Chapter VI

1 Discussion

When this work was begun, the function of the wtHtt remained a mystery. Since then two studies reported putative functions, either as part of an iron-regulatory pathway or membrane fusion processes (Hattula and Peranen, 2000; Hilditch-Maguire et al., 2000). The study presented here sought to address the question of wtHtt function as well.

Neuronal striatal cell lines that model cellular behaviour *in vivo* were used to study Htt effects. When challenged with an apoptotic stimulus, wtHtt expressing cells are protected, whereas muHtt cells are sensitized. This effect is observed when the N548 Htt truncation is expressed. Furthermore, even full length Htt constructs show the same apoptotic characteristics as the N548 truncation mutants (data not shown). Further deletion of the protein to an N-terminal 63aa fragment results in the loss of the pro-survival effect (data not shown). These data indicate that the protective effect of wtHtt requires at least a segment of the protein between aa63 and aa548. All the effects described here are verified in different clones of wtHtt or muHtt expressing cell lines and therefore do not represent a random integration effect of the stably transfected plasmids.

Previous work demonstrated that homozygous mice with a targeted disruption in the Htt gene do not survive to term and suffer early post-implantation embryonic lethality (Duyao et al., 1995; Nasir et al., 1995; White et al., 1997; Zeitlin et al., 1995). More recent morphometric and ultrastructural analysis performed on heterozygous mice, which survive to adulthood, identified neuronal loss with signs of apoptosis in the basal ganglia of adult animals (O'Kusky et al., 1999).

In the ST14A system, wtHtt specifically interferes with the cell death machinery. Serum withdrawal and differentiation leads to apoptotic death in parental cells. In contrast, these stimuli are ineffective in cells expressing wtHtt. The data indicate that wtHtt directly influences cell survival by acting as an anti-apoptotic protein during brain development. Htt is also an important survival factor earlier in development since its absence evokes increased apoptosis in the epiblast, a structure of the embryo known to give rise to the future ectoderm (Duyao et al., 1995). Moreover, Htt is upregulated in some cancer cell lines, potentially taking part in their cellular transformation and thus enabling them to escape apoptotic anti-cancer surveillance mechanisms. Taken together, these data indicate that wtHtt indeed acts mainly as a pro-survival, anti-apoptotic protein.

The anti-apoptotic activity of wtHtt is localized to caspase-9, more specifically to the catalytic domain of caspase-9, as this domain mediates interaction between the two proteins. Interaction is most likely not direct but requires additional cellular factors that either stabilize it, or serve as adapters. The identity of these factors remains unknown. As a consequence of wtHtt interaction, cells are protected from several apoptotic stimuli, including DR and mitochondria-induced apoptosis. cytochrome c-release is not affected, but caspase-9 processing is inhibited and caspase-9 activity is suppressed, as well as activity of downstream caspase-3 (data not shown)(Rigamonti et al., 2000). Indeed, wtHtt completely suppresses all caspase-9 activity, but is unable to prevent some caspase-9 processing. This is probably due to processing of caspase-9 by some caspase-9-independent mechanism, as the occurrence of the p35 cleavage product is largely unaffected, but the p37 product is inhibited in an *in vitro* processing assay.

The molecular basis for the inhibitory effect possibly lies in the observed interaction between caspase-9 and Htt. Interaction only takes place with the zymogen form of caspase-9, but not with the active enzyme. Therefore, Htt inhibits a step upstream of caspase-9 activation. Caspase-9 is activated in (at least) two steps: Cytochrome c-mediated oligomerization of Apaf-1 leads to the formation of the apoptosome, to which caspase-9 is recruited; this huge multi-protein complex activates caspase-9 by inducing a conformational change in the zymogen, which increases its intrinsic catalytic activity (Li et al., 1997; Stennicke et al., 1999), leading to auto-processing of caspase-9 molecules. Gel filtration experiments with apoptotic ST14A cell lines show inhibition of the widening of the Apaf-1 elution profile in Htt expressing cells, suggesting that formation of the apoptosome is disturbed by the presence of the N-terminal Htt fragment. This effect is partially observed with the muHtt fragment, indicating that muHtt still performs some functions of the wt protein.

