Communicative & Integrative Biology 8:3, e1038444; May/June 2015; Published with license by Taylor and Francis Group, LLC

Experience-dependent plasticity of adult-born neuron connectivity

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In contrast to most areas of the adult brain, the dentate gyrus (DG) of the hippocampus is endowed with the capability to generate new neurons life-long. While recent evidence suggests that these adult-born neurons exert specialized functions in information processing compared to pre-existing DG granule neurons, to which extent the establishment of their evolving connectivity may be regulated by experience has been elusive. We recently demonstrated that environmental enrichment (EE) induces a surprising input-specific reorganization of the presynaptic connectivity of adult-born neurons, and that this form of structural plasticity appears to large degree confined to a defined period of few weeks shortly after their generation. Here, I briefly discuss how these findings may uncover a previously unknown layer of complexity in the processes regulating the synaptic integration of adult-born neurons and propose that their circuit incorporation within the pre-existing hippocampal network is not prefigured but rather modulated by specific experiences.

Keywords: adult neurogenesis, experience, monosynaptic tracing, structural plasticity

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Submitted: 04/01/2015

Accepted: 04/02/2015

http://dx.doi.org/10.1080/19420889.2015.1038444

Addendum to: Bergami M, Masserdotti G, Temprana SG, Motori E, Eriksson TE, Göbel J, Yang SM, Conzelmann KK, Schinder AF, Götz M, Berninger B. A critical period for experience-dependent remodeling of adult-born neuron connectivity. Neuron 2015; 85:710-7.

Synaptic plasticity of adult-born hippocampal neurons

By the moment new immature neurons are generated from terminally dividing DG stem and progenitor cells, they undergo a sequence of morpho-functional changes culminating in the acquisition of features virtually undistinguishable from DG granule neurons generated during early developmental stages.[1-3] During this stepwise process of maturation, new neurons gradually establish their final connectivity and become stable components of the pre-existing tri-synaptic hippocampal circuitry.[2,4,5] Interestingly, during a relatively immature but yet critical stage between 4 and 6 weeks after their generation, adult-born DG neurons display a heightened excitability and an enhanced propensity to undergo long-term potentiation compared to their older counterparts.[6-8] While these features potentially contribute not only to the highly competitive nature of these young neurons by regulating their incorporation process into the pre-existing circuitry, they also provide insights into the unique proposed functions of adult-born granule neurons in processing complex patterns of information.[7,9,10] Intriguingly, the amount of new neurons eventually added to the network[11,12] as well as their synaptic maturation[13,14] can be modulated by experience (i.e. paradigms like voluntary exercise or EE). This increase in the number of new neurons has been associated to some beneficial effects on cognitive functions and affective behavior,[15,16] thus raising the key question to which extent this experience-dependent form of plasticity may also involve more profound alterations in the connectivity of newly-generated neurons.

Experience modifies the presynaptic connectivity of adult-born neurons

By utilizing an innovative rabies virus (RABV)-based method,[17] we have recently dissected with unprecedented temporal resolution the precise sequence of synaptic innervation controlling the circuit incorporation of neurons born in the adult brain.[18] This method makes use of a retrovirus for delivering to stem and progenitor cell-derived new neurons a glycoprotein (G) and a receptor (TVA), which are later required by the RABV to infect the very same neurons and then spread transynaptically to their first-order presynaptic partners. Optimization of this technique allowed us and other groups to trace the evolving connectivity of adult-born

DG neurons during their first weeks of life and demonstrate that their incorporation process follows sequential steps which are matched in time by the maturation stage of the neurons themselves. While local GABAergic innervation from interneurons mostly located in the sub-granular zone/inner granule cell layer provides the initial input to 10 days old newborn neurons,[18] the first appreciable source of glutamatergic inputs (by hilar Mossy cells) was detected only by the end of the second week of the neurons' age, in line with previous reports.[19,20] Interestingly, during the first 2–3 weeks of life after their generation, we detected a gradual broadening in the types of local presynaptic interneurons impinging onto adult-born neurons, at last involving interneurons in the molecular layer (e.g. axo-axonic and other MOPP cells; **Figure 1**).[18,21] Only after the apparent establishment of this local connectivity, most of the innervation arising from sub-cortical (e.g., septum and mammillary bodies) and cortical (entorhinal cortex, EC) neurons became progressively evident.[18,22] These data strongly suggest that adult-born DG neurons integrate first within local network modules before becoming the target of long-distance cortical projections, possibly indicating that besides contributing to regulate their overall maturation process, this highly dynamic refinement of local (mostly GABAergic) networks may be a key required step to guide and stabilize newborn neurons throughout their incorporation process into the hippocampal circuitry.

