Turn-ons for axons

When adult neurons are injured, myelin-associated glycoprotein (MAG) triggers signals to block the regrowth of axons, a process that is intensely frustrating to patients and researchers hoping to treat such injuries. On page 565, Yamashita et al. identify a receptor complex responsible for transducing this signal, elucidate part of the associated intracellular signaling pathway, and uncover a novel molecular interaction that may help explain the diverse activities of a neurotrophin receptor.

MAG signaling is known to inhibit axonal regrowth after injury, but the MAG receptor on neurons remained unknown. By analyzing neurons from wild-type and mutant mice, the authors discovered that p75NTR, a glycoprotein on the surface of many types of neurons, transduces the MAG signal. Since p75NTR also binds to neurotrophins, which promote axonal outgrowth, the same receptor seems to be capable of transducing both growth and inhibitory signals.

Rather than binding directly to p75NTR, MAG interacts with a complex of p75NTR and the ganglioside GT1b. This is the first time a ganglioside has been shown to act as a coreceptor, a finding that may set a precedent for future analysis of these molecules. MAG binding to the complex activates RhoA, which has previously been shown to inhibit neurite extension. The results suggest that GT1b acts primarily as a binding partner, whereas p75NTR is a signal transducing element for MAG.

Since gangliosides are found in lipid rafts, an intriguing possibility is that p75NTR interacts with different factors in a raft to transduce opposite types of signals, depending on its interaction with MAG or neurotrophins. Molecules that target specific components of these pathways might be able to induce desired growth patterns in injured neurons.

Nuclear proteins get around

Protein trafficking between the cytoplasm and the nucleus has been studied extensively; but how do proteins move from one site to another within the nucleus? On page 615, Leung and Lamond focus on the intranuclear trafficking of the RNA-binding protein NHPX, and describe an elegant series of experiments that demonstrates the existence of multiple intranuclear accumulation pathways. The study provides definitive evidence of protein sorting within the nucleus.

Although previous studies have suggested that proteins might follow directed paths between intranuclear bodies, the new work provides a detailed analysis of this phenomenon. NHPX localizes primarily to nucleoli, but is capable of binding to both small nucleolar RNAs (snoRNAs) and the spliceosomal U4 small nuclear RNA (snRNA). The authors followed fluorescent fusion proteins to determine that newly expressed NHPX transiently visits splicing speckles in the nucleus before accumulating stably in the nucleolus, a pattern confirmed in multiple cell lines. The move from speckles to nucleolus is apparently unidirectional, and requires new mRNA transcription, suggesting that other factors must be expressed to allow NHPX to leave the speckles.

Leung and Lamond also compare the trafficking of NHPX to that of the SmB protein. In contrast to NHPX, SmB accumulates first in Cajal bodies and in the nucleolus, before finally accumulating in speckles, indicating that the two proteins move through distinct sorting pathways with in the nucleus.

The unidirectional movement of NHPX, combined with its previously observed binding properties, suggests that NHPX might interact with U4 snRNA in speckles, possibly facilitating the maturation of nuclear proteins or RNP complexes before moving to the nucleolus. The authors are now trying to determine whether other nuclear proteins share the separate trafficking routes used by NHPX and SmB, and they hope to identify the molecular mechanisms responsible for these pathways.