Huntington’s disease (HD) is a fatal neurodegenerative disorder which usually occurs in mid-age. It is characterized by psychiatric disorders, involuntary movements and dementia, leading to death within 10-20 years.

Huntingtin is a 350 kDa protein that is altered in HD. The expanded trinucleotide CAG repeat of the huntingtin gene encodes an abnormally expanded polyglutamine stretch in the N-terminus of the protein. The abnormal form of huntingtin aggregates in vitro and forms neuronal intranuclear and cytoplasmic inclusions in HD patients. Furthermore, the expanded polyglutamine repeats have been proposed to cause neuronal degeneration in HD through abnormal interactions with other proteins containing short polyglutamine tracts such as the CREB binding protein (CBP). CREB promotes cell survival and is a major mediator of survival signals in mature neurons.

Huntingtin-interacting proteins

HIP1 (Huntingtin-interacting protein 1) was identified as a protein that associates with huntingtin. Binding of HIP1 to huntingtin is dramatically reduced following polyglutamine expansion, strongly implicating this interaction in the disease process. Huntingtin has also been shown to interact with the following proteins: GAPDH, HAP1, HIP7 (Huntingtin-interacting protein 7, Optineurin) and HIP2 (Huntingtin-interacting protein 2). HIP2 is a ubiquitin conjugating enzyme which binds selectively to a large region at the N-terminus of huntingtin. HIP2-driven ubiquitination of huntingtin marks it for selective degradation via the proteasomal pathway. HIP2 may mediate foam cell formation by the suppression of apoptosis.

HIP9 (Huntingtin-interacting protein 9) is the alpha subunit of the adaptor protein complex 2 (AP-2) which participates in membrane traffic pathways. AP-2 plays a key role in clathrin-dependent endocytosis. Cargo proteins are ferried into clathrin-coated vesicles (CCVs) which fuse with the early endosome. HIP9 (AP-2 alpha subunit) is responsible for orienting AP-2 on the membrane (binding accessible polyphosphoinositide-decontaining lipids) and also recognizing and binding to endocytosis signal motif [ED]-X-X-X-[L,I] of endocytic transmembrane accessory proteins via its C-terminal cytosolic tail.

HIP14 is a novel huntingtin-interacting protein. Its interaction with huntingtin is inversely correlated to the polyglutamine length of huntingtin. HIP14 protein, which is enriched in the brain, has been reported to show partial co-localization with huntingtin in the striatum. It is found in a subset of neurons affected in HD. One related protein is HIP14-like (HIP14L), which has 69% homology to HIP14.

Huntingtin-associated protein-1 (HAP1) is highly expressed in brain and has been demonstrated to mediate the neuropathology of HD. HAP1 interacts with huntingtin, with two cytoskeletal proteins (dyactin and pericentriolar autoantigen protein 1) and with a hepatocyte growth factor regulated tyrosine kinase substrate. The interactions with cytoskeletal proteins and a kinase substrate indicate a role for HAP1 in vesicular trafficking or organelle transport.
# Products for HD research

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