Size-Based Sorting Enhances Antigen Presentation by Microglia

(see pages 2674–2688)

Most cells continuously take up extracellular solutes via pinocytosis, a form of endocytosis in which the plasma membrane nonselectively engulfs extracellular fluid and encapsulates it in small endocytic vesicles called pinosomes. Antigen-presenting immune cells—including microglia that have been activated by CNS injury or disease—use pinocytosis to ingest soluble proteins, which they degrade to peptide fragments. The fragments are then bound to major histocompatibility complex II (MHCII) molecules and returned to the plasma membrane, where they can be recognized by T cells to trigger an immune response. In multiple sclerosis (MS), a T-cell-mediated demyelinating disease, activated microglia present myelin-derived antigens, thus stimulating the activity of myelin-targeting T cells and exacerbating the disease. Understanding the steps that occur between pinocytosis and antigen presentation in microglia might therefore yield insights into potential treatments for MS.

To better understand these steps, Chen et al. studied the movement of fluorescently labeled proteins and polysaccharides in cultured rat microglia. Pinocytosed molecules were initially colocalized in single pinosomes. Newly formed pinosomes quickly acidified and were surrounded by MHCII-containing lysosomes. Within 15 min, pinocytosed proteins were broken down by proteinases in the acidified compartments, and the peptide fragments moved from the pinosome to lysosomes, leaving larger polysaccharides behind. When small polysaccharides were pinocytosed with proteins, the protein fragments and polysaccharides were both transferred to the same lysosomal compartments, suggesting that the transfer depended on the size of molecules, rather than recognition of a specific sorting signal.

Size-based sorting of pinocytosed molecules required ATP, GTP, proteins involved in fusion between late endosomes and lysosomes, and dynamin (a protein involved in membrane fission). Inhibiting dynamin disrupted size-based sorting by preventing the transfer of some small molecules to lysosomes and permitting the transfer of some large molecules. At the same time, inhibiting dynamin reduced both secretion of interferon-γ and proliferation of T cells cocultured with microglia, indicating that it reduced the efficiency of antigen presentation by microglia. Treatments that similarly interfere with the size-based movement of molecules from pinosomes to MHCII-containing lysosomes in microglia might therefore slow the progression of MS.

Microglia Contribute to Rett Syndrome by Secreting Glutamate

(see pages 2516–2529)

Rett syndrome (RTT) is an X-linked neurodevelopmental disorder characterized by normal development in infancy followed by slowed growth; deterioration of motor, mental, and language skills; and the appearance of autistic features. RTT is caused by mutations in methyl-CpG-binding protein 2 (MeCP2), a protein that regulates transcription by binding to methylated CpG dinucleotides in DNA. The most obvious neurological feature of RTT is reduced brain size: neurons are smaller, with less complex dendritic arbor and fewer dendritic spines. Despite the role of MeCP2 in transcriptional regulation, however, brain-wide gene expression is relatively normal in MeCP2-deficient mice, suggesting that gene expression changes are subtle or restricted to a small subset of cells.

MeCP2 is highly expressed in neurons, and neuron-specific expression of MeCP2 can rescue RTT-like symptoms in otherwise MeCP2-deficient mice. Expression of MeCP2 in glia is much lower than in neurons, but recent evidence suggests that glia also contribute to RTT neuropathology. For example, incubating cultured wild-type mouse neurons with medium conditioned by MeCP2-null microglia damaged dendrites. The neurotoxicity stemmed from increased production and release of glutamate by MeCP2-null microglia (Maezawa and Jin 2010, J Neurosci 30:5346). This increase was attributed to increased expression of glutaminase, which synthesizes glutamate from glutamine, and connexin hemichannels, through which microglia release glutamate.

New evidence suggests that glutamate production in MeCP2-deficient microglia is further enhanced by increased uptake of glutamine. Having previously identified the glutamine transporter SNAT1 as a target of MeCP2-mediated transcriptional repression, Jin et al. now report that SNAT1 levels were elevated approximately threefold in MeCP2-deficient microglia compared to wild-type. Interestingly, however, SNAT1 was not upregulated in MeCP2-deficient neurons or astrocytes, suggesting cell-type specific regulation by MeCP2. Inhibiting SNAT1 returned glutamate production by MeCP2-deficient microglia to control levels. Furthermore, conditioned medium from a microglial cell line overexpressing SNAT1 caused dendritic damage in wild-type neurons, and the damage was prevented by blocking NMDA receptors, suggesting it was mediated by glutamate toxicity.

Together with previous studies, these results suggest that MeCP2 represses several genes involved in glutamate production and release from glia. Inhibiting the proteins encoded by these genes may therefore reduce glutamate-induced excitotoxicity, thus reducing dendritic loss in RTT.