

Functions of Chromatin-Remodeling Enzymes in Nervous System Regeneration

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The peripheral nervous system (PNS) and the central nervous system (CNS) regeneration efficiencies after lesion are not the same. Compared with PNS regeneration, CNS regeneration is very limited. Schwann cells (SCs), the myelinating glial cells of the PNS, can dedifferentiate and redifferentiate to foster regeneration after lesion whereas oligodendrocytes, the myelinating glial cells of the CNS, do not show the same plasticity as SCs. We hypothesized that chromatin-remodeling enzymes can control the plasticity of SCs and that histone demethylases (HDMs) and histone deacetylases (HDACs) are key chromatin-remodeling enzymes that can control the activity of critical target genes for regeneration.

I focused on the potential functions of HDMs in the regeneration process after lesion. I screened eleven HDMs that can demethylate repressive histone methylation marks. I found that some of them can control the expression of target genes differently in SCs and OLs. KDM3A and JMJD2C, two HDMs that we found to have an important role in PNS regeneration after sciatic nerve crush lesion. We found that HDAC2 controls an early response to injury after sciatic nerve crush lesion. Specifically, we show that HDAC2 interacts with Sox10 to control Sox10 activity during remyelination. Additionally, I focused on finding how HDAC2 can control Sox10 activity. I found that HDAC2 deacetylates eEF1A1, and acetylated eEF1A1 drags Sox10 out of its target genes thereby decreases the remyelination efficiency in PNS after lesion. I used theophylline, a drug known to increase HDAC2 activity, to increase eEF1A1 deacetylation and thereby keep Sox10 on its target genes and enhance remyelination. Theophylline injection has successfully increased remyelination after PNS lesion. I also used theophylline after a demyelinating CNS lesion to evaluate whether theophylline can also be used to improve remyelination in the CNS. Multiple sclerosis (MS) is the most common demyelinating disease of the CNS. According to WHO's 2013 data, there are almost 2.3 million MS patients in the world. I found that theophylline also enhances remyelination in a demyelinating MS mouse model. To check the potential of the findings in this part of the thesis, I carried out immunofluorescence analyses of acetylated eEF1A in human MS lesions. I found increased levels of acetylated eEF1A in the MS lesion sites, which shows that theophylline could be useful to increase remyelination in MS patients.

Jury:

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