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Hopping from One Cell to Another: Huntington's Disease Propagates

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Prion-like propagation of protein inclusions in many neurodegenerative diseases has received a great deal of attention. In this issue of Experimental Neurobiology, Kim et al. [1] describe a useful *in vivo* model for the cell-to-cell transmission of polyQ aggregates, which are associated with Huntington's disease in *Caenorhabditis elegans* (*C. elegans*) using bimolecular fluorescence complementation (BiFC) technique.

Millions of people suffer from progressive neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Diagnosis and treatment of these diseases cost billions of dollars per year. Unfortunately, their pathogenesis still remain too elusive to allow the rational design of therapeutic interventions that should stop or reduce their progression. It has been established that they show the common pathological features of protein aggregate inclusions, although the main component of protein inclusions of each disease differs. AD shows extracellular senile plaques and cytosolic neurofibrillary tangles comprising mainly Aβ and hyperphsophorylated tau, respectively. PD shows cytosolic Lewy bodies or Lewy neurites composed of mainly α-synuclein. HD also shows nuclear protein inclusions composed of mainly mutated huntingtin with expanded polyQ. Furthermore, the process of protein inclusion formation has been considered to play a major role on the pathogenesis of many neurodegenerative diseases and become therapeutic targets for more than 2 decades [2]. Interestingly, recent research shows their regional and intercellular spreading irrespective of cytosolic or extracellular proteins and these processes are suspected to be significant in the pathogenesis of neurodegenerative diseases. In particular, intercellular spreading of cytosolic proteins such as hyperphosphorylated tau, α-synuclein, and mutated huntingtin has attracted much attention because it may provide mechanistic insights to the pathogenesis and motivational drive to develop novel therapeutic interventions such as blocking secretion and reuptake [3,4].

Intercellular spreading of mutant huntingtin has been recently demonstrated in cell and mouse model systems [5]. Nevertheless, given that a variety of model systems complementing each other are critical to study the disease, Kim et al. [1] developed an *in vivo* model system in *C. elegans* to complement the cell and mouse model systems. They generated BiFC transgenic lines in which polyQ proteins are overexpressed in both pharyngeal muscles and neurons connected with the pharyngeal muscle in *C. elegans* and demonstrated that the transmission does occur between these two cell types and the lines with long polyQ exhibited stronger BiFC fluorescence than the lines with short polyQ, which correlated with degenerative phenotypes in an age dependent manner. BiFC is a widely used fluorescence technique that has been successfully applied to assess protein-protein interactions and protein dimerization and/or oligomerization in living cells. It has been already proved to be useful to study cell-to-cell transmission of protein aggregates such as tau [6] and α-synuclein [7]. In addition, the *C. elegans* has a relatively short life cycle (~3.5 days), fast reproduction cycle with a high progeny number (~300), short life span (~2 weeks), which makes it applicable to a wide variety of high-throughput manipulations [8]. Accordingly, this system shows a high potential to be applied to a screening of genetic and chemical

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modifiers of the propagation of polyQ proteins to complement the weaknesses of cell and mouse model systems.

Although prion-like propagation of protein inclusions has been attracted a great attention, there are still matters of controversy and many hurdles remain to be overcome [9, 10]. Nevertheless, a variety of model systems including this system will be helpful to better understand the causes of diseases. Fortunately, the authors have already developed a similar *in vivo* model system to monitor cell-to-cell transmission of α-synuclein [11], implying that a comparison between these two model systems make us understand the common and different features of these diseases, further uncovering the pathogenesis of various neurodegenerative diseases.

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