By taking advantage of this RABV-based approach, in a last piece of work we examined whether and how the circuit incorporation of adult-born neurons may change in response to experience, i.e., by exposing mice to EE and/or voluntary exercise. Our experiments revealed that EE exposure profoundly modifies the connectivity of newborn neurons, leading not only to an important increase in the proportion of traced presynaptic partners, but also to the recruitment of CA3 and CA1 inhibitory feedback circuits that were virtually not detectable under control housing conditions.[23] Importantly, this form of experience-dependent structural plasticity of new neurons appeared almost exclusively restricted to a critical period between weeks 2 and 6 after their generation, providing novel insights into their proposed unique contribution to hippocampal information processing during this relatively immature stage.[7] What is more, when we returned mice to their original standard cages (i.e. non-enriched) for several additional weeks, most of the previously observed local changes in intra-hippocampal GABAergic connectivity appeared to have pruned back or normalized to a degree similar to control mice. Notably, however, the $_{EC}$ inputs were still robustly increased as also evidenced by a higher density in the dendritic mushroom spines of adult-born neurons. While these findings reveal that experience can produce stable changes in the connectivity of these newly-generated neurons at least with regard to cortical inputs, they also disclose a form of plasticity induced by environmental impoverishment that took place after closure of the classical critical period of plasticity in adult-born neurons, which may presumably contribute to refine their precise final connectivity until full maturation is achieved.

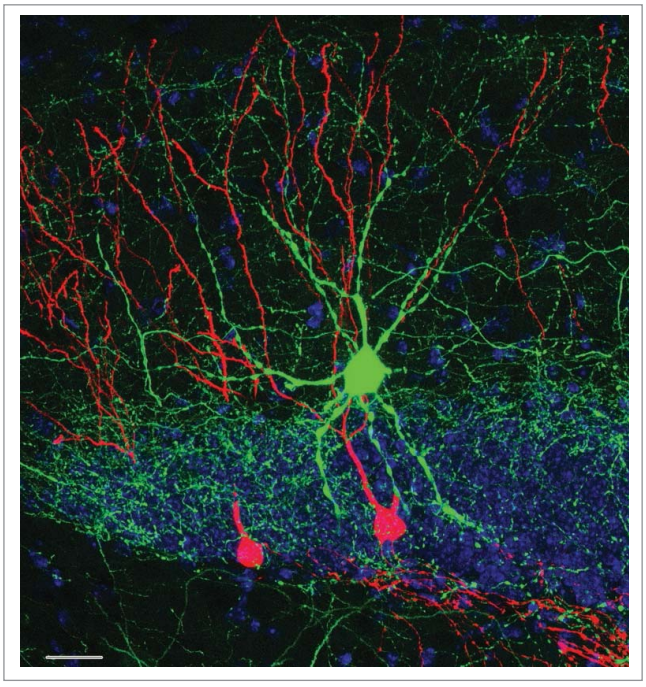

Figure 1. RABV-mediated tracing of adult-born neuron presynaptic partners. The picture illustrates an example of a RABV-traced presynaptic interneuron (green) located in the inner molecular layer of the DG and densely innervating the granule cell layer. In the background, some DsRed+ adult-born neurons were labeled 6 weeks before with a retrovirus. Blue: DAPI. Bar, 20 μm.

Our work provides a first clear demonstration that complex experiences can modify the final connectivity of newly-generated neurons in the adult brain, and therefore supports their specific involvement in information processing and hippocampal-dependent behavior. However it also opens new important questions. For instance, is the transient increase in GABAergic innervation following EE an evidence for the presumable role of GABA in refining the final connectivity of adult-born neurons in response to experience, and eventually leading to the consolidation of $_{EC}$ inputs? To which extent these experience-dependent changes of adult-born neurons within their critical period of plasticity may be mirrored by homeostatic adaptations in the connectivity of pre-existing mature granule neurons? And finally, can we expect a remodeling of GABAergic inputs to be a central feature also for the network incorporation of new neurons obtained via specific cell-based replacement approaches to repair adult brain circuits, for instance following local reprogramming or transplantation? The answer to these questions will

undoubtedly clarify the function of adult neurogenesis at the circuit level and provide a framework to better understand, and possibly prevent, how maladaptive changes in new neuron connectivity can participate to circuit dysfunction in the adult brain.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

This work was supported by the UoC advanced post-doc grant program and Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD) to M.B.

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