Translational Neuroscience

From the bench to the bedside: Genetics of intellectual disability, Gustatopic mapping, Molecular origins of oligodendrogliomas, Back pain and the brain, and more…

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NEW GENETIC ETIOLOGIES OF INTELLECTUAL DISABILITIES[5]

Despite the large socioeconomic and health care impact of intellectual disability, surprisingly little is known about the heritable nature of this disease beyond the 10%-or-so thought to be due to x-linked genes. In this study, the authors took advantage of the high rates of consanguinity found in Middle Eastern countries to map new genes responsible for autosomal recessive intellectual disability (ARID) by examining such families with members that had moderate to severe cognitive impairment. This gene mapping was accomplished using a combination of standard and next-generation strategies for linkage analysis (in short, a way of finding genes of interest by their proximity to known genetic markers). Fascinatingly, in ~85% of families studied, causal genetic abnormalities were identified, with ~68% of genetic abnormalities localized to a single mutation. While about a third of these mutations were in genes known to be causes of ARID, the rest were novel. In all, about 50 new genes now implicated in ARID were identified. These genes spanned the entire spectrum of integral cellular function, ranging from transcription and translation to critical metabolic processes such as fatty acid synthesis, protein degradation, and cell cycle regulation. Some genes had specific functions within neurons or at synapses. The key message is that as the genetic underpinnings of complicated neuropsychiatric disorders continue to be uncovered, the potential for understanding and intervening in these diseases grows exponentially. Perhaps, one day neurosurgeons will be stereotactically injecting viral vectors targeted at rescuing malfunctioning neurodevelopmental genes in utero. Science fiction? … Not so much anymore.

MAPPING TASTES IN THE BRAIN[4]

Throughout all forms of life, taste serves a fundamental biological function: it allows for the discrimination of safe, energy-rich nutritional sources available for consumption. While much is known about the taste receptors in the periphery, little is known about how this information is stored in the primary gustatory cortex. Is it similar to the olfactory cortex, where studies have shown a lack of ordering of odorant-responsive neurons? Or is it similar to the primary visual/somatosensory/auditory cortices, with very specific topographic arrangement? To determine this, the authors used two-photon calcium imaging, a way of visualizing the activity of large groups of cortical neurons in vivo by peering through a cranial window. This allowed for the administration of specific tastants and subsequent visualization of the cortical neurons that were activated. Interestingly, they found that the different taste modalities (sweet, sour, umami, etc.)
displayed fixed topography within the primary gustatory cortex, similar to other sensory modalities such as the somatosensory and visual cortices. The key difference, however, is that in the periphery, the taste receptors are not spatially organized the way that these other sensory organs are. Perhaps most interesting is that the authors showed the primary gustatory cortex spans a very small portion of the insula. So, what is going on in the rest of the insula? Could it be an area where multiple sensory modalities integrate? Future studies aimed at tracing the targets of sensory neurons may tell us.

GETTING DOWN TO THE MOLECULAR 
BASIS OF OLIGODENDROGLIOMAS[2]

It has been known for quite some time that more than half of all oligodendrogliomas exhibit losses of chromosomes 1p and 19q. Because this chromosomal abnormality impacts the behavior of the tumors with regards to their response to therapy, it is routinely tested for at many institutions. While reigning opinion has been that this chromosomal loss disrupts a tumor suppressor gene, the putative genetic changes have yet to be identified. In this paper by Bettegowda et al., human anaplastic oligodendrogliomas were sequenced, and two main candidate genes were identified: FUBP1 (chromosome 1p) and CIC (chromosome 19q). CIC is thought to act on a very well-studied pathway that controls cell survival, differentiation, and mitosis [the mitogen-activated protein kinase (MAPK) pathway], while FUBP1 is thought to negatively regulate a well-studied proto-oncogene (that is, a gene that increases cell growth and cell division), Myc. The next step is to understand how changes in these genes impact prognosis and treatment response. I would not be surprised when pathologists start testing directly for these two genes in resected oligodendrogliomas, as Johns Hopkins has already filed a patent “relating to the application of the mutations described in this work to the diagnosis and treatment of cancer.”

CHRONIC BACK PAIN AND THE BRAIN[1]

Chronic pain is a complicated problem, spanning multiple brain regions and affecting the connectivity between these regions. In this study by Baliki, blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI); a type of functional MRI that looks as signals representing blood oxygenation, with areas of high BOLD signal thought to correlate with higher neuronal activity) was used to investigate brain function in subjects with chronic low back pain. Specifically, they analyzed the “rhythms” of the brain at resting state – that is, the characteristics of rhythmic activity of large groups of neurons thought to represent activity across functional neuronal networks. In patients with chronic low back pain, they found some changes in the power and spatial representation of cortical rhythms in the anterior cingulate cortex, insula, and medial prefrontal cortex (mPFC). When they looked further at high-frequency activity, they found that the mPFC, parietal cortex, and posterior cingulate cortex all displayed higher power in chronic low back pain. Interestingly, these anatomical areas correspond to a physiological concept known as the default mode network, brain regions that are active at rest and allow the brain to monitor and orient the body (a form of consciousness). The question then becomes, what do these changes mean in terms of function? As is turns out, the abnormal rhythms in the mPFC also correlate with abnormal connectivity in regions of the brain known to modulate pain, such as the anterior cingulate, secondary somatosensory, and insular cortices. The relationship between the mPFC and pain was further strengthened by a high correlation between mPFC activity and subjective ratings of pain intensity made by the patients. In all, this is another interesting study that reinforces the notion that chronic low back pain involves pathology beyond the back itself and underscores the need to understand how surgery for chronic low back pain changes brain dynamics. I look forward to future work looking at whether these altered rhythms and connectivity reverse (or not) following surgical intervention.

