A Toxic Monomeric Conformer of the Polyglutamine Protein

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Conformational alterations leading to aggregation and deposition of misfolded proteins in the brain have been recognized as a common molecular pathogenesis of neurodegenerative diseases including Alzheimer's, Parkinson's, amyotrophic lateral sclerosis, and the polyglutamine (polyQ) diseases, which are classified as the conformational diseases. The polyQ diseases are a group of at least nine inherited neurodegenerative diseases including Huntington's disease and the spinocerebellar ataxias, which are caused by abnormal expansions of the polyQ stretch within the disease-causing proteins. Expansion of the polyQ stretch is thought to confer toxic properties on the pathogenic proteins through alterations in their conformation, leading to their assembly into insoluble aggregates and eventual accumulation as inclusion bodies inside affected neurons. However, it has been controversial for a long time as to how these pathogenic proteins change their structure to assemble into insoluble aggregates, and which specific conformers of these proteins formed during the aggregation process cause cytotoxicity in the pathogenesis of these conformational neurodegenerative diseases.

In this paper, we performed structural analyses of the polyQ protein with a pathogenic expanded polyQ stretch to elucidate the structural alterations and cytotoxic conformers of the expanded polyQ protein formed during aggregation. We successfully demonstrate that that the expanded polyQ protein undergoes a conformational transition to a β-sheet dominant structure in the monomeric state, resulting in formation of insoluble β-sheet-rich amyloid-like fibrillar aggregates (Figure). Most importantly, the soluble β-sheet monomer of the expanded polyQ protein exhibits cytotoxicity, indicating that its cytotoxicity arises from the conformational transition to a β-sheet dominant structure (Figure). We further show that the polyQ binding peptide QBP1, which we previously showed to suppress polyQ-induced neurodegeneration *in vivo*, prevents the β-sheet conformational transition of the polyQ protein monomer (Figure). We therefore conclude that the toxic β-sheet conformational transition of disease-causing protein monomers is a promising therapeutic target not only for the polyQ diseases, but also for the other conformational neurodegenerative diseases such as Alzheimer's and Parkinson's diseases.

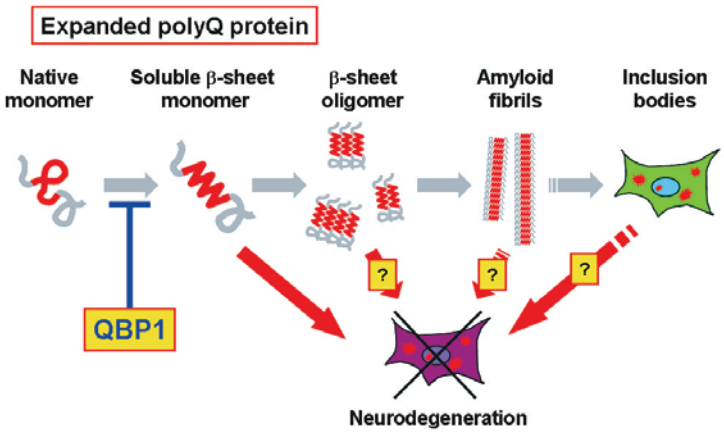

Figure. Structural alterations of the polyglutamine protein and the molecular pathogenesis of the polyglutamine diseases

PGC7/Stella Protects Against DNA Demethylation in Early Embryogenesis

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Epigenetic gene regulation plays essential roles for development of multicellular organisms and cell differentiation. DNA methylation is one of the pivotal mechanisms in the epigenetic regulation. However, the molecular mechanisms for the control of DNA methylation remain by and large unclear. In this study, we clearly demonstrated that PGC7/Stella is a modifier of DNA methylation in early embryogenesis.

PGC7/Stella is a gene which is expressed in only early embryos, primordial germ cells (= very immature germ cell precursors), and oocytes. Previous gene targeting analysis has revealed that PGC7/Stella is essential maternal factor for early development. Based on these findings, we scrutinized the function of PGC7/Stella. Identification of a binding partner of PGC7/Stella and detailed analyses made it clear that the time point of the crucial function of PGC7/Stella was very narrow, namely between fertilization and the first cell division. Then we analyzed the DNA methylation status of the genome in the zygotes derived from control and PGC7/Stella null mice, because the most prominent event in this developmental stage is a drastic genome-wide reduction of DNA methylation. Although the global demethylation commences soon after fertilization, it does not evenly take place throughout the entire genome. One example is "epigenetic asymmetry", which means that that demethylation of maternal genome is delayed compared to that of paternal genome. The other example is that some classes of genes such as retrotransposons and imprinted genes are escaped from the global demethylation.

Immunohistochemical analysis using the anti-5-methyl-cytosine (5MeC) antibody showed that the maternal genome of the zygotes derived from PGC7/Stella-null eggs was demethylated while that from the control egg was methylated (Fig 1). These results clearly show that PGC7/Stella is required to protect against DNA demethylation of the maternal genome after fertilization, i.e. PGC7/Stella is essential for the establishment of epigenetic asymmetry. Next, we examined the methylation status of two types of genes, retrotransposons and genomic imprinted genes, which are not affected by the global DNA demethylation. Bisulfite gene sequencing analysis clearly demonstrated that the DNA methylation of some of these genes was abrogated in the PGC7/Stella-null zygotes. Taken together, PGC7/Stella is concluded to be an essential for protecting against DNA demethylation during early embryogenesis (Fig. 2).

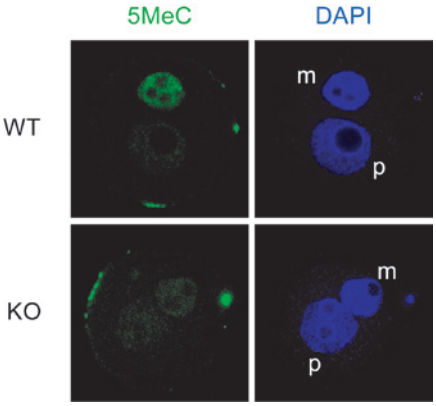

Fig. 1 Methylation status of the parental genome (p, paternal genome; m, maternal genome) in fertilized eggs.

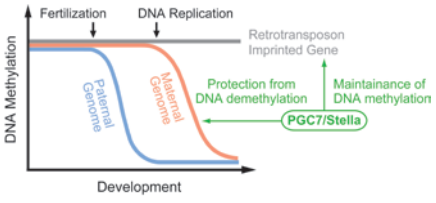

Fig. 2 PGC7/Stella is required to protect against DNA demethylation in early embryogenesis.