NERVE REPAIR

Ins and outs of Nogo

Victims of traumatic spinal cord injury often learn that it's not possible to repair their 'broken backs' and are faced with the prospect of paralysis; the injured axons of central neurons are disconnected from their targets in the spinal cord. But these axons do try to repair themselves: their tips actually reseal, re-form a growth cone and attempt to regenerate a new axon segment. In fact, lesions of peripheral axons can actually be repaired. However, the problem in the central nervous system is that there are molecules that suppress this regenerating capacity.

A protein called Nogo, whose gene was first cloned at the beginning of last year, seems to be one such inhibitory molecule. Nogo-A — the full-length version — is highly abundant in myelin produced by oligodendrocytes in the central nervous system, but not in peripheral myelin produced by Schwann cells. Nogo-A has two transmembrane domains, and the only part of the protein that is exposed to the extracellular surface is a 66-amino-acid linker termed Nogo-66. It has been argued that the cytoplasmic region of Nogo-A is the part of the molecule that inhibits axon regeneration at sites of oligodendrocyte injury. However, a role for Nogo-66 has not been ruled out. Does the extracellular domain of Nogo also have inhibitory activity?

In a recent report in *Nature*, Fournier *et al.* reveal important information that might help to answer this and other questions on the role of Nogo in the regeneration puzzle. The authors explored what functional domains of the protein are responsible for the inhibitory activity. They showed that Nogo-66 inhibits axon growth but does not alter cell morphology. By contrast, the cytoplasmic domain of Nogo does affect the morphology of neurons and other cell types. The authors come down in favour of Nogo-66 as the axonal-regeneration-inhibiting activity and argue that the cytosolic domain of Nogo does not act directly on the neurons but, instead, modifies their substrate. Furthermore, Fournier *et al.* cloned a receptor for Nogo-66 and showed that it is a glycosylphosphatidylinositol-anchored protein capable of mediating inhibition of axon regeneration. The receptor is expressed in the central grey matter; more specifically, in neurons known to regenerate in the presence of antibodies against Nogo.

The identification of the Nogo-66 receptor has implications for our understanding of the basic mechanisms of neural regeneration and plasticity, and will no doubt raise the possibility of therapeutic applications. Perhaps disrupting the interaction of Nogo-66 with its receptor might help to promote axonal regeneration after spinal cord damage or other forms of traumatic injury. Clearly, this possibility will depend on formal evidence that Nogo can actually inhibit axonal regeneration in vivo, a piece of the puzzle so far unsolved.

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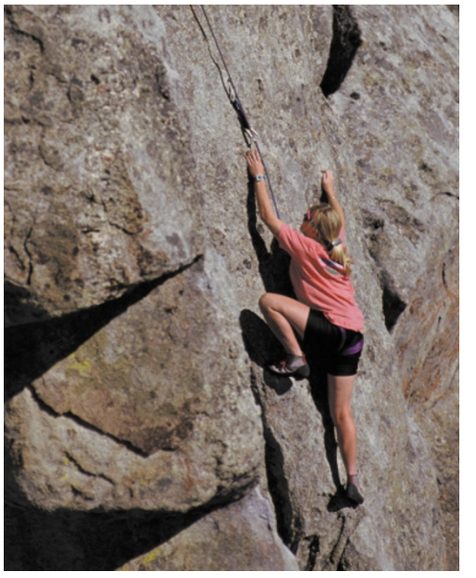
ENCYCLOPEDIA OF LIFE SCIENCES Nerve regeneration: mammalian

NEURONAL MIGRATION

Do the locomotion?



The neurons of the mammalian cerebral cortex are arranged in six layers, which are laid down in an inside-out sequence during development. The majority of neurons that make up these layers migrate radially from the ventricular zone, travelling over increasing distances as the cortex expands. It is generally accepted that most are guided to their destination by an extensive network of radial glial fibres. However, as Nadarajah *et al.* emphasize in the February issue of *Nature Neuroscience*, this type of glial-assisted migration, termed locomotion, is not the only mechanism that cortical neurons have at their disposal. They suggest that somal translocation — that is, displacement of the cell body rather than migration of the whole cell — might be more prevalent during early cortical development than was previously recognized.

In a series of elegant time-lapse microscopy experiments on slices of embryonic mouse cortex, the authors defined the morphological features that distinguish these two modes of radial migration. In locomotion, the entire cell remains closely apposed to a glial fibre and the length of the leading process remains more or less constant as the cell migrates. In somal translocation, the leading process, which is often branched, is anchored to the pial surface of the cortex and the cell body seems to be pulled towards it. The leading process shortens, which could reflect contraction of the process or displacement of the nucleus within the cytoplasm.

The mode of migration does not seem to be cell-type-specific, but somal translocation is observed more frequently during the early stages of cortical development, when the distances travelled by the cells are relatively small. Also, many cells that initially locomote seem to use somal translocation to make final adjustments to their position. Why do these two modes of radial migration exist? The authors propose that somal translocation is a relatively primitive mechanism, which was adequate for cells moving over relatively short distances. This is supported by the observation that neurons in the earliest cortical layers are the oldest cells phylogenetically as well as developmentally. Glial-guided locomotion could have evolved in higher vertebrates to overcome the difficulty of navigation over larger distances and through an increasingly complex cortical environment.

A considerable amount of recent research has focused on the molecular basis of cortical development. Mutations in genes encoding proteins such as reelin and Cdk5 are known to severely disrupt cortical organization, but there are significant differences in their phenotypes that have proved difficult to explain. The finding that somal translocation might be essential for certain stages of cortical development raises the possibility that these factors are required for different modes of neuronal migration.

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