Journal Club

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# Adult-Born Granule Cells Contribute to Dentate Gyrus Circuit Reorganization after Traumatic Brain Injury

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Review of Kang et al.

Post-traumatic epilepsy (PTE) is a serious consequence of traumatic brain injury (TBI). PTE develops following a latent postinjury period during which alterations in neuronal network excitability are thought to occur, leading to the development of recurrent and unprovoked seizures. In particular, pathophysiological changes in the dentate gyrus (DG) have been suggested as key mediators of epileptogenesis following TBI.

In order to understand the development of PTE, researchers have focused on aspects of the condition that are shared with other forms of epilepsy, such as temporal lobe epilepsy. One of the most striking observations in patients with either type of epilepsy is the sprouting of granule cell (GC) axons (known as mossy fibers) in the inner molecular layer of the DG, where GC dendrites are located (Swartz et al., 2006). Normally, mossy fibers form excitatory synapses onto CA3 pyramidal cells, hilar mossy cells, and GABAergic interneurons, but rarely synapse onto other GCs (for review, see Amaral et al., 2007). This lack of recurrent synapses

is thought to inherently limit the spread of excitation in the DG. Modeling studies predict that mossy fiber sprouting would compromise this, allowing activity to spread and even become self-sustaining: conditions that are favorable for seizures (Santhakumar et al., 2005). In addition to synapsing with GCs, sprouted mossy fibers have also been shown to target inhibitory interneurons (Puhahn-Schmeiser et al., 2021). However, the contribution of such sprouting to the development of epilepsy is currently unclear.

While the relevance of mossy fiber sprouting in epilepsy is still debated (Buckmaster, 2014), it highlights an important concept in epilepsy research, namely, the long-term reorganization of the local DG circuit. This reorganization may also involve abnormal integration of adult-born GCs. Under normal physiological conditions, new neurons are continuously produced throughout adulthood in the DG of rodents. These adult-born GCs integrate into preexisting circuits (for review, see Kempermann et al., 2015). As adult-born GCs mature, they begin to shape the DG circuit in several ways, such as by recruiting feedback inhibition onto mature GCs (Temprana et al., 2015; Drew et al., 2016). However, if these adult-born GCs do not integrate properly into the circuit, they may become a source of aberrant circuit reorganization. Indeed, previous studies in models of temporal lobe epilepsy have shown that adult-born GCs display abnormal plasticity, which is dependent on their maturational

stage at the time of the epileptogenic insult (Kron et al., 2010). The functional consequences of abnormal plasticity for the reorganization of the DG circuit were recently identified by the characterization of newly generated synapses arising from GCs born at different times with respect to epileptogenic insult (Hendricks et al., 2017, 2019). However, it remains to be determined whether a GC maturational stage-dependent reorganization of excitatory and inhibitory neuronal circuits occurs in the DG after TBI.

In a recent study, Kang et al. (2022) investigated whether mouse GCs born at different times differentially contribute to shaping the DG local circuit after controlled cortical impact (CCI), a model of TBI. Circuit reorganization was assessed by studying excitation and inhibition of GCs by other GCs: specifically, recurrent excitation in which a GC excites another GC; and feedback inhibition, in which a GC inhibits another GC via an interneuron. Cohorts of GCs born at three different times relative to CCI were selectively labeled with channelrhodopsin2 (ChR2) and EYFP in different mice. Specifically, GCs that were mature at the time of injury (early-born), GCs that were born just before injury (adult-born pre-CCI), or GCs that were born just after injury (adult-born post-CCI) were labeled. Synaptic reorganization was assessed in hippocampal slices by stimulating ChR2-expressing GCs and recording evoked responses in ChR2-negative cells, including parvalbumin-expressing ($PV^+$) interneurons and unlabeled mature

GCs. To assess long-term effects, experiments were performed 8-10 weeks after TBI, a time point when adult-born GCs have integrated into the circuit and have mature properties (Zhao et al., 2006).

