Telomerase Activity and Differential Expression of Telomerase in Zebrafish Retina: A Possible Role in Neuronal Survival

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After receiving a PhD degree in Anatomy and Neuroscience at the Medical College of Wisconsin in 1985, Henry K Yip went to work with Dr Bernice Grafstein at the Cornell University Medical College in New York on a National Spinal Cord Injury Foundation Fellowship. He then took a NIH Postdoctoral Fellowship at Washington University in St Louis in 1987. He joined the University of Utah as an assistant professor in 1989. He has been a member of the Department of Anatomy at the University of Hong Kong since 1992.

His main research contributions have been in the understanding of the role of neurotrophic factors in the regeneration and development of the nervous system. His group was the first to clone the telomerase gene in zebrafish and showed that expression of the catalytic subunit of telomerase (TERT) in differentiated neurons. More recently, he is interested in assessing the involvement of telomerase and helix-loop-helix factor Id in neuronal survival and the development of neuronal lineages in the retina.

A central issue is the understanding why the fish RGC has a greater ability to repair itself after injury than does the mammalian RGC. When fish RGC axons are cut, they regenerate and the cell body does not die; in contrast, after axotomy of mammalian RGC axons, like any other CNS neurons, there is a failure of the axon to regenerate and the cell body dies. There are currently two general classes of explanation that have been put forth to help account for the difference between the ability of fish RGC and mammalian RGC axons to regenerate. There may be fundamental differences between fish and mammalian CNS glia or there may be fundamental differences between fish and mammalian CNS neurons. Recent work suggests that both explanations may be correct.

A simple potential explanation for why mammalian RGCs die after axotomy, whereas fish RGCs do not might be that different signaling mechanisms control their survival: Whereas the responsiveness of fish RGCs to axonal injury promotes neuronal survival and axonal regeneration, the responsiveness of mammalian RGCs to axonal injury induces neuronal death and axonal degeneration. In addition, it is also known that injured adult CNS do not regrow as do embryonic axons because of an age-dependent loss of ability to regenerate their axons. Taken together these findings suggest that an important area of research will be to understand how the survival of neurons is regulated and whether the nature of this regulation differs for fish and mammalian RGCs. Furthermore, neuronal survival is a prerequisite for axonal regeneration and target reinnervation and ultimately functional recovery. Despite the large amount of evidence demonstrating the difference of response between fish RGCs and mammalian RGCs, the molecular mechanisms underlying neuronal survival, repair and regeneration after axon injury have yet to be identified.

Telomerase is a reverse transcriptase that adds repeats of a DNA sequence (TTAGGG) to the ends of chromosomes (telomeres) in mitotic cells, thus maintaining their length and preventing cell cycle arrest and cell death. During development of the nervous system, telomerase activity levels are high in neural progenitor cells, but then they decrease as cells differentiate or die. The catalytic subunit of telomerase (TERT) remains at relatively high levels during the process of neuronal differentiation and then decreases sharply during the period when synapses form and programmed cell death occurs. TERT promotes survival of developing brain neurons. Suppression of telomerase activity and TERT expression promotes apoptosis of neurons, whereas overexpression of TERT prevents apoptotic cell death by suppressing DNA damage and/or apoptotic signals activated by damaged DNA. Recent studies of the transcriptional regulation of the TERT gene suggest that this enzyme may mediate cell survival-promoting actions of neurotrophic factors. The elucidation of the functions of telomerase activity and TERT in neuronal survival may explain the different ability of injured fish and mammalian RGCs to survive and regenerate: Whereas telomerase activity levels are high in injured fish RGCs, they remain low or absent in the injured mammalian RGCs and that the level of telomerase activity can be upregulated by cell survival-promoting actions of neurotrophic factors.