19 JNK inhibitor ameliorates the SCA1 phenotype by inhibiting Bergmann glial inflammation

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Spinocerebellar ataxia type1 (SCA1) is an adult-onset neurodegenerative movement disorder caused by a pathogenic polyglutamine expansion (CAG repeat) in the protein Ataxin-1 (ATXN1). SCA1 is a condition characterized by progressive problem with movement. People with this condition initially experience problems with coordination and balance (ataxia). Main pathological hallmark of the disease is Purkinje cell loss in cerebellum. Despite the ubiquitous expression of ATXN1, the selective vulnerability of Purkinje cells is not well understood. Recent work from two prominent mouse models (knock-in and transgenic) suggest that other than existence of Purkinje cell intrinsic toxicity the involvement of surrounding astroglia in Pukinje cell vulnerability has been reported. Moreover, astogliosis has been associated with loss of Purkinje cells in several examples of cerebellar dysfunctions. Evidence for the involvement of reactive astrogliosis (Bergmann glia and other astroglia population) came from the reports showing the increased levels of GFAP (glial fibrillary acidic protein) expression that is tied to increased levels of pro-inflammatory factors in SCA1 cerebellum. It is still puzzling how glial cells respond to the neuronal damage with the morphological and function changes, hence becoming reactive glial cells. Here we reported for the first time, the mechanism behind the involvement of Bergmann glial cells in inflammation and there by account for SCA1 disease phenotype. We found that the SCA1 cerebellum is evident with the elicited JNK-dependent phosphorylation of c-Jun specifically in Bergmann glia cells and there by induces the levels of pro-inflammatory factors. We then treated the SCA1 mice with the JNK-specific inhibitor (SP6000125) for two months to inhibit the c-Jun phosphorylation in Bergmann glial cells. JNK inhibitor clearly abolish the JNK-dependent c-Jun phopshotylation in Bergmann glial cells and improve the rotarod phenotype of SCA1 mice. We are now testing whether the treatment with JNK inhibitor able to abolish the inflammatory factors in SCA1 mice or not. It is still unclear how exaclty mutant ATXN1 induce the phosphorylation of c-Jun in Bergmnann glia cells spedifically? Our future studies are aimed to address this caveat. These findings gives a novel direction to the Bergmann glial inflammation and SCA1 pathology and helps in implementing new therapeutic targets in SCA1 disease.