This Week in The Journal

How Mesenchymal Extracellular Vesicles Boost Stroke Recovery

Maria Medalla, Wayne Chang, Samantha M. Calderazzo, Veronica Go, Alexandra Tsolias, et al.

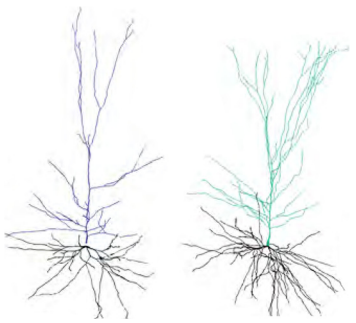
(see pages 3385–3407)

Mesenchymal stem cells (MSCs) derived from bone marrow have shown promise in treating injuries throughout the body, including the brain. Although it was originally hypothesized that MSCs differentiated to replace damaged cells, it was soon discovered that the effectiveness of MSCs actually comes from factors they secrete. Indeed, the beneficial effects of MSC transplants can be replicated by peripheral infusion of MSC-derived extracellular vesicles. Such vesicles are thought to mediate transfer of specific proteins and RNAs between cells, and in the case of brain injury, they are thought to enhance endogenous repair mechanisms and reduce pathological inflammation.

Moore and colleagues previously reported that infusion of MSC-derived extracellular vesicles enhanced the recovery of hand dexterity in monkeys after transection of arterioles (a model of stroke) in primary motor cortex (M1). Because pyramidal neurons in layer 3 of the ventral premotor cortex (vPMC) adjacent to the lesion are thought to contribute to such recovery, Medalla, Chang, et al. recorded from these neurons in brain slices taken 14–16 weeks after M1 lesion to learn how extracellular vesicles might enhance recovery.

Several electrophysiological, synaptic, and morphological properties of vPMC pyramidal neurons were altered after M1 lesion. For example, the spike rate was elevated, partly because firing frequency adaptation (a progressive decline in spike rate during prolonged depolarization) was reduced. M1 lesion also reduced EPSC frequency in vPMC neurons, but it increased IPSC frequency, thus, tilting the excitatory/inhibitory balance toward inhibition. Finally, apical dendrites were less complex in vPMC of injured brains than in those of controls. Treatment of injured monkeys with extracellular vesicles attenuated these effects and increased the proportion of calbindin-expressing interneurons activated during performance of a hand dexterity task. Notably, greater spike frequency adaptation, excitation/inhibition ratio, EPSC frequency, and MAP2 density (a measure of dendritic stability), as well as more widespread activation of calbindin neurons and reduced activation of excitatory neurons were associated with faster recovery of hand dexterity.

These data suggest that MSC-derived extracellular vesicles enhance functional recovery after M1 damage by reducing the excitability of pyramidal neurons and increasing the activity of calbindin-expressing interneurons in layer 3 of vPMC. This might reduce the activation of task-irrelevant circuits. How extracellular vesicles exert these effects remains to be elucidated.



Lesion of M1 leads to reduced dendritic complexity in vPMC pyramidal cells (left). This effect is reversed by intravenous administration of MSC-derived extracellular vesicles (right). See Medalla, Chang, et al. for details.

The Source of Nociceptor-Evoked Cortical Gamma Oscillations

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(see pages 3478 –3490)

Acute pain results from the activation of peripheral nociceptors, but the perceived magnitude of pain resulting from a given stimulus differs across individuals and is influenced by cognitive, emotional, and motivational states. Such variability has complicated efforts to study the neural mechanisms of pain. This difficulty has been compounded by the fact that brain areas activated by nociceptive stimuli are also activated by other salient stimuli. Encouragingly, however, recent work has suggested that the amplitude of gamma-frequency oscillations in the somatosensory cortex provides a reliable indication of the perceived intensity of pain in both rodents and humans. Nonetheless, because the brain surface recordings used to detect these oscillations lacked sufficient spatial resolution to pinpoint their source, whether the oscillations reflect pain perception or motor responses to painful stimuli has been debated. Therefore, Yue et al. measured bilateral activity simultaneously with epidural electrocorticography (ECoG) and intracortical microelectrode recordings in superficial and deep layers of primary somatosensory (S1) and motor (M1) cortex to definitively identify the source of nociceptor-evoked gamma oscillations.

Noxious radiant heat stimuli applied to the forepaws of rats evoked gamma oscillations bilaterally in superficial and deep layers of both S1 and M1. Importantly, however, the magnitude of these oscillations was greatest in the superficial layers of S1 contralateral to the stimulated forepaw. Moreover, oscillations measured with epidural ECoG showed a more consistent phase relationship with oscillations measured in superficial layers of contralateral S1 than with oscillations measured in other areas. Finally, the modulation of interneuron spike rates (which are thought to drive gamma oscillations) was greater and more coherent with epidurally recoded gamma oscillations in contralateral S1 than in other recorded areas.

These data indicate that gamma oscillations measured at the brain surface in response to nociceptive stimulation are generated by the firing of interneurons in the superficial layers of S1, supporting the hypothesis that these oscillations reflect the magnitude of pain perception. The downstream effects of these oscillations remain to be fully elucidated, but previous work suggests that they increase sensitivity to nociceptor stimuli by activating pain networks throughout the brain (Tan et al., 2019, Nat Commun 10:983). Suppressing these oscillations might therefore attenuate pain perception.

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