Is Huntington disease a developmental disorder?

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The construction of an organism is a complex process that involves a developmental challenge: the orchestrated proliferation, migration and differentiation of cells, leading to the assembly of organs. Huntingtin—the protein that is mutated in the neurodegenerative disorder Huntington disease—is widely expressed in the early developing mouse embryo, in which it has an essential role. The most compelling proof that huntingtin is essential for early development is that inactivation of the murine gene results in defects in extra-embryonic tissues and embryonic death at embryonic day 7.5 (Dragatsis *et al*, 1998). My group has recently directly linked a cellular function of huntingtin to brain development (Godin *et al*, 2010a). Indeed, huntingtin regulates cortical neurogenesis through, at least in part, its role during spindle pole orientation.

The growing evidence that huntingtin functions during development opens the door to viewing Huntington disease as a developmental disorder. Development could be abnormal in carriers of the mutant protein and precede the manifestation of the disease by decades. Changes during development might not have phenotypical consequences until the mature cells are required to function later in life. Indeed, a given protein will not function in the same context during development and adulthood, and the resulting phenotypes of these functions will not be the same. Furthermore, compensatory mechanisms that respond to abnormal development might be overwhelmed when the organism is ageing. We have not yet identified all of the neurodevelopmental defects—both functional and morphological—involved in Huntington disease. However, there are changes in the brain before the onset of disease, including a smaller intracranial adult brain volume in pre-manifest Huntington disease carriers (Nopoulos *et al*, 2010). It is tempting to

consider that this might be a consequence of altered brain development.

A complex molecular picture of the biology of huntingtin is emerging, suggesting that it is a scaffold protein that could couple many cellular events. Huntingtin regulates the assembly of the dynein–dynactin complex for axonal transport and Golgi apparatus organization (Caviston *et al*, 2007; Gauthier *et al*, 2004). During cell division, this role extends to a complex that also contains NuMA, a component that is essential for the organization of microtubules at the spindle pole (Godin *et al*, 2010a). Furthermore, NuMA and the Golgi-containing protein LGN form a complex that regulates the interaction between astral microtubules and the cell cortex (Du & Macara, 2004). Therefore, huntingtin could also participate in the distribution of the dynein–dynactin complex at the cell cortex and, as a consequence, regulate mitosis at several points. Similarly, huntingtin could regulate the assembly of other supra-molecular complexes that are involved in various cell pathways, as suggested by the diverse nature of its interactors (Kaltenbach *et al*, 2007). For example, huntingtin interacts with the β -catenin destruction complex and thus participates in the tight regulation of the steady-state levels of β -catenin (Godin *et al*, 2010b; Kaltenbach *et al*, 2007). This might be crucial to regulate the Wntless/Wnt signalling pathway, known for its central role during development and adulthood. Thus, the functions attributed to huntingtin so far are important cellular processes in the early stages of development and adulthood, and contribute as initial or secondary disease mechanisms to several neurodegenerative disorders. This might not be a coincidence!

Finally, the scaffold nature of huntingtin might be important for histogenesis in general and explain the widespread abnormalities observed in Huntington disease.

A high level of huntingtin is found in the testes and one of the peripheral manifestations of the disease is testicular pathology, with a reduced number of germ cells and abnormal seminiferous tubule morphology (van Raamsdonk *et al*, 2007). Testes require functional intracellular transport for their normal development, and asymmetrical division is particularly important for germline stem-cell maintenance. Thus, an abnormal developmental programme induced by defective huntingtin function would alter cells and, thereby, the homeostasis of the tissues expressing this protein.

Several other disorders are caused by the toxic presence of an abnormal polyglutamine expansion. These ‘polyglutamine diseases’ have this mutation in common; however, the mutated proteins are unrelated and the disorders are phenotypically distinct, affecting different brain regions and neurons. A defect in the function of the mutated proteins explains the separate mechanisms of neuronal degeneration observed. Huntington disease is a dominant disorder, but the vision of it as a gain-of-function disease with loss-of-function manifestations could be outdated. The situation seems to be more complicated, and most patients express not only one copy of the mutant huntingtin, but also half the amount of the wild-type protein. It is time to rethink the idea that studying huntingtin protein is irrelevant to Huntington disease. In the light of recent advances in the understanding of its function, one might even suggest that taking developmental biology into account could provide new insight into the pathological mechanisms of this so far incurable adult-onset disorder.

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