Molecular mechanisms of postinjury axonal regeneration in primate retinal ganglion cells

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Purpose: To examine molecular mechanisms which are involved in regeneration of primate retinal ganglion cell axons in the monkey-human paradigm.Methods: Retinas were obtained from newborn to adult monkeys *(Callithrix jacchus)* immediately after death, freed from surrounding tissue and used to prepare explants which were cultured *in vitro*. Growth of axons was monitored using phase contrast microscopy and time-lapse video cinematography. Immunohistochemistry, Western blotting, qRT-PCR, proteomics and genomics were performed to characterize molecules associated with axonal growth. Then, siRNA experiments were conducted to identify the causal involvement of selected molecules in triggering axonal growth. Results: Primate retinal ganglion cells (RGCs) are known to lose the ability to regenerate cut axons during postnatal maturation, but the underlying molecular mechanisms are unknown. We screened for regulated genes in monkey RGCs during axon growth in retinal explants obtained from eye cadavers on the day of birth from New World marmosets (*Callithrix jacchus*), and hybridized the regeneration-related mRNA with cross-reacting cDNA on human microarrays. Neuron-specific human ribonucleoprotein N (snRPN) was found to be a potential regulator of impaired axonal regeneration during neuronal maturation in these animals. In particular, up-regulation of snRPN was observed during retinal maturation, coinciding with a decline in regenerative ability. Axon regeneration was reactivated in snRPN-knockout adult monkey retinal explants. These results suggest that coordinated snRPN-driven activities within the neuron-specific ribonucleoprotein complex regulate the regenerative ability of RGCs in primates, thereby highlight a potential new role for snRPN within neurons and the possibility of novel postinjury therapies. Conclusions: The data show that even after postnatal maturation, the molecular mechanisms for postinjury axonal growth are still existing, and can be reactivated to result in growth cone formation and lengthy axon extension. Understanding of the molecular mechanisms of axonal regeneration will help to develop therapeutic concepts for brain injuries.