**Abstract**

Diffuse axonal injury is a principal pathology in traumatic brain injury (TBI) and the resulting axonal loss, disconnection, and brain atrophy contribute significantly to clinical morbidity and disability. In the last decade, we have identified molecular signals that trigger axonal degeneration, including SARM1 and the DLK/LZK MAPK cascade, and we have found that such signals operate in models of TBI. In addition, we can target select enzymes in these pathways with genetic and small-molecule strategies. The partial nature of injury in many traumatized axons and our ability to target axon-destruction pathways opens up new therapeutic opportunities for TBI and neurodegenerative disease.

---