dSarm-ing Axon Degeneration

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An assembly map. Damasceno *et al.* have charted the types of superstructures into which polyhedral particles can assemble using only two readily determined parameters, a shape factor and a coordination number. For any given polyhedron, the map predicts its assembly category (one of the shaded areas in the map). In a Bravais lattice, all lattice points are equivalent, which is not the case for a non-Bravais lattice. Abbreviations: fcc, face-centered cubic; bcc, body-centered cubic; tcp, topologically close-packed.

archical assembly. However, a unified view is found when results are mapped in terms of two parameters: the "coordination number" in the fluid phase (that is, the number of nearest neighbors surrounding each polyhedron in the fluid) and the isoperimetric quotient, which depends on the particle shape and measures the deviation of the shape from the sphere. Damasceno *et al.* determined that highly faceted polyhedra, which are almost spherical and also have a high coordination number, will assemble into plastic crystals. Polyhedra that are highly nonspherical, with a smaller number of facets and a low coordination number, tend to form liquid crystals. Nonspherical polyhedra that have an intermediate coordination number will assemble into crystals. Almost the entire set of polyhedra that crystallized, according to simulations, fell into one of these three major regions (see the figure).

The coordination number in the fluid phase and the coordination number in the ordered phase were nearly identical in almost all cases. Thus, the packing category for a new type of nanoparticle (whether synthesized in the laboratory or computer-generated) can be determined using the map drawn by Damasceno *et al.*, given its coordination number in the fluid and its shape parameter (both easily determined).

A conspicuous number of polyhedra formed glassy states, and there are overlapping regions where two or even more types of structures could arise from the same polyhedra. The frequent formation of glassy states, possible improvements in mapping, and the investigation of other cases not yet probed by systematic calculations all require further research. In addition, particles with more complex shapes—for example, with concave surfaces or branches—are more likely to become trapped into locally "jammed" configurations and to form disordered assemblies when the volume fraction is increased. These types of particles can, however, still spontaneously assemble into ordered superstructures if they follow hierarchical assembly schemes like those adopted by biomolecules, in which complicated building blocks sequentially organize into assemblies of growing complexity.

An example is the organization of DNA into symmetric supramolecular structures, which do not require high volume fractions of units to form (*15*), but where favorable kinetic and thermodynamic paths drive organization even at very low volume fractions of the units. A nanoparticle analog of hierarchical self-assembly was recently reported for colloidal branched nanocrystals (*16*), which did not form close-packed structures but nonetheless self-organized in a hierarchical way. Many more examples can be expected as the synthesis of monodisperse colloidal nanoparticles with unconventional shapes progresses. For now, a comprehensive framework for predicting the assembly of any particle based only on the shape and interparticle forces is still out of reach (*17*).

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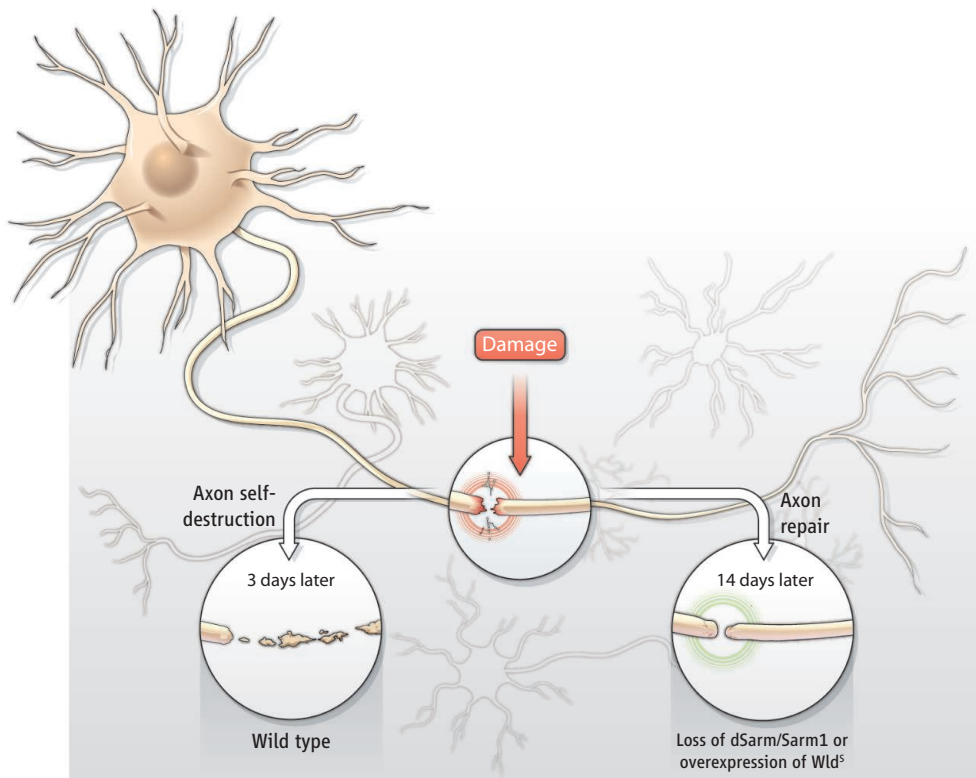
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An axon self-destruction program may underlie neurodegeneration in injury and diseased states.

