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RESEARCH HIGHLIGHT

Neuroglial Crosstalk by Mitochondria

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Glia-neuron interaction is an integral part of signaling networks in the brain. Abundant evidence has suggested a pivotal role for glia in neuronal survival and activity [1–3], yet the mechanisms that lead to neuroglial crosstalk have not been well elucidated, nor has the diverse function of the exchange and transfer for materials between the two types of cells. Intriguingly, glia have been demonstrated as the recipients of axonal mitochondria from retinal ganglion cells [4]. This transcellular degradation of mitochondria provides an excellent example of how glia and neurons communicate, and prompts us to reconsider the importance and implications of how dysfunctional neuroglial crosstalk might underlie possible causes of brain diseases.

Recently, a report by Hayakawa *et al*. published in *Nature* [5] has uncovered a reverse pathway for mitochondria release from glia to neurons. In this paper, the authors demonstrated that mitochondria are released from astrocytes in extracellular particles of 300–1,100 nm, found in the conditioned media from rat cortical astrocytes, and positive for MitoTracker Red, suggesting that the mitochondria within these particles are functional. Importantly, the authors identified the CD38-cyclic ADP-ribose (cADPR)-calcium signaling as the key regulatory pathway that mediates astrocytic mitochondria release. Increasing the CD38-cADPR-calcium signaling in two ways, either via CRISPR/Cas9 activation plasmids or cADPR stimulation that activates the CD38 signaling, increased the functional endpoints of extracellular mitochondria in astrocyte-derived conditioned medium, suggesting a crucial role for CD38 signaling in regulating astrocytic mitochondria production and release.

What do these functional mitochondria do? Do they actively transmit signals or are they "leftovers" of glial action? One plausible guess is that they serve as glial effectors to affect adjacent neurons. Interestingly, the authors identified two key aspects that these glial mitochondria regulate. First, under oxygen-glucose deprivation, a condition mimicking ischemic injury like stroke, rat cortical neurons suffer from death and a fall of cellular ATP levels. When these neurons are provided with astrocyte-derived conditioned medium containing mitochondria, their ATP levels and viability are restored. On the other hand, addition of conditioned medium from which the mitochondria have been filtered out by size restriction, fails to restore the ATP levels and viability, suggesting that astrocytic mitochondria have neuroprotective effects on adjacent neurons.

Under similar conditions, where astrocytes and neurons are co-cultured with their mitochondria separately labeled using MitoTracker Red (for astrocytes) and CellLight mitochondrial GFP (for cortical neurons), astrocyte mitochondria are detected in soma and axons, or fused with GFP-labeled neuronal mitochondria, suggesting an astrocyte-to-neuron mitochondria transfer. Upon oxygen-glucose deprivation, these neurons die and dendrite elongation is disrupted. Co-culturing neurons in such conditions with healthy astrocytes (with normal mitochondria transfer) re-establishes neuronal survival and rescues the

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dendrite elongation. Nonetheless, co-culturing neurons with CD38-silenced astrocytes reduces the transfer of mitochondria and fails to rescue the dendrite elongation. Taken together, these results indicate that astrocytic mitochondria are transferred to neurons in a CD38 signaling-dependent manner to promote both neuronal survival and plasticity after stroke.

In an *in vivo* mouse model of focal ischemia, mice were subjected to focal ischemia followed by injection with extracellular particles containing MitoTracker Red-labeled mitochondria collected from primary cortical astrocytes. Assaying neurons in the peri-infarct cortex from these mice indicated the presence of MitoTracker-labeled astrocytic mitochondria. Astrocytic mitochondria were similarly present in neurons adjacent to fluorescently-labeled astrocytes in FVB/N-Tg (GFAPGFP)14Mes/J transgenic mice subjected to focal ischemia. Neurons from either source also exhibited upregulation in the levels of cell survival-related proteins such as pAKT and BCL-XL, and were also enriched with mitochondrial TOM40. Interestingly, administration of *Cd38* siRNA to these models resulted in a reduction in GFAP fluorescent mitochondria in the cerebrospinal fluid (CSF) and MAP2-labeled neuronal mitochondria, suggesting that CD38 is required for astrocyte-to-neuron mitochondria transfer after stroke. Accompanying these phenomena, CD38 suppression also decreased the oxygen consumption in CSF-derived extracellular mitochondrial particles, a reduction in the level of the neuroplasticity marker GAP43, and worsened neurological outcomes, as represented by neuroscores and grid-walking tests.

Hayakawa *et al*. reported a distinct pathway that involves glia-to-neuron mitochondria transfer for promoting neuronal survival and plasticity after stroke. Unlike the disposal mechanism for axonal mitochondria transferred to glia, glia-derived mitochondria are transferred to neurons via CD38-cADPR-calcium signaling, to potentially amend the damage and restore neuronal function after brain injury. These findings provide excellent foundations for future exploration of the bidirectional communication between glia and neurons, further advancing our understanding on the basis of brain function and human nature.

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