von-Hippel Lindau (VHL) hereditary cancer syndrome

Images removed due to copyright considerations. See Figures 1 through 5, Table 1, and Box 1 in Kaelin Jr., WG. 200. 2002. Molecular basis of the VHL hereditary cancer syndrome. Nature Rev. Cancer 2; 673-682.

Huntington's disease (HD)

To date, 10 neurological diseases, including Huntington's and several *ataxias*, are caused by the **lengthening of glutamine (Q) tracts** in various proteins with no obvious functional or evolutionary relationships. This phenomenon results from a mutation involving a ***CAG* repeat expansion** in the corresponding genes. Even though the Q expansions arise in unrelated proteins, the diseases share three striking features:

(1) The existence of a stretch of **35-45** glutamine residues in the mutant protein.

(2) The Q-expanded proteins are expressed in many tissues, yet **pathology** is largely **restricted to neurons**.

(3) The Q-expanded proteins or fragments thereof form **nuclear inclusions** that also contain **ubiquitin, proteasomes and chaperones**.

Although they differ in their clinical presentation and neuropathological profile, the patients display different combinations of **motor, psychiatric, cognitive, and sensory symptoms**.

In Huntington's, the disease is caused by a mutation in the gene encoding for **Huntingtin** (a protein of unknown function, although has been recently implicated in the control of gene transcription). Huntingtin has been found to be ubiquitinated and also interacts with the ubiquitin-conjugating enzyme E2-25.

In principle, the polyQ diseases could result from functional inactivation of each protein. However, expression of polyQ sequences attached to other proteins (such as GFP) can cause cell death. Thus, it seems that neurodegeneration is, in fact, a toxic manifestation of the expanded Q tract. PolyQ forms **polar zippers** (amyloid-like fibrils consisting of β strands of the mutant protein) that result in protein **aggregation**, in the form of intranuclear or cytoplasmic **inclusions**. **Transglutaminase**-mediated cross-linking of glutamine in polyQ tracts to lysines in the same or other proteins can account for both the formation of inclusions and their insolubility. Administration of **cystamine**, a transglutaminase inhibitor, reduces the aggregate formation, retarding the development of neurological phenotype and prolonging the life span of brain cells in transgenic mouse models.

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See Figure 1 in Tarlac, V. and Storey, E. 2003. Role of proteolysis in polyglutamine disorders. J. Neurosci. Res. 74: 406-416.

Several **hypotheses** have been advanced to explain why expanded glutamine regions cause neuronal degeneration:

- The polyQ fragments may form **cationic channels in membranes**.
- Intranuclear aggregation may **interfere with the function of transcription factors** that also contain glutamine tracts, thereby causing misregulation of gene expression.
- PolyQ and several other neurodegenerative diseases may result from **impaired proteolysis**, either because the protein/fragment becomes inherently difficult to degrade or because it can end up overwhelming and inhibiting the ubiquitin-proteasome pathway.

As we have seen for other neurodegenerative diseases, evidences point out to the possibility that intracellular protein inclusions could represent a means for the cell to effectively sequester toxic misfolded proteins, thereby shielding organelles from damage. In such case, the inclusions would have a **neuroprotective function**. However, continued production/accumulation of the aberrant proteins would, as in other neurodegenerative disease activate stress-related pathways which would finally end up in **neuronal**

autophagy and cell death (it seems that in a last attempt of the cells to get rid of the accumulated huntingtin, cleavage of the protein as a result of caspases activation also takes place).

The presence of ubiquitin in the aggregates of most polyQ diseases would seem to indicate that ubiquitination is not impaired, although rates of proteolysis could be affected by changes in the polyUb chain length, so the mere presence of Ub doesn't necessarily mean that an adequate degradation signal has been generated. However, certain evidences point out to the hypothesis that polyQ tracts might reduce the rate of polypeptide chain transfer into the central proteolytic chamber by either inhibiting the ATPases in the 19S subunits of the proteasome or by being difficult to unfold.

An interesting hypothesis involves **alternative forms of the proteasome:** The 20S proteasome central subunit can associate with the 19S to produce the classical 26S proteasomes, but instead it can also bind the **donut-shaped 11S REG or PA28 heptamers**. Hybrids binding 11S REGs to one end of the 20S proteasome and 19S subunit to the other end of the 20S can also be formed. REGα/β subunits are thought to play a role in antigen presentation by class I MHC molecules and they activate proteasomal hydrolysis following hydrophobic, acidic or basic residues. REGγ is, by contrast, found in the nucleus and is particularly enriched in nervious tissue. As a homo-heptamer activates hydrolysis after basic residues but suppress the sites responsible for the cleavage of Gln bonds. The hypothesis is that hybrid 26S proteasomes have little difficulty in pumping soluble polyQ tracts into the central proteolytic chamber, but if there is impaired cleavage within Gln tracts due to bound REGγ, polyQ peptides would accumulate within the proteasomes, inactivating them.

Image removed due to copyright considerations. See Figure 5 in Rechsteiner M, Realini C, Ustrell V. The proteasome activator 11 S REG (PA28) and class I antigen presentation. Biochem J. 2000 Jan 1; 345 Pt 1: 1-15.

Could the functional status of the UPS differ between individuals due to genetic or epigenetic influences unrelated to the polyglutamine disease, and can this difference play a role in governing the age of disease onset?

The CAG repeat length in the mutant accounts for ~70% of the variance of age of onset for HD (the number of CAG repeats is inversely correlated with the age of disease onset, suggesting that the rate at which the mutant proteins misfold is related to the length of the polyQ tract). But individual differences in UPS activity could also influence the time it takes for mutant proteins to accumulate in the patient's brain. Thus, the rate of age-related decline in UPS activity could define the efficacy with which the brain handles the mutant proteins, thereby influencing the age of onset of symptoms in an individual patient.