New models for Zika pathology

The Brazilian Zika virus (ZIKV), known to be transmitted by certain strains of mosquito, is a worrisome and growing threat to humans. When infected with the virus, pregnant women are more likely to give birth to children with developmental disorders, such as microcephaly, a condition that is characterized by a smaller-than-average head circumference and, often, neurological complications. A fear that mosquito bites might lead to severe brain defects in newborn children has launched a renewed interest in research on ZIKV.

Until recently, scientists had not explored the effects of the virus on neural development in an animal model, leaving a significant gap in understanding the causal link between ZIKV and microcephaly. In a series of recent reports, multiple labs have now published findings demonstrating a link between ZIKV infection and adverse brain development. In one study, researchers used both *in vivo* mouse models and *in vitro* human pluripotent stem cells to examine how ZIKV infection affects neural development (*Nature* doi:10.1038/nature18296; published online 11 May 2016).

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The researchers obtained ZIKV from a clinical case in Brazil, and then infected pregnant mice of SJL and C57BL/6 strains. Interestingly, newborn C57BL/6 mice were not infected by their mothers. However, SJL mice born to infected mothers exhibited whole-body growth delay compared to sham control mice. The brains of SJL pups also contained ZIKV viral RNA, confirming that ZIKV can be transmitted from mothers to unborn babies. After inspecting the ZIKV-infected newborn mice, the researchers confirmed that the brains of these mice showed reduced cortical thickness and reduced cell numbers, features that mimic microcephaly cases in human newborns. Additionally, cells in multiple brain areas exhibited an 'empty' appearance, which suggests that the cells were not surviving through this developmental period. The newborn mice also displayed ocular complications, another clinical feature found in some human newborns of ZIKV infected mothers.

The researchers further examined the effects of ZIKV *in vitro* on human neural cells derived from stem cells, human neurospheres and cerebral organoids, and found that infection with ZIKV caused significant cell death.

Although significantly more research is needed to confirm a cause-and-effect relationship between ZIKV and human microcephaly, the development of mouse models to study ZIKV infection and transmission to offspring provides an important tool for pinning down mechanisms and generating effective treatments.

James E. Niemeyer

REEXAMINING THE LOGIC OF OLFACTORY TRANSDUCTION

Animals are constantly bombarded by a wide-range of environmental stimuli that they must rapidly and accurately process in their central nervous systems. Regardless of a stimulus' modality, be it light, sound, chemical or mechanical, sensory processing in the mammalian brain begins with signal transduction in the periphery of the nervous system. Primary sensory neurons, such as photoreceptors in the eye, express specialized receptor proteins that undergo conformational changes in the presence of an appropriate stimulus, generating electrical signals that propagate into the brain. The receptor's mechanism of signal transduction in primary sensory neurons helps determine the organization and functional logic of sensory processing.

Mammalian olfaction provides a great system for neuroscientists seeking to understand peripheral transduction and sensory processing in the brain. Despite the large array of unique chemical receptors involved in the olfactory system (approximately 1,400 in mice and 1,000 in humans), individual olfactory receptor neurons (OSNs) express only a single type of chemical receptor. Additionally, OSNs that express the same receptor type extend and gather their axons into distinct and separated zones (glomeruli) in the first olfactory relay station in the brain. This 'one neuron–one receptor' expression pattern, combined with the anatomical segregation of axons that transfer sensory signals, has defined the functional logic of olfactory processing for over two decades.

In a recent study by a group at Harvard, a new twist on this logic has been discovered in certain primary olfactory sensory neurons (*Cell* doi: 10.1016/j.cell.2016.05.001; published online 26 May 2016). Using a combination of genetics and functional imaging in mice, Greer *et al.* identified that a specific set of OSNs transduce olfactory signals using various receptor proteins in the MS4A protein family. These OSNs make up the 'necklace' subsystem, which is named for the necklace-like shape that these neurons form in the deep recesses of the olfactory nasal epithelium. MS4A receptors are structurally different from the typical G-protein-coupled receptors that are present in most OSNs, and various types of MS4A receptors are expressed promiscuously across necklace OSNs, violating the 'one neuron–one receptor' rule. Each OSN in the necklace subsystem therefore responds to signals transduced by multiple types of MS4A receptors, pooling odor information together rather than segregating it into unique channels. This discovery uncovers a novel logical operating principle for the olfactory system and suggests that multiple unique streams of information are processed in parallel, potentially allowing for enhanced odor perception and behavioral decision-making.

Dustin M. Graham