Apoptotic Regulation by the Huntingtin Protein

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Abstract

Huntington's Disease is a neurodegenerative disease that leads to progressive cell death of a select set of neurons. It is caused by the expansion of a stretch of glutamines in the N-terminus of the Huntingtin (Htt) protein. This gain-of-function event results in increased apoptosis of striatal neurons. Wild-type (wt) Htt is an ubiquitously expressed protein whose function remains largely unknown. Mice with a targeted disruption of the Htt gene die early in utero.

In this work, the question of the function of wtHtt and the apoptotic pathways engaged by the poly-Q expanded mutant (mu) Htt is addressed. Results show that wtHtt is an anti-apoptotic protein that protects striatal cell lines from various apoptotic stimuli. Htt acts downstream of mitochondrial Cytochrome c release and interacts with the catalytic domain of Caspase-9. This interaction leads to decreased Cytochrome c-dependent cleavage of pro-Caspase-9 and decreased catalytic activity, probably through inhibition of proper apoptosome formation. The results also show that muHtt does retain some of the function of the wt protein, most markedly interaction with Caspase-9. In addition, muHtt induces apoptosis in striatal cell lines by a mechanism that involves Caspase-3 activation. Most importantly, pro-apoptotic activity of muHtt is also observed in C. elegans.

Zusammenfassung

Chorea Huntington (HD) ist eine autosomal-dominante, neurodegenerative Krankheit, die zu selektivem, progressivem neuronalen Zellverlust führt. Ursache ist eine Mutation im Gen IT15, das das Huntingtin (Htt) Protein kodiert. Die Folge ist eine pathogene Expansion einer Reihe von Glutaminen im N-terminus von Huntingtin, was in Apoptose von Neuronen im Striatum resultiert. Wildtyp Htt ist ein ubiquitär exprimiertes Protein unbekannter Funktion. Mäuse, in denen Htt Expression durch homologe Rekombination ausgeschaltet wurde, sterben früh während der Schwangerschaft in utero.

Die Funktion wtHtts und die pro-apoptotischen Signalwege poly-Q mutierten (mu) Htts werden in dieser Arbeit untersucht. Die Ergebnisse zeigen, daß wtHtt anti-apoptotisch in einem neuronalem Zellkulturmodel wirkt. Diese anti-apoptotische Funktion entfaltet sich nach Cytochrom c-Efflux aus den Mitochondrien durch Interaktion mit der katalytischen Domäne von Caspase-9. Dies führt zu reduzierter katalytischer Aktivität von Caspase-9. MuHtt zeigt einige Funktionalitäten wtHtts, einschließlich Interaktion mit Caspase-9. Darüberhinaus aktiviert muHtt pro-apoptotische Signalwege. Diese pro-apototische Wirkung ist reproduzierbar in C. elegans.

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'There is a theory which states that if ever anyone discovers exactly what the Universe is for and why it is here, it will instantly disappear and be replaced by something even more bizarre and inexplicable.

There is another, which states that this has already happened.'

(Adams, 1980)

'I'll make you feel something anon if my art fail me not!'

(Marlowe, 1616)