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Extracellular Vesicles: Goodies for the Brain?

Brain homeostasis requires extensive signaling and information exchange between all types of neural cells, including neurons and glia. Recent studies indicated a pivotal role of extracellular vesicles (EVs) in communication between neural cells and furthermore, in the conversation between neural cells and the periphery. EVs comprise a group of varied secreted vesicles (plasma membrane-derived microvesicles and endosome-derived exosomes), which recently came into focus regarding their ability to shuttle biomolecules including RNA between cells and their potential to phenotypically modulate target cells. Apparently, all types of neural cells release EVs, which have been implicated in several physiological and pathological processes such as neuromodulation, synaptic plasticity, neuron-glia-interaction, and the spreading of neuropathological agents. Notably, EVs with the characteristics of exosomes seem to have a remarkable role in neuroprotection and neuroregeneration. Oligodendrocytes release exosomes in response to neurotransmitter signaling, that transfer cargo to neurons and enhance the tolerance of recipient neurons toward different types of cell stress (Frühbeis *et al*, 2013). These exosomes convey multilevel information by transferring stress-protective enzymes (Hsp70, SOD1, and catalase), activation of pro-survival signaling pathways and modulation of gene expression. In similar fashion, EVs secreted by Schwann-cells are internalized by neurons in the peripheral nervous system and promote axonal regeneration after injury by increasing axon elongation (Lopez-Verrilli *et al*, 2013). Thus, EVs transferred from myelinating glia cells to neurons convey neuroprotective and pro-regenerative messages and provide local support to facilitate axonal maintenance, homeostasis, and axonal growth. It is therefore conceivable that application of glial exosomes may offer a therapeutic opportunity to benefit neurons and prevent axonal death in the course of demyelinating diseases or other sorts of neural injury.

Moreover, there is compelling evidence that EVs released by cells in the periphery can enter the CNS and accomplish pro-neural activity. EVs derived from hematopoietic cells are able to pass the blood–brain barrier and deliver genetic information in form of mRNA and miRNAs to CNS neurons, in particular under inflammatory conditions (Ridder *et al*, 2014). It has been suggested that IFNγ-stimulated dendritic cells release EVs that promote CNS myelination and might be applied for remyelination therapies (Pusic *et al*, 2014). Furthermore, recent developments in the field of cell therapy strongly suggest that the systemic regenerative potential of stem cells observed in several neurological disorders is not revealed by cell engraftment, but largely due to paracrine signals delivered by EVs entering the CNS or modulating inflammatory responses. In a rat model of ischemia, intravenous administration of EVs originating from mesenchymal stromal cells improved functional recovery, which was related to enhanced neurite remodeling, neurogenesis, and neovascularization due to EV-mediated transfer of miRNAs to neural target cells (Xin *et al*, 2013). Neural stem cells (NSCs), which facilitate functional recovery upon systemic application in a number of neural diseases, release EVs after exposure to pro-inflammatory cytokines that are considered to mediate immunomodulation in the host environment (Cossetti *et al*, 2014).

In conclusion, EVs derived from cells within the nervous system as well as EVs entering the CNS from the periphery emerge as potent conveyors of complex messages in benefit of neural health. Future studies will be needed to uncover their full potential as therapeutic agents and to unravel their mode of action.

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New Signaling Pathway for Gut–Brain Interactions

Inflammatory Bowel Disease (IBD), which comprises Crohn's disease and ulcerative colitis, is a chronic inflammatory condition with a relapsing course. As IBD is associated with psychiatric disorders such as depression and anxiety as well as cognitive impairment, it was suggested that these psychological factors might predispose an individual to develop the disease. Now it is clear that there is bi-directional communication between the gut and the central nervous system (Kennedy *et al*, 2012) and our recent finding identifies a new mechanism by which IBD might cause behavioral manifestations (Zonis *et al*, 2015).

The generation of new neurons continues throughout adulthood in the subgranular zone of the dentate gyrus of the hippocampus. It is well accepted that adult hippocampal neurogenesis is involved in memory and learning (Aimone *et al*, 2014) and various aspects of emotion and the stress response (Cameron and Glover, 2015). Thus, disruption of hippocampal neurogenesis could have profound effects on a wide range of behaviors. Among many other factors, inflammation and pro-inflammatory cytokines negatively affect neurogenesis. Peripheral inflammation can signal the brain by activating the vagus nerve and Toll-like receptors in the circumventricular organs, and pro-inflammatory cytokines can enter the brain through saturable transport systems. Engagement of this immune-to-brain communication ultimately leads to the activation of resident microglia, which is a major source of pro-inflammatory cytokines in the brain.

Previously we found that during acute systemic inflammation, cytokines upregulated in the hippocampus trigger $p21^{Cip1}$ (p21) induction in cells of neuronal lineage (Zonis *et al*, 2013). p21 is a cyclin-dependent kinase inhibitor that restrains cell cycle progression, thereby reducing neurogenesis. Neuronal progenitors treated *in vitro* with the pro-inflammatory cytokine interleukin-6 (IL-6) exhibit p21 induction and decreased proliferation, whereas IL-6 had no effect on the proliferation of progenitor cells derived from mice lacking p21. Thus, a direct inhibitory effect of IL-6 on neurogenesis is mediated by the induction of p21.

Unlike acute transient inflammation, chronic inflammatory disease might have continuing and long-lasting effects on neurogenesis. To assess the effects of chronic peripheral inflammation, we utilized the dextran sodium sulfate mouse model of IBD (Strober *et al*, 2002). This model produces colonic epithelial cell lesions and later chronic intestinal inflammation beginning 20 days after treatment. We found increased plasma levels of IL-6, indicative of the presence of systemic inflammation and this was accompanied by increased expression of Iba1, a marker of activated microglia, and the induction of IL-6, IL-1β, and p21 in the hippocampus. We also found a decrease in the number of newly developing neurons, likely due to cytokine-induced p21 expression in early neuronal progenitors. Subsequent *in vitro* experiments with neuronal progenitor cells confirmed that in addition to IL-6, the pro-inflammatory cytokines IL-1β, and TNF-α also increase p21 expression (Zonis *et al*, 2015).

Our findings demonstrate that cytokine-induced p21 might have an important role in restraining neurogenesis during acute and chronic inflammation. These data reveal a previously unknown and potentially important signaling pathway for gut–brain interactions. Continuous immune signaling as a consequence of peripheral inflammation occurs in many chronic disorders, such as autoimmune disease, cancer, diabetes and obesity, and these illnesses manifest behavior abnormalities including cognitive impairment and depression. It is possible that the disruption of hippocampal neurogenesis might underlie some of the behavioral sequelae of IBD and other disorders associated with chronic inflammation (Figure 1).

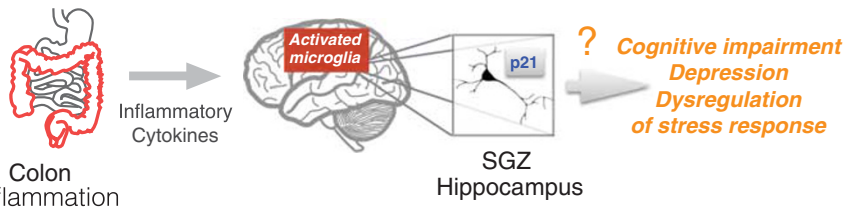

Figure 1. A proposed model for gut–hippocampus interaction. Peripheral inflammatory cytokines released during chronic intestinal inflammation activate microglia with subsequent induction of cytokines and p21 in early neuronal progenitors, effectively halting hippocampal neurogenesis and affecting behavior. SGZ-subgranular zone.

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