Planting and pruning in the brain: MHC antigens involved in synaptic plasticity?

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MHC antigens count among the classical "immune" molecules. They act as platforms presenting antigenic peptides to the specific receptors on T cells. MHC class I molecules interact with the $CD8^+$ "killer" T cell lineage, whereas class II molecules present antigen to CD4 "helper" T cells. In addition, some MHC proteins can be recognized by natural killer (NK) cells, where, depending on the nature and context of a particular receptor, they trigger either activating or suppressive signals. Additional roles such as in embryonic development or tissue organization have been postulated, but so far these hypotheses have not stood the test of molecular immunology (1). Now, this trend seems to be changing. In a recent issue of PNAS, Oliveira *et al.* (2) reported that MHC class I or Ib antigens are required to regulate synaptic pruning on neuronal bodies that undergo retrograde degeneration after axonal transection.

A role of MHC determinants in neural tissue response is surprising because, according to an imperial dogma, MHC determinants are missing in the CNS. The lack of MHC is one major factor interfering with immune reactivity in the healthy CNS, securing the brain's "immune privilege." However, this is not the entire story, because MHC products, along with many other "immune" genes, are readily inducible in the CNS tissues under various pathological conditions, including autoimmune inflammation, microbial infection, and neuronal degeneration. The surprising relationship between brain degeneration and immune reactivity has been strikingly demonstrated in rodent models of motor nerve axotomy (3).

MHC expression in the nervous system is actively regulated by neurons. Intact, electrically active neurons vigorously suppress induction of MHC genes both in the perineuronal glial microenvironment and on the neuron's own membrane, but loss of electric neuronal activity allows MHC induction by proinflammatory signals. Secretion of neurotrophic factors may have a role in this down-regulation (4). Thus, neuronal activity dictates the immune status of CNS milieus. Whenever neurons cease to function properly, the generally immune-hostile CNS mutates into an immune-friendly milieu, favoring immune protection by surveillance as well as autoimmune attacks.

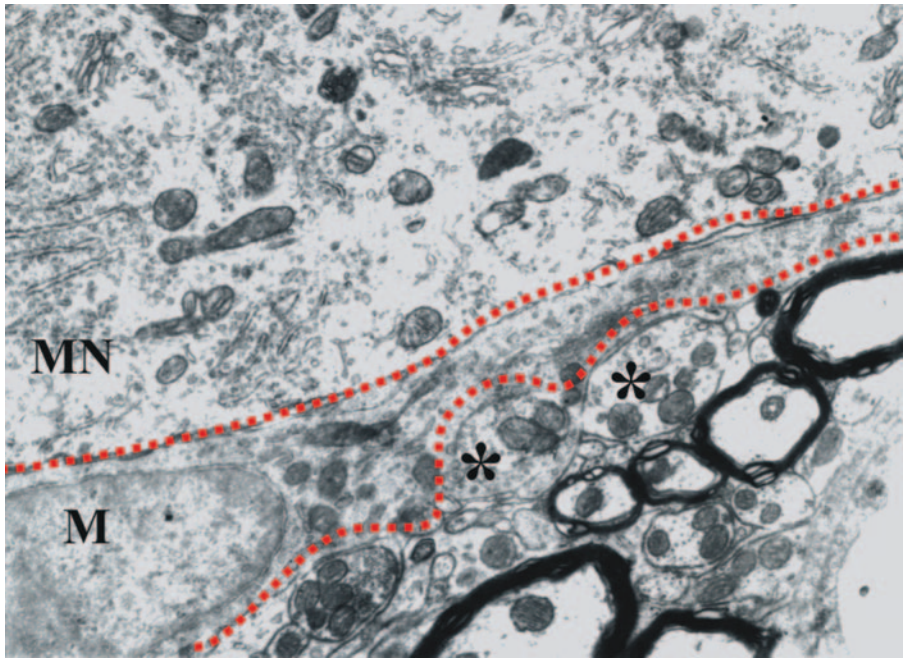

Fig. 1. Microglia and synaptic pruning around axotomized motor neuron. Microglia cell (M) detaches boutons (*) from neuronal body (MN). (Scale bar, 2 μm.) (Image courtesy of Georg W. Kreutzberg, Max Planck Institute for Neurobiology.)