INFLAMMATION AND RECOVERY FOLLOWING SPINAL CORD INJURY[7]

Inflammation following spinal cord injury (SCI), characterized by a conglomerate response of astrocytes, neurons, and microglia, results in the production of cytotoxic inflammatory cytokines and can have detrimental effects on recovery. In this paper by Rathore et al., lipocalin 2 (Lcn2), an immune-associated protein that binds iron and triggers apoptosis, was studied in reference to its role in CNS inflammation and injury. Using a spinal cord contusion model of SCI, the authors first showed significant increases in Lcn2 expression as quickly as 1 day following SCI and lasting as long as 21 days. This expression was found in neutrophils, neurons, and endothelial cells. To see whether Lcn2 expression resulted in a detrimental effect on recovery following SCI, the authors generated mice whose Lcn2 genes were congenitally deleted and subjected them to the SCI paradigm. Interestingly, mice that lacked Lcn2 expression had significantly better recovery of locomotor skills starting at 5 days after SCI. Sure enough, this survival benefit also corresponded to greater tissue sparing and ventral horn neuron density following SCI as well. To get at a mechanism, the authors assessed levels of pro-inflammatory cytokines following SCI in the genetically engineered mice. As one would expect, there was both a
reduction of inflammatory cytokine release as well as less neutrophil infiltration into the injured spinal cord in the Lcn2-deficient mice. Neuroinflammation has become an exploding field within neuroscience, with large potential translational benefits in the neurosurgical management of disease. While steroids have fallen out of favor as treatment for SCI, science is showing us that we had the correct general idea.

MICROGLIA ESSENTIAL FOR BRAIN DEVELOPMENT[6]

When microglia come to mind, the immediate associated is with the immune response under pathological conditions. Recent work, however, has shown that microglia also play integral roles in normal brain development. In this work by Paolicelli et al., the authors expanded upon previous observations that microglia are highly active in normal brain, with neurons expressing a chemokine (Cx3cl1) whose receptor is solely expressed by microglia. Using fluorescent proteins expressed in microglia, they found that microglial processes engulf both pre- and postsynaptic proteins in the developing mouse hippocampus. Interestingly, when they disrupted this process by generating mice that lacked Cx3cl1, they found that within the developing hippocampus there was an excess of synaptic proteins, higher spine densities (suggesting a deficit in pruning of the synapses), and neurons with a more immature physiological phenotype, when compared to normal controls. The hippocampi of Cx3cl1-deficient mice also displayed alterations in synaptic plasticity and a reduction in seizure susceptibility. So, what is it that Cx3cl1 does to allow for appropriate synaptic pruning and maturation? It appears that this chemokine is necessary to ensure adequate numbers of microglia are available for surveillance of developing synapses. This line of work is particularly fascinating, since it sheds unique light on another potential mechanism of developmental anomalies and dysmaturation of the brain.

AGE-RELATED COGNITIVE DECLINE: IS IMPAIRED DNA REPAIR TO BLAME?[5]

Prior work has shown that aging, both in animal models and in humans, results in accumulated neuronal DNA damage likely due to high oxidative stress within the neurons’ environs. While some indirect evidence exists that such DNA damage could result in neurological impairment (spanning from mild cognitive impairment to late-Alzheimer’s disease), little direct work has been done to verify causality. In this paper by Borgesius et al., mice having a mutation in a DNA repair gene, ERCC1, were studied. This mutation is hypomorphic, meaning that one allele of the gene is completely deleted and the other allele’s ERCC1 protein product displays reduced activity. Because of this mutation, these animals are at much greater risk for accumulated DNA damage. The authors found that by 4 months of age, the brains of these mice displayed markers of increased reactive gliosis as well as increased neuronal and glial cell death. There were lower densities of neurons within the hippocampus (particularly CA1 and the dentate gyrus) as well as increased axon degeneration in several areas of white matter. Even though there were increases noted, overall neuronal loss in these regions was only modest. As expected, neuronal loss appeared to be secondary to accumulated DNA damage. After describing the histological changes in these mice, the authors turned their attention to physiology. They showed that synaptic plasticity was altered in ERCCI-deficient mice. Because this model had ERCCI loss in many cells throughout the body, the authors wanted to be sure that the changes they were noting were not confounded by other organ abnormalities secondary to ERCCI loss. To accomplish this, they then generated a second group of animals that had reduced ERCCI in excitatory forebrain neurons (i.e., cortex and hippocampus). Sure enough, similar histological changes were noted in the brains of these mice as before, except that they occurred at a slightly slower pace (an approximately 2-month lag). And again, these animals displayed reduced synaptic plasticity. To relate these observations to behavior, the authors subjected the animals to a hippocampal learning test. Congruent to the cellular observations, animals with ERCCI deleted from the forebrain neurons displayed reduced hippocampal learning as they aged compared to normal animals. In a second paradigm that tests amygdala function, ERCCI-deficient mice displayed reduced contextual fear conditioning (a task requiring hippocampus and amygdala) as well. The take-home message: I’m stocking up on anti-oxidants now!

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