Taken together, these data suggest a possible molecular mechanism for Htts anti-apoptotic activity (Fig.1). Htt interacts with the catalytic domain of caspase-9 and inhibits its catalytic activity. Possibly, as a side effect of binding to caspase-9, Htt also inhibits formation of a properly assembled apoptosome, likely brought about by steric hindrance due to its size. Furthermore, the ability of Htt to not only interact with caspase-9, but also with the catalytic domains of other initiator caspases, further stresses its function as mainly inhibiting catalytic activity. Thus, Htt acts like an IAP, preventing caspases to fully realize their catalytic potential (Goyal, 2001). The fact that the N-terminal fragment mediates interaction also suggests that the anti-apoptotic function of Htt becomes activated during apoptosis, again paralleling IAP. Regulation of the anti-apoptotic activity is potentially

brought about through phosphorylation by the anti-apoptotic protein kinase Akt, but further studies are needed to confirm this.

During HD striatal neurons are selectively eliminated by an apoptotic mechanism. How this mechanism is activated or why it takes years for clinical symptoms to develop is still unclear. While expanded poly-Q peptides are cytotoxic for a variety of cells, in HD mainly striatal neurons are killed (Sharp and Ross, 1996). This effect is likely brought about by the context of the larger Htt protein that might shield the poly-Q stretch from exposure. caspase-mediated release of the N-terminal cleavage fragment relieves some of the protection and leads to increased accumulation of the cleavage product, which activates apoptotic pathways, thus starting a self-amplifying loop that ultimately results in cell death. In fact, the ST14A cell system recapitulates this effect. MuHtt-N548 increases apoptosis by a variety of stimuli, whereas the full length muHtt exhibits decreased cytotoxic effects. While N548 muHtt cells are killed by serum withdrawal, BAD and caspase-3, FL-muHtt cells do not die by serum withdrawal (data not shown) (Rigamonti et al., 2000). Because the N548 fragment roughly corresponds to the released cleavage product, the ST14A-muHtt cells represent a model system for striatal neurons during HD. These cells, and by analogy all cells that have elevated levels of the N-terminal poly-Q expanded Htt fragment, become sensitized to a broader range of apoptotic stimuli. They eventually succumb after a critical threshold has been reached or a particular apoptotic pathway has finally been activated. Thus, the ST14A cell system reflects the situation *in vivo*.

However, this sensitization scenario still fails to explain the mechanisms of initial muHtt cleavage, but the observations made by FPLC

fractionation of ST14A lysates might provide an explanation. Even in ST14A cells kept at regular growth conditions, a Htt cleavage product of the same size and elution pattern as the overexpressed N-terminal fragment is observed. Why and how FL-Htt is cleaved to generate this fragment remains unclear. However, the presence of this fragment has grave consequences for HD pathology. If indeed a N-terminal Htt fragment is present at all times, this fragment will carry an expanded poly-Q in HD. But it is exactly this N-terminal muHtt fragment that sensitizes striatal neurons to apoptosis. Thus, no initial toxic insult is needed for neurodegeneration to occur, but it will happen rather "naturally".

The results in the ST14A system also explain the gain-of-function effect of muHtt. As shown, muHtt still protects weakly from a limited number of apoptotic stimuli (DR, BIK and BAK). However, it also activates pathways that lead to caspase-3 activation, thereby gaining additional functionality. It was shown previously that Htt colocalizes with caspase-8 and that expanded poly-Q peptides are able to activate caspase-8 (Sanchez et al., 1999). While this offers an explanation for muHtt-induced caspase-3 activation, it is not exclusive of other scenarios. Currently, a lot of work focuses on potential transcriptional effects of the nuclear muHtt fragment (Cha, 2000; Nucifora et al., 2001).

If wtHtt is an anti-apoptotic protein and muHtt is pro-apoptotic, the question arises whether wtHtt is able to protect from muHtt-induced cell death. Very recent studies with Htt -/- mice, which have been rescued by a YAC expressing FL-muHtt, are sterile and exhibit massive apoptosis in the testes (Leavitt et al., 2001). This phenotype is rescued by introduction of wtHtt, further confirming Htts anti-apoptotic function. It is unclear at this point, however, whether wtHtt is also able to rescue these mice from the

neurological HD phenotype that develops later in life. The data presented here suggests that wtHtt is not able to protect from muHtt, because the pathway engaged by muHtt activates the common arm of apoptosis downstream of Htts proposed point of action. However, special circumstances could exist in certain tissues, like testes, that allow wtHtt rescue from the detrimental effects of muHtt. If the observations presented here are correct, then striatal neurons cannot be protected and thus these mice are predicted to still develop HD.

Recently it has been shown that symptoms of HD are dependent on the continous presence of muHtt in a mouse model expressing muHtt Exon1 under inducible expression control (Yamamoto et al., 2000). As soon as expression of muHtt is turned off, the HD phenotype is arrested. Thus, the presence of muHtt is required for disease progression, suggesting that the apoptotic pathway engaged by muHtt is under strict control and is not able, once activated, to amplify itself.