What are the consequences of immune molecules appearing in the wake of neuronal dysfunction? Some investigators consider postdegenerative inflammation as a complication of neuronal degeneration, which adds further damage to the ongoing pathogenic process.

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In striking contrast, others argue that inflammation is a favorable process: it represents the body's attempt to favor tissue regeneration, like in peripheral wounds, where sterile inflammation promotes healing. Indeed, "beneficial" autoimmune responses have been proposed as a treatment to support axonal regeneration (5).

Recently, there is emerging evidence that MHC molecules may have functions beyond immune reactivity. Dulac and colleagues (6) and Mombaerts and colleagues (7) described transcription of class I-like (class Ib) molecules in the vomeronasal organ of mice, a sensory organ involved in mammalian pheromone perception. These class Ib proteins of the H-2M type were identified on sensory neurons, apparently associated with pheromone receptors (6, 7). Possibly, but not necessarily, related to these findings, a recent report showed that peptide eluted from MHC class Ib complexes activated vomeronasal receptors *in vitro* and affected the behavior of mice *in vivo* (8).

Boulanger and Shatz (9) propose another role of neural MHC, namely,

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one in the development and organization of neuronal networks. They first noted MHC class I expression in some CNS neurons, an expression that was enhanced after epileptic seizures and lowered after neuronal paralysis (10). Later work demonstrated different class I/Ib types distributed through the CNS in different patterns. Interestingly, synaptic connections were stabilized (measured as increased long-term potentiation and the lack of long-term depression) in class I-deficient mutant mice (11).

Now, Oliveira *et al.* (2) describe a phenomenon that also links MHC expression and synaptic communication but relates to the disruption of synapses. The work rests on a classic finding by Blinzinger and Kreutzberg (12), who first described "synaptic stripping." Thirty-five years ago, they observed that retrograde degeneration and regeneration of facial neurons caused by peripheral nerve transection involved pruning of synapses from the affected neuronal bodies, presumably by the action of activated microglia cells (Fig. 1). Oliveira *et al.* have found that transection of (spinal) motor nerves led to the reduction of synapses (measured by staining the synapse marker protein synaptophysin) in the relevant spinal cord areas, and that this reduction was greater in class I-deficient spinal cords than in mice with regular MHC expression. A closer look (by electron microscopy) revealed that inhibitory synapses were more profoundly affected by MHC expression than their activating counterparts.

Clearly, Oliveira *et al.* (2) make an important contribution, describing an unexpected, provocative finding. However, as is quite typical for pioneering studies, the work raises substantial additional questions. Thus, the authors relate the stripping response to MHC expression in the neurons. This is definitely possible, but an alternative possibility has not been ruled out: as the authors are aware, neuronal somata are enshrouded by a tight layer of activated microglia cells (Fig. 1), which definitely express higher levels of MHC class I than the adjacent cells. In fact, is this microglia response altered in class I-deficient mice?

Then, is it really the deficits of classical MHC class I that are causative? Most experiments compared wild-type mice with β2-microglobulin mutants, animals that, in addition to MHC deficiency, have a profoundly disturbed iron metabolism, a defect that may well account for at least some neuronal dysfunction. The peptide transporter (TAP) mutants used in one experiment may provide only limited support. In these mice, MHC class I expression is partially reduced but by no means absent (13). Also, non-peptide-binding class Ib molecules are unaffected in TAP mutants. Incidentally, most of the previous studies of neuronal MHC expression focused heavily on gene transcription. However, it should be noted that expression of MHC class I protein requires the coordinated expression of several component proteins, including the class I heavy chain and the β2-microglobulin light chain, along with the TAP transporters. In many neurons, the H chain may be transcribed, but, in the absence of β2-microglobulin, there is no class I protein assembly on the cell surface (14).

Are the neuronal MHC proteins acting as signal structures or do they "just" contribute to stabilization of synaptic contacts? In either case, a complementary binding structure would be required. Shatz and colleagues (11) have proposed elements of the T cell receptor (TCR) complex. Indeed, they and others found the CD3 *z* chain in some neurons, but, so far, additional members of the T cell signaling cascade have not been discovered. Furthermore, mRNA for a nonrearranged TCR β chain was amplified from neuronal cells (15, 16), but protein expression was not reported.

The role of MHC antigens on neurons is fascinating, but it is less than understood at this time. Future, more detailed investigations will yield surprises.

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