Kang et al. (2022) first examined whether distinct cohorts of GCs shape feedback inhibition after CCI. Optogenetic stimulation of GCs in all cohorts evoked IPSCs in at least some ChR2-negative mature GCs. However, stimulation of adult-born pre-CCI GCs evoked IPSCs in >70% of recorded mature GCs, substantially more than that evoked by similarly aged GCs from sham-injured mice. This large upregulation of evoked IPSCs compared with respective sham controls was not seen for adult-born post-CCI GCs or early-born GCs, although the latter showed a nonsignificant trend toward an increase. The evoked IPSCs were confirmed to be mediated by polysynaptic feedback inhibition through their pharmacological and electrophysiological properties. These results suggest that GCs that are immature at the time of injury undergo abnormal plasticity that leads to an increased inhibition of surrounding mature GCs.

Next, the authors sought to identify the targets of the adult-born pre-CCI GCs that underlie increased feedback inhibition. The DG is composed of several types of inhibitory interneurons that mediate different forms of inhibition (for review, see Houser, 2007). In the DG, a dominant form of feedback inhibition is lateral inhibition among GCs via fast-spiking GABAergic PV$^+$ interneurons (Espinoza et al., 2018). Kang et al. (2022) recorded from basket cells, a subtype of PV$^+$ interneurons, and found reduced intrinsic excitability after injury. Despite this, optogenetic stimulation of adult-born pre-CCI GCs evoked larger EPSCs and triggered action potential firing in a greater proportion of PV$^+$ basket cells than in sham-injured controls. GCs born before CCI thus appear to form strong excitatory synaptic inputs onto PV$^+$ basket cells, driving the increased inhibition of mature GCs. These findings are in contrast to the reduced cortical activation of PV$^+$ interneurons previously found to occur early after TBI, predicted to compromise PV$^+$-interneuron-mediated feedforward inhibition of GCs (Folweiler et al., 2020). These temporally distinct changes in the synaptic reorganization of inputs to PV$^+$ interneurons may underlie the differences in DG excitability seen during these periods (Santhakumar et al., 2001), with early DG hyperexcitability potentially mediated by reduced feedforward
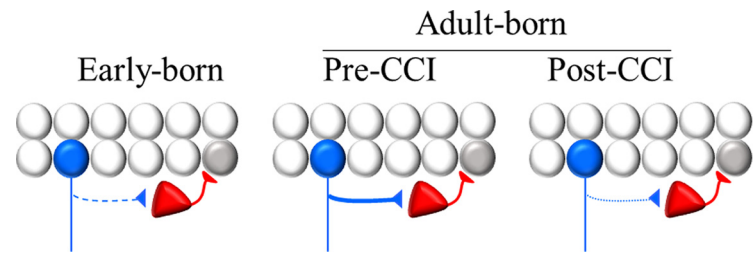


Figure 1. Schematic of the main conclusions from Kang et al. (2022) illustrating a maturational stage-dependent contribution of GCs to feedback inhibition after CCI. Mature GCs that are born during the early postnatal period (P8-P12; early-born) show a moderate increase in their contribution to feedback inhibition (indicated with a dashed line) compared with similarly aged GCs in sham-injured mice. Whereas GCs that are immature at the time of injury (adult-born pre-CCI) show a substantial increase in feedback inhibition (thick line), GCs born after injury (adult-born post-CCI) have a limited contribution to feedback inhibition that is not different from what would be expected from this population under normal conditions (dotted line). Blue represents ChR2-expressing GC from each cohort. Red represents PV$^+$ basket cell. Gray represents a ChR2-negative mature GC used for electrophysiological recordings.

inhibition of GCs followed by later increased feedback inhibition of GCs, contributing to the return to baseline excitability observed at 1 month after injury.

The increased synaptic strength between adult-born pre-CCI GCs and PV$^+$ basket cells could potentially have resulted from a change in presynaptic release probability, change in postsynaptic receptors, and/or sprouting of mossy fibers. Although Kang et al. (2022, their Fig. 2) found mossy fiber sprouting in the DG of CCI mice, the synaptic data cannot be solely attributed to mossy fiber sprouting since GCs synapse with PV$^+$ basket cells under physiological conditions. The authors thus concluded that the increased synaptic excitation of PV$^+$ basket cells may be because of increased synaptic contacts and/or changes in the excitatory network.

