrical stimulation of their efferent pathway (Villasana et al., 2015) which suggests their potential to integrate functionally into a given neuronal circuit possibly facilitating the reorganization of a damaged neuronal network. Contrary to the hypothesis of functional integration of new neurons in the above-mentioned work, the authors highlight that new neurons born after damage develop but maintain an aberrant morphology. Our results also show that at an early stage after damage, new neurons display an aberrant morphology. But that at later time points the gross morphology of new neurons resembles that of neurons born under control conditions (Aguilar-Arredondo and Zepeda, 2018). These observations are also supported by recent experiments from our lab showing that after damage to the DG, newly-born neurons develop a regular morphology and send their projections to CA3 (unpublished) (**Figure 1**). These results suggest

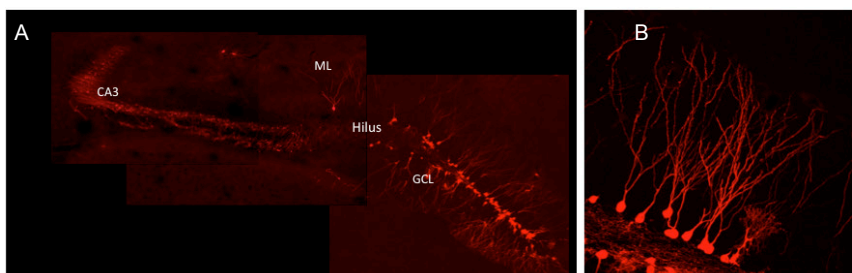


Figure 1 Neurons born after a focal lesion to the dentate gyrus (DG) develop a regular morphology and send their afferents to CA3 in an inducible transgenic mouse that expresses Td-tomato after tamoxifen injection.

(A) Coronal reconstruction of the damaged DG shows 30 days old cells (red) in the granular cell layer (GCL) projecting to CA3. (B) Magnification of cells born after damage show a regular localization in the GCL and a typical dendritic arbor branching towards the molecular layer (ML) (Aguilar-Arredondo, unpublished).

that proper morphological development of neurons born after damage may depend on the interplay between the niche where they are produced and the region where they ultimately integrate.

Functional recovery after damage has also been observed to occur along the morphological reorganization of the damaged structure (Zepeda et al., 2013; Aguilar-Arredondo and Zepeda, 2018). Our observations include a dramatic reduction of the lesion volume along time. Previous evidence showing that new neurons migrate towards the lesion area (Arvidsson et al., 2002; Yamashita et al., 2006) gives rise to an interesting question, namely, to what extent do migrating neurons contribute to the structural remodelling of the damaged area? From our results we cannot conclude that the neurons born after damage contribute to the reduction of the lesion area by “filling-in” the damaged zone, nor that they contribute by migrating to the immediately surrounding areas, as previously observed (Zhang et al., 2004; Yamashita et al., 2006). Instead, we propose that new neurons contribute to the gross anatomical reorganization of the structure probably by intercalating within the granular layer and displacing the pre-existent granular cells thus promoting the reshaping of the structure, including the lesion area.

In the quest for understanding how new neurons contribute to brain repair and functional recovery it is worth considering that they may impact beyond their ultimate anatomical integration into a circuit. In this regard, new neurons may not only support the restoration of damaged circuits through their synaptic integration, but also by providing growth or signalling factors that modulate the function of remaining cells. In fact, new neurons may impact differently along time after damage since they have distinctive properties depending on their stage of maturation. If integration of new cells is transient for a restricted time to allow the recovery of the damaged site or if integration is permanent is an interesting possibility to be explored in detail.

A recent study shows that the conditional ablation of young doublecortin cells previous to the induction of ischemia in mice, results in more pronounced motor deficits and in an increased volume of the lesion, suggesting a role for the new neurons in functional and anatomical reorganization (Jin et al., 2010). Based on these findings, it would be of interest to evaluate the maturation and synaptic integration of targeted cells born after damage to determine if they participate in the restoration of a functional network and to analyse if ablation of new neurons born after damage delays/impairs recovery or alternatively, reinstates functional deficits.

There is still a long way to go until it can be proven beyond doubt that new cells born after damage establish appropriate specific connections, integrate efficiently and re-establish the function of lost neuronal networks. In perspective, providing causal relations between these events and recovery of motor, sensory and cognitive functions may offer important pieces of knowledge for unveiling the role of neurogenesis in the puzzle of brain repair.

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