

Exploring and targeting cerebellar pathologies using genetic and pharmacological approaches

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ABSTRACT

Cerebellar ataxias are severe neurodegenerative disorders with an early onset, and a progressive and inexorable course of the disease. Here we report a new paradigm in neurodegenerative ataxias with the identification of a disease causing single point mutation in the gene encoding Elongator complex subunit 6 (Elp6) in the wobbly mouse. This mutation destabilizes the complex, which compromises its function in translational regulation, leading to protein misfolding, proteotoxic stress and eventual neuronal death. In addition, we show that substantial microgliosis concomitant with the degeneration of Purkinje neurons in wobbly mice, is triggered by the NLRP3 inflammasome pathway. Through both pharmacological inhibition and genetic approaches, we demonstrate that blocking NLRP3 function in vivo significantly delays neuronal degeneration and the onset of ataxia in mutant animals. Our data provide a mechanistic insight into the pathophysiology of cerebellar ataxia caused by an Elongator mutation, substantiating the increasing body of evidence that alterations of this complex are broadly implicated in the onset of a number of diverse neurological disorders.

Medulloblastoma (MB) is another common pathology affecting the cerebellum. It is the most common malignant pediatric brain tumour and a leading cause of cancer-related mortality and morbidity in children. The development and testing of novel targeted therapeutics for MB remains a major preclinical challenge, heavily reliant on in vivo mouse models. Using a transposon mutagenesis approach in mice, we identified genes that functionally cooperate with Hedgehog signalling to promote tumorigenesis in a Ptch1 mouse model of MB. Furthermore, we have functionally defined key regulatory networks that illustrate both the differences and commonalities between tumour subgroups indicating a number of potential therapeutic strategies. In our lab, we use a variety of genetically engineered and patient-derived xenografts (PDX) mouse models of MB and we take various genetic and pharmacological approaches to target cancer genes that drive the MB development and progression.