Published in final edited form as:
Drug Discov Today. 2014 July ; 19(7): 949–950. doi:10.1016/j.drudis.2014.04.013.

Huntington's disease: from disease mechanisms to therapies

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Huntington's disease (HD) is a relentlessly degenerative disorder of the central nervous system, affecting the striatum most prominently, but also the cerebral cortex and other subcortical structures. It is characterized by progressive dementia with chorea (brief, irregular movements that are not rhythmic but appear to flow from one muscle to the next), athetosis (slow, writhing movements), impaired coordination, abnormal speech, swallowing difficulties and neuropsychiatric symptoms, such as depression. Although HD has been around since at least the Middle Ages, early definitive descriptions were made during the mid-19th century by Charles O. Waters and, later, by Johan C. Lund. A comprehensive and influential description of HD was subsequently made by George Huntington in 1872, and the disease has since borne his name. By examining the medical histories of several generations of a family exhibiting similar symptoms, Huntington recognized that their diseases were linked. Later, William Osler's interest in HD brought increased attention throughout the medical community. Smith Ely Jelliffe and Charles Davenport made major contributions to the understanding of the genealogy of the disease during the early 20th century, establishing that it was autosomal dominant and documenting several key features of its inheritance, such as anticipation, whereby age of symptom onset, severity, or both worsen in succeeding generations [1].

Research into HD continued steadily throughout the 20th century, with several pathogenic themes emphasized, particularly excitotoxicity, beginning during the mid 1970s [2]. A major breakthrough occurred in 1983 when the US–Venezuela Huntington's Disease Collaborative Research Project identified the approximate location of a causal gene. In 1993, the research group isolated the disease gene at chromosome 4p16.3, marking this as the first autosomal disease gene identified using genetic linkage analysis [3]. The genetic change was a triplet nucleotide repeat (CAG) expansion, giving rise to a long polyglutamine stretch in the huntingtin (Htt) protein.

The discoveries of the Htt protein and its polyglutamine expansion fostered several subsequent research advances. Among these, modeling the disease in various animals, such as the R6/2 transgenic mouse developed in 1996, greatly facilitated experiments focusing on disease pathogenesis [4]. The discovery in 1997 that fragments of mutant Htt misfold led to

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the identification of nuclear inclusions, now a pathologic hallmark [5]. Studies around that time emphasized a novel role of transcriptional dysregulation in disease pathogenesis [6]. Furthermore, a large number of studies have investigated the interactions, localizations, and functions of both wild type and mutant Htt protein. Increased polyglutamine expansion length has correlated with increased severity in human studies as well as in a variety of model systems, explaining the phenomenon of clinical anticipation identified a century earlier [3,7]. Still, a few significant challenges have hampered research into Htt. In particular, the very large size of the protein makes it technically difficult to study biochemically, and even determining the roles of the long polyglutamine repeat in gain- or loss-of-function in cells has been challenging.

In this issue of *Drug Discovery Today*, recent key insights into the cellular pathogenesis and therapy of HD are outlined. First, Jean-Marc Burgunder reviews the genetics of HD [8]. He discusses the classic CAG expansion and its increased length in succeeding generations, the aforementioned anticipation, and also how genetic modifiers might have a role in disease presentation. He further emphasizes how related inherited disorders with prominent choreoathetosis, a cardinal feature of HD, might provide additional, converging insights into HD pathogenesis.

Next follows a series of articles addressing key cellular themes implicated in HD pathogenesis. Sepers and Raymond discuss synaptic dysfunction and excitotoxicity, describing elegant studies probing signaling pathways that impinge on striatal neuron dysfunction and degeneration [9]. Reddy discusses a novel role for mitochondrial fission, with a mechanistic description of how mutant Htt might upset the delicate balance between mitochondrial fission and fusion in neurons, leading to mitochondrial dysfunction and subsequent cell death [10]. Kumar *et al.* discuss the role of the persistent oxidative, bioenergetic, and oxidative stress resulting from a failure of adaptive gene programs (transcriptional dysregulation) to counteract these stresses [11]. Last, Cortes and La Spada discuss the emerging roles of alterations in crucial autophagy pathways in HD pathogenesis [12]. Each of these articles also suggests possibilities for therapies that selectively target these cellular pathways.

The final two articles in this special issue focus on therapeutic assessment and development. There is a clear need to complement clinical measures with biomarkers, and this is an area of active investigation for HD. Andre *et al.* discuss the development and optimization of biochemical, functional, and neuroimaging markers [13]. They further emphasize the importance of markers that can be assessed in HD gene carriers before symptom onset, when disease-modifying therapies could be most effective. These are particularly relevant because disease penetrance is essentially 100% for those with the polyglutamine expansion. Finally, Chen *et al.* discuss exciting advancements in cell-based therapies, which have the potential for functional restoration in patients with HD symptoms [14].

These concise review articles are timely and exciting, describing studies that apply cutting-edge approaches to understand HD pathogenesis and find new ways to treat it. Future work will almost certainly center on how the various pathogenic themes are linked. Furthermore, HD shares several features with other, more common neurodegenerative disorders, such as

Alzheimer's disease and Parkinson's disease. Thus, the century-and-a-half interest in HD that has generated so many pioneering insights related to HD diagnosis, pathogenesis, and treatment will likely spur additional insights into the pathogenesis of other disorders marked by neurodegeneration.

References

1. Harper, P. Huntington's disease: a historical background. In: Bates, G., et al., editors. Huntington's Disease. 3rd. Oxford University Press; 2002. p. 3-24.
2. Coyle JT, Schwarcz R. Lesion of striatal neurones with kainic acid provides a model for Huntington's chorea. Nature. 1976; 263:244–246. [PubMed: 8731]
3. HD Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993; 72:971–983. [PubMed: 8458085]
4. Mangiarini L, et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell. 1996; 87:493–506. [PubMed: 8898202]
5. Davies SW, et al. Formation of neuronal intranuclear inclusions underlies the neurological dysfunction in mice transgenic for the HD mutation. Cell. 1997; 90:537–548. [PubMed: 9267033]
6. Cha JH. Transcriptional dysregulation in Huntington's disease. Trends Neurosci. 2000; 23:387–392. [PubMed: 10941183]
7. Finkbeiner S. Huntington's disease. Cold Spring Harb Perspect Biol. 2011; 3:a007476. [PubMed: 21441583]
8. Burgunder, JM. Genetics of Huntington disease and related disorders. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM1]
9. Sepers, MD.; Raymond, LA. Mechanisms of synaptic dysfunction and excitotoxicity in Huntington disease. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM2]
10. Reddy, PH. Increased mitochondrial fission, synaptic damage, and neuronal dysfunction in Huntington's disease: implications for molecular inhibitors of excessive mitochondrial fission. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM3]
11. Kumar, A., et al. Transcriptional dysregulation in Huntington's disease: a failure of adaptive transcriptional homeostasis. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM4]
12. Cortes, CJ.; La Spada, AR. The many faces of autophagy dysfunction in Huntington's disease: from mechanistic pathways to therapeutic opportunities. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM5]
13. Andre, R., et al. Biomarker development in Huntington's disease. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM6]
14. Chan, AWS. Cell-based therapies for Huntington's disease. Drug Discov Today. 2014. http://dx.doi.org/XXX[LM7]

Biography

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