Epigenetic regulation of axonal regeneration- new path to axonal regeneration following axonal injuries

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Summary

Spontaneous axonal regeneration is not possible following axonal injury in the Central Nervous System (CNS). This is the primary cause of the lack of functional recovery in several neurological disorders, including Stroke, traumatic brain (TBI) and spinal cord injury (SCI). Currently, these disorders cause a chronic disability in more than 11 million people in the US (prevalence data, 2010). Effective therapies that may promote functional axonal regeneration and recovery in these diseases are missing. This is in part due to a lack of understanding of the basic molecular mechanisms that govern the intrinsic capacity of injured axons to re-growth following injury. Adult neurons whose axons or cell bodies lie in the CNS have a very limited pro-regenerative gene expression program in response to injury and this is believed to contribute to their restricted capacity for re-growth. Here, I hypothesize that this poor “pro-regenerative gene expression program” is largely due to the fact that the chromatin is locked in a non-permissive state, which allows only for a low pro-regenerative transcription rate. This would be a key limiting factor when neurons are injured and have to respond to unexpected external signals with an “ad hoc” gene expression response. The rate of gene transcription and expression depend upon the state of chromatin that is tightly controlled by epigenetic mechanisms, which include (1) DNA methylation and (2) histone post-translational modifications. I will discuss how in several experimental models of axonal and spinal injury in vivo transcription and epigenetic regulation control the capacity of injured axons to sprout and regenerate. These studies may provide a radical novel “epigenetic understanding” of the molecular basis for the limited capacity of adult CNS neurons to regenerate and may offer new molecular targets to foster functional recovery in several neurological disorders such as stroke, TBI and SCI.