Plucked from the tree, a leaf withers. Such a loss of vitality upon removal from the whole appears so natural that one may take it for granted as a passive and unstoppable process. But is it? Although cell death was long thought to be a passive process, we now know that at least one form of cell death, apoptosis (from Greek "falling away"), is an active process that can be blocked by inhibiting a specific signaling pathway (*1*). On page 481 of this issue, Osterloh *et al.* (*2*) find that the death of a portion of a nerve cell, the axon, after it is sev-

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ered from the cell body, can be dramatically slowed by the inactivation of just one gene. The discovery has important implications for understanding the molecular mechanisms of axon degeneration, as well as for developing drugs against neurodegenerative diseases.

An axon is a long, polarized extension from the neuronal cell body that transmits a neuron's output signals to downstream cells. When an axon is acutely injured, the segment distal to the lesion site undergoes morphological changes that lead to its fragmentation and clearance within a few days (see the figure). This process of "Wallerian degeneration," named after Augustus Waller who described it in 1850 (*3*), was traditionally viewed as passive deterioration due to the lack of cell

Degeneration delayed. After an axon is severed from the neuronal cell body, the segment distal to the lesion normally undergoes a series of morphological changes that include granulation and fragmentation before it completely disintegrates within 3 days. If the neuron expresses the Wld^S fusion protein, or lacks dSarm (in fly) or Sarm1 (in mice), the distal axon segment remains intact for 2 to 4 weeks after the lesion.

body–derived nutrients. However, in 1989, a mutant mouse strain, *Wallerian degeneration slow* (*Wld^S*), showed that severed axons remain intact for weeks, as opposed to 3 days in wild-type mice (*4*). This suggested that Wallerian degeneration is normally mediated by an active process, as with apoptosis. However, unlike apoptosis (*5*), little is known about the constituents of this putative axon self-destruction pathway. The axon protection seen in *Wld^S* mice is caused by a chromosomal rearrangement that results in the overexpression of Wld^S, a chimeric protein consisting of the amino-terminal part of an enzyme for polyubiquitination and NMNAT, a biosynthetic enzyme for nicotinamide adenine dinucleotide (*6*). Wld^S is not made in normal mice and thus does not inform on the endogenous mechanisms that mediate axon degeneration. Candidate gene studies have yielded only two in vivo examples of axon degeneration inhibition: a mutation in DLK/Wnd delays Wallerian axon degeneration in both fly and mouse (*7*); and suppression of ubiquitin proteasome activity, which slows injury-induced axon degeneration in flies (*8*). In both cases, the inhibition of axon degeneration is considerably weaker than that caused by Wld^S overexpression. Therefore, major players in Wallerian degeneration, if they exist, remain to be identified.

Enter *dsarm/Sarm1* (*Drosophila* sterile alpha and Armadillo motif and its mouse ortholog *Sarm1*), the first mutant whose inhibition of axon degeneration rivals that of Wld^S protection. Osterloh *et al.* discovered *dsarm/Sarm1* using a forward genetic screen, wherein animals with randomly generated mutations are screened for a desired phenotype and relevant genes are identified only after such mutants are isolated. In contrast to a candidate gene approach, forward genetic screens do not rely on any hypotheses regarding which genes may control axon degeneration. Osterloh *et al.* carried out their screen with an established Wallerian degeneration model in the fruit fly *Drosophila melanogaster* (*9*). Using *Drosophila* enabled them to base the screen on genetic mosaic analyses, a unique advantage that allows the isolation of mutant genes that could otherwise be lethal. Both the unbiased nature and mosaic design of the screen were crucial for their discovery. *dsarm* encodes a highly conserved Toll-like receptor signaling adaptor (*10*) with no previous link to axon degeneration. Although the fly *dsarm* mutation is lethal, the authors created mosaic animals in which only olfactory receptor neurons lost the *dsarm* gene. When the neuronal cell bodies were removed, their severed axons in the brain remained intact for 30 days, more than half the lifetime of a fly. This is in astonishing contrast to severed wild-type axons, which degenerate and are completely cleared within a week. Remarkably, the axon pro-

tection effect of dSarm is well conserved in mammals. Transected axons of sciatic nerves in *Sarm1* mutant mice were protected from degeneration for 2 weeks; denervation of neuromuscular terminal was delayed to over 6 days. Both phenotypes are comparable in extent to Wld^S protection.

The identification of dSarm/Sarm1 provides direct evidence for an endogenous axon self-destruction program. Understanding this mechanism has wide implications, as Wallerian degeneration shares morphological similarities with axon degeneration during normal brain development (axon pruning) and with the "dying back" degeneration in neurodegenerative diseases. There are similarities and differences in these processes. For example, whereas inhibiting the ubiquitin-proteasome system blocks developmental axon degeneration and delays axon degeneration after injury, Wld^S only protects axon degeneration after injury (*8*, *11*, *12*). In that regard, dSarm/Sarm1 resembles Wld^S because its function also appears to be highly specific for injury-induced axon degeneration. Wld^S also attenuates the progression of pathological symptoms in several mouse models of neurodegenerative diseases, such as Parkinson's disease, multiple sclerosis, motor neuron disease, and glaucoma (*13*). Thus, it will be of particular interest to determine whether Sarm1 also plays a role in the axon loss in mouse models of neurodegenerative diseases; if so, Sarm1 represents an attractive drug target for combating these diseases.

If there is a specific process that actively triggers axon death, as seems likely, what is its function during normal conditions? The success of the approach taken by Osterloh *et al.* suggests that additional components in the Wallerian degeneration pathway could be identified in a similar fashion, thereby providing clues to answer this question.

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