

We also started building the model by using the information available through published research articles, database entries (from databases: Entrez Protein (NCBI), HGNC, GenomeCube (RZPD), BIND and KEGG) and data that was generated through the SMP Protein.

Modelling the Pathway

The function of huntingtin is still unknown but several huntingtin-associated proteins, e.g. HAP1, HIP-1, ubiquitin-conjugating enzyme (HIP-2) or glyceraldehyde 3-phosphate dehydrogenase (GAPDH), have been reported (Harjes and Wanker 2003). Some were already mentioned in the introduction above (see also in Figure 1).

A key role seems to be played by the huntingtin interacting protein 1 (HIP-1). By immunostaining in cortical pyramidal neurons of mouse brain, it was shown that the interaction

between Hip-1 and huntingtin on the one hand, and between Hip-1 and Hippi on the other, are mutually exclusive, and that Hip-1/Hippi complexes can activate caspases, the effector enzymes of apoptosis (Gervais et al. 2002).

Hip-1 interacts with huntingtin but the affinity of Hip-1 for mutant htt is much lower than its affinity for wild-type htt. So in diseased mouse brains, levels of the Hip-1/Hippi complex are relatively higher than the levels of the Hip-1/htt complex. The proenzyme procaspase-8 is recruited to Hip-1/Hippi complexes. This suggests that Hip-1 and Hippi cooperate to induce apoptosis in a caspase-8-dependent manner (dimerisation activates procaspase-8, thereby initiating the apoptotic cascade).

Figure 2 summarises these relations schematically.

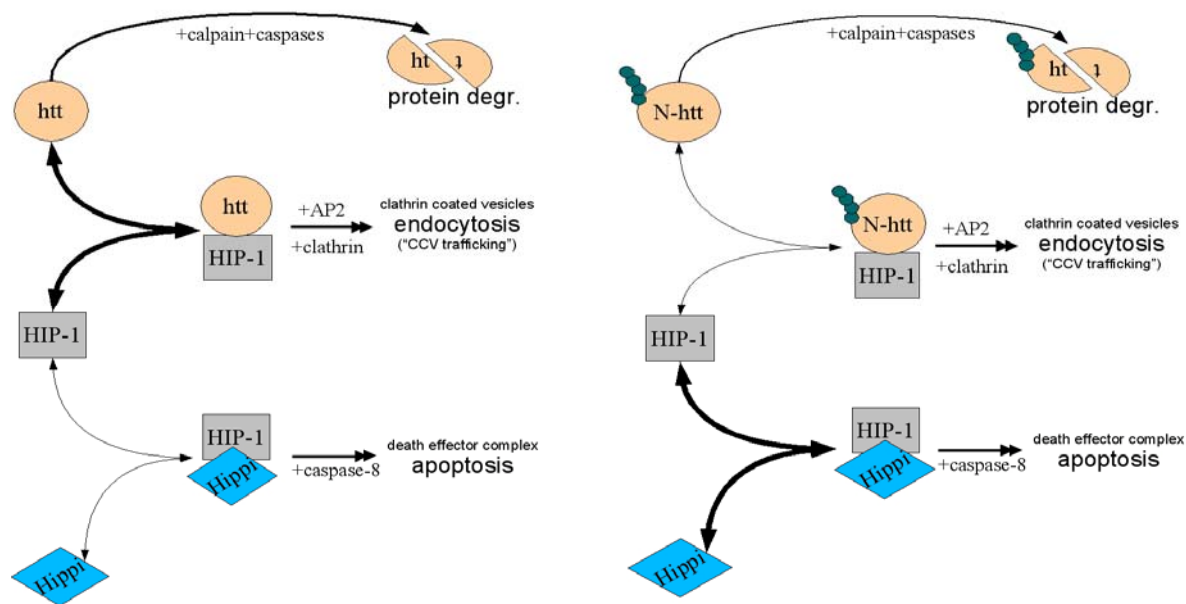


Fig 2: A schematic representation of the interplay of the two forms of huntingtin (normal htt; mutant N-htt) with HIP-1 and Hippi. In humans, htt becomes N-htt if the length of the polyQ is greater than 36 amino acids.

A mathematical model can facilitate the quest for intrinsic mechanisms of cellular control and regulation by signal transduction pathways. In such a model the dynamic interactions of the proteins that form the complex signalling network are encoded as non-linear ordinary differential equations (ODE's). This allows for the modelling of transient changes in protein concentrations (whereas a protein protein interaction network is a rather static representation).

Model Interrogation

For simulating and interrogating the model standard software is used (free and licensed, e.g. XPP, MatLab).

A mathematical model can be interrogated at any state of its development but the more refined it is the more predictive power it has. First preliminary results from the analysis and simulation of the model have to be investigated further, before conclusions can be drawn.

Disease-Relevant Proteins

A comparison of the list of proteins mentioned above with the proteins already used in the Y2H screenings and in the experiments of the other SMP Protein sub-projects is next in order to check the availability of clones, antibodies etc. If necessary (in the case of proteins not yet considered by the experimental groups), possibilities of acquisition have to be discussed.

Outlook

The robustness of the model against perturbations and its sensitivity to input signals will be analysed, and the emergence of multistability and oscillations by positive and negative feedback loops investigated. Further interrogation of the model and computer simulations will produce hypotheses and predictions that can be tested experimentally. This again allows to further improve, iteratively refine, and expand the model.

Lit.: 1. Etienne-Manneville S & Hall A. Rho GTPases in cell biology. *Nature*. 2002 Dec 12;420(6916):629-35. 2. Gusella JF et al. A polymorphic DNA marker genetically linked to Huntington's disease. *Nature*. 1983 Nov 17;306:234-8. 3. The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. *Cell*. 1993 Mar 26;72(6):971-83. 4. Gervais FG et al. Recruitment and activation of caspase-8 by the Huntingtin-interacting protein Hip-1 and a novel partner Hippi. *Nature Cell Biology* 2002 Jan 14;4:95-105. 5. Goehler H et al. A Protein Interaction Network Links GIT1, an Enhancer of Huntingtin Aggregation, to Huntington's Disease. *Mol Cell*. 2004 Sep 24;15(6):853-65. 6. Harjes P & Wanker EE. The hunt for huntingtin function: interaction partners tell many different stories. *Trends Biochem Sci*. 2003 Aug;28(8):425-33.