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Identifying changes in Purkinje cell chromatin dynamics as novel drivers of neuronal vulnerability in spinocerebellar ataxias

Abstract

Spinocerebellar ataxias (SCAs) are a group of inherited brain disorders that cause problems with movement, balance, and speech. These diseases are marked by the gradual loss of a special type of brain neurons called Purkinje cells. These large and complex neurons are located in the cerebellum, the part of the brain that controls coordination. Despite years of research, scientists still do not fully understand why Purkinje cells are especially vulnerable in SCAs.

My research focuses on unraveling the root causes of Purkinje cell degeneration in one form of the disease, spinocerebellar ataxia type 7 (SCA7), using cutting-edge technologies to study individual cells. So far, we have found that these cells show a widespread breakdown in gene activity, including the loss of key identity markers known as zebrin-II related genes. This problem appears to be shared across different types of SCAs, suggesting common mechanisms of pathogenesis. In SCA7, we also observed that Purkinje cell nuclei shrink in size and begin to form unusual droplets, or "condensates". These structures seem to interfere with how genes are turned on and off, possibly because of changes in how DNA is packed and accessed, a process known as chromatin regulation.

Based on these findings, I believe that changes in the way DNA is packaged inside Purkinje cells may trigger a chain reaction that disrupts normal gene activity and leads to their degeneration. To test this idea, this project will examine how the structure of chromatin changes during the progression of SCA7 and other forms of ataxia (SCA1 and SCA3).

I will use powerful tools such as mass spectrometry and advanced imaging and sequencing methods to study how DNA packaging is altered, and I will investigate how the unusual condensates form and interfere with gene expression. I will also look at how the 3D structure of the genome changes over time and whether this leads to increased instability. Finally, I will confirm whether the same problems happen in human Purkinje cells derived from patient induced pluripotent stem cells and in tissue from patients with SCA7.

By identifying the earliest molecular events that make Purkinje cells vulnerable, this research will build foundations for developing new strategies to slow or even prevent the progression of spinocerebellar ataxia and related neurodegenerative diseases.