Role of a novel nuclear GTPase CRAG in axon guidance and polyglutamine diseas

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Polyglutamine diseases are inherited neurodegenerative diseases caused by the expansion of polyglutamine tract. Expanded polyglutamine proteins accumulate abnormally in intranuclear inclusions partially correlated with promyelocytic leukemia protein (PML) bodies. Here we identified a novel neural GTPase, named CRAG which contains a nuclear localization signal sequence (NLS) and forms unique intranuclear inclusion body in response to various stimulations such as repulsive axon guidance factor semaphorin3A or UV irradiation. Active form of CRAG translocates to the nucleus, associates with and activates ubiquitin ligase of PML, leading to a large ring-like structure of PML body with ubiquitination which is characteristic of polyglutamine diseases. Actually, CRAG nuclear inclusions were detected specifically in brains of Machado-Joseph disease patients. Importantly, CRAG promoted a rapid degradation of misfolded polyglutamine proteins in the nuclear inclusions through ubiquitin-proteasome pathway and canceled their cell toxicity. Consistently, siRNA-mediated knockdown of CRAG in neuronal cells blocked the nuclear translocation of polyglutamine proteins and promoted cell death. We proposed that CRAG is a specific activator for PML ubiquitin ligase and a potent candidate responsible for nuclear translocation, inclusion body formation and clearance of misfolded polyglutamine proteins and that CRAG may transduce stress signals into the nucleus through the transcriptional modification at PML bodies, thereby protectively involving in the pathogenesis of polyglutamine diseases. In this symposium, implication of CRAG for axon guidance mechanism and molecular target of polyglutamine diseases will be discussed.