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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).

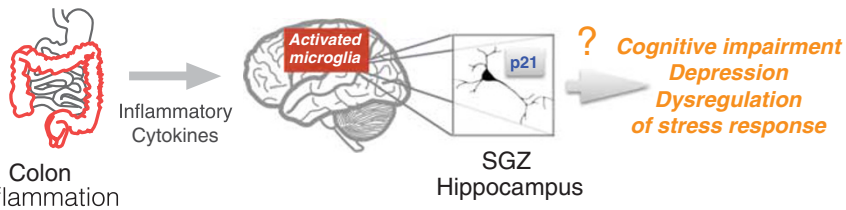

Figure 1. A proposed model for gut–hippocampus interaction. Peripheral inflammatory cytokines released during chronic intestinal inflammation activate microglia with subsequent induction of cytokines and p21 in early neuronal progenitors, effectively halting hippocampal neurogenesis and affecting behavior.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

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Vera Chesnokova[1] and Robert N Pechnick[2]

[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA; [2]Department of Basic Medical Sciences, College of Osteopathic Medicine of the Pacific, Western University of Health Sciences, Pomona, CA, USA

E-mail: Vera.Chesnokova@cshs.org

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Neural Basis of Mindfulness Interventions that Moderate the Impact of Stress on the Brain

The scientific study of mindfulness has skyrocketed. Mindfulness can be defined as 'non-judgmental attention to present-moment experiences' and is thought to comprise several complex processes, including attentional control, emotion regulation, and self-awareness (Tang *et al*, 2015). Although the neuroscience underlying mindfulness is at an early stage, there are some intriguing findings that begin to unravel the effects of mindfulness on mental health, stress, and resilience. For example, those individuals who rated themselves as more mindful, i.e. had greater 'dispositional mindfulness', generally report lower levels of perceived stress (Prakash *et al*, 2015). This is important because the level of stress is strongly related to physical and mental health as well as cortical thinning. In comparison, dispositional mindfulness has been related to structural and functional differences in several neural structures, including the medial prefrontal cortex, hippocampus, amygdala, anterior and posterior cingulate, and orbitofrontal cortex (Tang *et al*, 2015). Therefore, dispositional mindfulness may prove to be an important construct to examine individual differences that can help to predict risk for and relapse to mental disorders.

Mindfulness-based stress reduction (MBSR) has been proposed for almost every psychiatric condition. In a meta-analysis (Sedlmeier *et al*, 2012), mindfulness interventions had medium to large effect sizes for changes in emotionality and relationship issues, medium effect sizes for measures of attention, and small effect sizes for cognitive measures. MBSR has been associated with increased cortical thickness in the insula and somatosensory cortex, which can be associated with reduction of worry, state anxiety, depression, and alexithymia (Tang *et al*, 2015). Moreover, changes after mindfulness training in the insula have been related to increase in interoceptive awareness, i.e. the ability to monitor afferents from inside the body, which is emerging as an important construct for anxiety disorders and addiction (Paulus and Stewart, 2013). Thus, some of the same brain systems that have been implicated in dispositional mindfulness are also affected by mindfulness-based interventions and show a certain degree of plasticity of these systems.

Our understanding of the molecular mechanisms of mindfulness and changes induced by mindfulness-based interventions is at its infancy. Recent studies have reported that MBSR training results in a smaller post-stress inflammatory response (Rosenkranz *et al*, 2013), which includes interleukin-6. MBSR also increased telomerase activity and those individuals with the greatest increase also reported the greatest reductions in chronic stress, anxiety, dietary restraint, dietary fat intake, cortisol, and glucose (Daubenmier *et al*, 2012). These findings suggest that mindfulness interventions affect both inflammatory and epigenetic mechanisms, which are important for mood and stress-related disorders, respectively. Therefore, elucidation of the molecular substrates that underlie individual differences in mindfulness may be one of the most fruitful areas for future research. Taken together, mindfulness and mindfulness-based interventions have profound effects on mental health, affect brain systems that are important for emotion regulation and self-awareness, and alter inflammatory and epigenetic responses, yet much needs to be done to make these interventions a part of precision psychiatry.

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Martin P Paulus[1]
[1]Laureate Institute for Brain Research, Tulsa, OK, USA
E-mail: mpaulus@laureateinstitute.org

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Dynorphin, Dysphoria, and Dependence: the Stress of Addiction

The hypothesis that the dynorphin-kappa opioid receptor system may be a key component of the neuroplasticity associated with stress-induced mood disorders and the 'dark side' of