Last, Kang et al. (2022) examined the contribution of each cohort of GCs to recurrent excitation following CCI. Surprisingly, optogenetic stimulation of ChR2-expressing GCs in all cohorts rarely evoked EPSCs in ChR2-negative mature GCs. Further, external conditions used to evoke hyperexcitability also failed to reveal any recurrent excitation. Overall, these data indicate that, in the CCI model of TBI, early-born and adult-born GCs do not contribute to recurrent excitation. Instead, changes in local circuits appear to be limited to increased input from adult-born pre-CCI GCs to PV$^+$ basket cells, which results in more extensive feedback inhibition of mature GCs.

The findings by Kang et al. (2022) highlight a possible critical period during which adult-born GCs can contribute to circuit reorganization after TBI. The maturation and integration of adult-born GCs into the DG circuit follow a sequential process, in which GABAergic and glutamatergic signaling is important throughout (for review, see Jahn and Bergami, 2018). TBI markedly impacts the DG circuit, with loss of both GABAergic and glutamatergic neurons, as well as changes in the excitability of surviving cells (for review, see Hunt et al., 2013). The GCs born before CCI are <2 weeks postmitosis at the time of injury, a period when GABA-mediated depolarization is involved in GC maturation (Ge et al., 2006; Chancey et al., 2013). GCs that were immature at the time of injury may not be exposed to the necessary GABAergic signaling, perhaps driving their abnormal integration into local feedback inhibitory circuits. In accordance with this, circuit reorganization by adult-born GCs in a model of temporal lobe epilepsy was recently suggested to be driven by increased GABAergic activity following epileptogenic insult (Lybrand et al., 2021). As GC maturation progresses, the impact of the circuit on their development evolves (Schmidt-Hieber et al., 2004; Tashiro et al., 2006). This later maturational stage was not investigated by Kang et al. (2022); thus, it would be worthwhile to determine whether immature GCs that are older at the time of injury differentially contribute to circuit reorganization.

Remarkably, GCs born after injury did not show any enhanced contribution to feedback inhibition or recurrent excitation after CCI, suggesting limited involvement in circuit reorganization. This is consistent with previous work showing that GCs born after injury exhibit normal synaptic innervation and excitability, despite increased dendritic branching and migration in the GC layer (Villasana et al., 2015). Whether neurogenesis after TBI is beneficial or pathologic remains unclear. While neurogenesis may be required for cognitive recovery after TBI (Blaiss et al., 2011), limiting TBI-

induced neurogenesis reduces seizure susceptibility (Neuberger et al., 2017). If adult-born post-CCI GCs do contribute to PTE, the findings by Kang et al. (2022) would suggest that this might be via a mechanism other than reorganization of feedback inhibition and recurrent excitation. Further work will be required to understand the underlying mechanism.

Could increased feedback inhibition lead to the development of PTE? The view that seizures occur as a result of an imbalance between inhibition and excitation risks oversimplification. For instance, evidence is emerging for roles of PV$^+$ interneurons in both generating and maintaining seizures (for review, see Magloire et al., 2019). The increased feedback inhibition observed by Kang et al. (2022) suggests that adult-born GCs may influence the activity of a larger proportion of mature GCs after CCI. In this case, PV$^+$ interneurons could paradoxically promote seizure generation by enhancing coordinated spiking in a group of principal cells, a mechanism previously shown in temporal cortex slices (Sessolo et al., 2015).

Alternatively, increased feedback inhibition could reflect a homeostatic mechanism. The DG circuit is hyperexcitable early after injury when GCs born before injury are beginning to integrate into the circuit (Lowenstein et al., 1992). A bias toward synapsing with PV$^+$ interneurons could compensate for this excitability, potentially limiting seizure duration (Hosford et al., 2016). It will be important to determine how selective ablation of GCs born pre-CCI impacts the development of PTE.

Overall, the study by Kang et al. (2022) provides new evidence for a maturational-stage-dependent contribution of adult-born GCs to network reorganization after TBI (schematically depicted in Fig. 1). The restriction to feedback inhibition brings into the question the hypothesis that recurrent excitation via mossy fiber sprouting is responsible for driving synaptic reorganization that leads to PTE. Although the implications for the development of PTE remain unclear, the current study highlights a role for a specific subpopulation of adult-born GCs in TBI-induced plasticity.

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