These data, together with experiments described in this work, lend support to a "Trojan Horse" hypothesis (Fig. 1) of muHtt function. Since muHtt interacts with caspase-9 (in order to perform its wild type function), it acquires the potential to activate directly the downstream caspase-3. While this hypothesis is consistent with data showing poly-Q aggregation with caspase-8 (Sanchez et al., 1999), it, however, still needs to explain the observations that in experiments with primary striatal neurons muHtt acts in the nucleus to induce cell death, but not in the cytoplasm (Saudou et al., 1998). As a consequence of this observation, current thinking favours abnormaly regulated transcription by muHtt as a cause for neurodegeneration in HD.

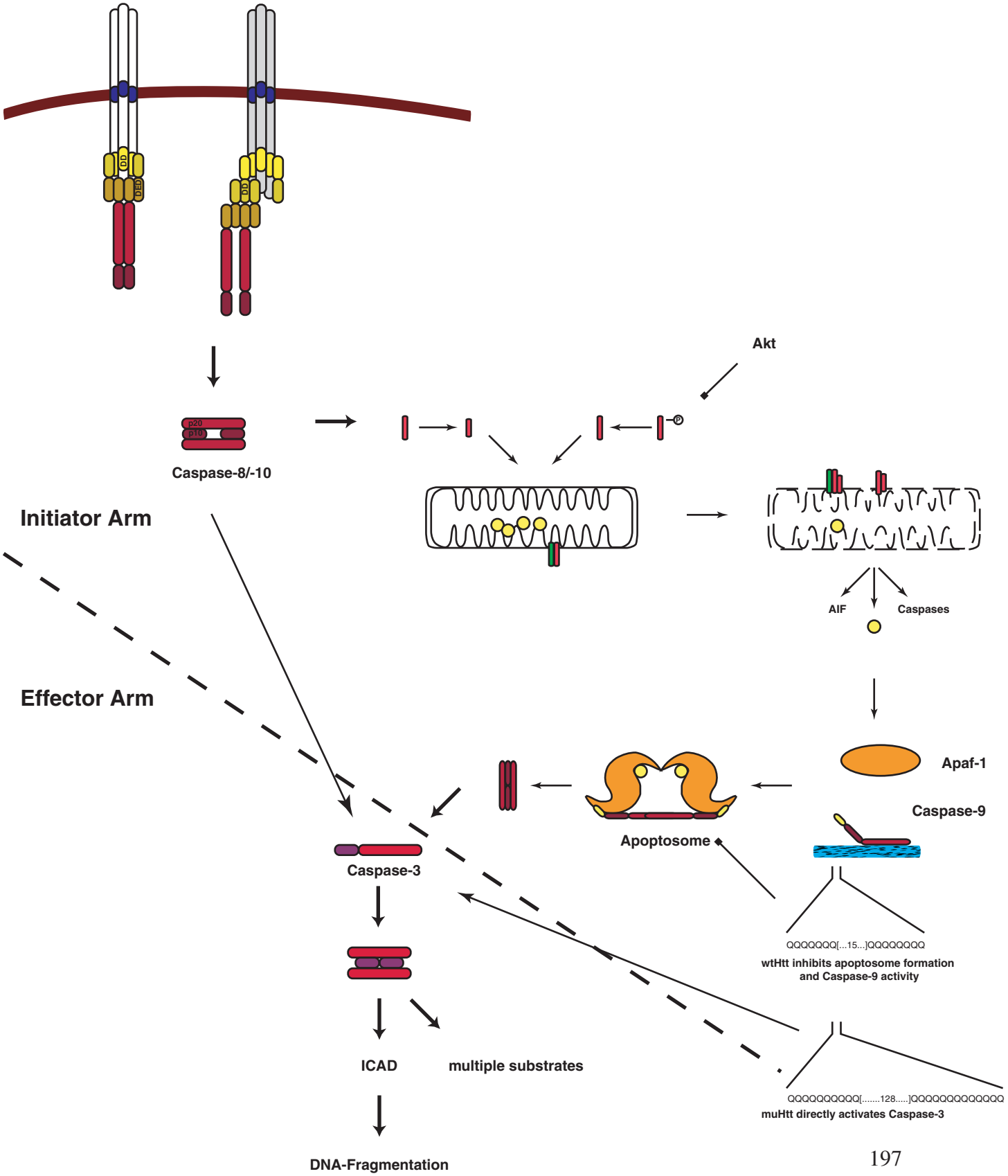
Nonetheless, the effects that are the basis for the "Trojan Horse" hypothesis are not only supported by observation in the ST14A system, but, importantly, also by data gathered in the *C. elegans* system. Both, CED-3 and CED-4, interact with muHtt, and nematodes expressing the N-terminal muHtt fragment increase their number of developmentally regulated programmed cell deaths. Because CED-3 and CED-4 constitute the (sole) core components of the *C. elegans* death machinery, interaction of muHtt with these molecules is the likely cause for CED-3 activation and apoptosis. Experiments are under way to further clarify the mechanism. By analogy, the same mechanism can be extrapolated to mammalian cells and thus represents a mechanism for HD pathology. If the "Trojan Horse" hypothesis is correct, the long incubation times of HD are explained by inefficient activation of caspase-3 by muHtt. Only when a certain threshold of caspase-3 activity is reached, will caspase-3 activate other parts of the cell death machinery. Possibly, a lifetime of accumulation of the N-terminal Htt fragment is needed to overcome the safety-catch mechanism of caspase-3 (Roy et al., 2001). Furthermore, ubiquitination of the abnormal Htt fragment and its subsequent degradation by the proteasome adds a second protective layer to counteract any detrimental Htt effects. Thus, it is conceivable that long incubation times are needed for HD to develop. Longer poly-Q stretches are more able to activate caspase-3, leading to juvenile onset HD.

Caspase-3 belongs to the common effector arm of apoptosis and acts downstream of caspase-8 and caspase-9. Furthermore, it directly cleaves ICAD, which leads to release and activation of CAD, the apoptotic DNase. If the protective function of wtHtt indeed acts at the level of caspase-9, then wtHtt is unable to protect from muHtt-induced apoptosis. This seems to be

the case, because if muHtt is expressed at similar levels as endogenous wtHtt in mice, these mice still develop HD symptoms (Hodgson et al., 1999).

In conclusion, a function of wtHtt is determined. Htt is an important anti-apoptotic protein that acts to prevent caspase-9 mediated apoptosis thus affecting the common effector arm of apoptosis. The molecular basis for its activity lies in the interaction between Htt and caspase-9, which prevents assembly of the apoptosome and activation of caspase-9. MuHtt retains some of the protective activity of the wt protein, markedly interaction with caspase-9. In this case, this effect is detrimental, as it introduces a "Trojan Horse" into a protective complex, which leads to direct activation of the downstream effector arm of apoptosis via caspase-3.

Overview of Apoptotic Pathways



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Appendix

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Bauer, J H; Li, Y and Vincenz, C 'WtHtt inhibits apoptosis through interaction with caspase-9' (manuscript in preparation)

Bauer, J H; Cho, S C; Ellis, R E and Vincenz, C 'MuHtt increases apoptosis in *C. elegans*' (manuscript in preparation)

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Abbreviations

aa	amino acid
Apaf	Apoptotic Protease Activating Factor
ATP	Adenosinetriphosphate
Bcl	B-cell lymphoma
BH	Bcl-2 homology
bp	Base Pairs
CAD	caspase-activated DNase
CARD	caspase Recruitment Domain
caspase	Cysteine Aspartase
CED	Cell Death Abnormal
CNS	Central Nervous System
D	Dalton
DD	Death Domain
DED	Death Effector Domain
DISC	Death-Inducing Signaling Complex
DN	Dominant-Negative
DNA	Deoxyribonucleicacid
DR	Death Receptor
(E)GFP	(Enhanced) Green Fluorescent Protein
Egl	Egg Laying Defective
FCS	Fetal Calf Serum
GST	Glutathione-S-Transferase
HD	Huntingtons Disease
Htt	Huntingtin
HSP	Heat Shock Protein
IAP	Inhibitor of Apoptosis

ICAD	Inhibitor of CAD
IIN	Intranuclear Inclusion Bodies
IP	Immunoprecipitation
NGF	Nerve Growth Factor
mu	mutant
R	Receptor
RNA	Ribonucleicacid
SF(D)M	Serum Free (Deprived) Medium
S/N	Supernatant
TNF	Tumor Necrosis Factor
TM	Transmembrane
TUNEL	Terminal Transferase-mediated dUTP Nick-End Labeling
wt	wild type

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Wang, X; **Bauer, J H**; Li, Y; Shao, Z; Zetoune, F S; Cattaneo, E and Claudius Vincenz 'Characterization of the p75NTR apoptotic signaling pathway using a novel cellular model' *Journal of Biological Chemistry* (in press)

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