Transcriptional Dysregulation in Huntington's Disease

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Huntington's disease (HD) is an inherited neurological disorder that presents in adulthood (see Chaps. 48, 49). It is characterized by involuntary movements known as chorea, as well as cognitive impairments, personality changes, depression and behavioral disturbances. These changes are elicited in response to neurodegeneration of the caudate and putamen, beginning with the medium spiny neurons, as well as of specific regions of the cortex during later stages of the disease. HD is caused by a CAG expansion in the first coding exon of the huntingtin gene, resulting in a polyglutamine expansion in the huntingtin protein (Htt). Polyglutamine expansions are linked to striatal atrophy and the aggregation of huntingtin into inclusion bodies. The number of expansions influences both presence of the disease and the age of onset, with more expansions leading to a more severe phenotype. The striatal cell death is believed to be linked to widespread dysregulation of transcriptional regulation.

Microarray studies have shown changes in the expression profile of brain tissue of HD patients that are apparent before neurological symptoms present. A number of pathways have been implicated in HD that involve transcriptional regulation either directly by mutant Htt, or by altering the activity of transcriptional regulatory proteins interacting with the mutant protein. Htt can directly bind DNA or co-repressor complexes. Transcriptional regulators known to interact with Htt include specificity protein 1 (Sp1), TATA-box-binding protein-associated factor II, 130kDa(TAFII130), cAMP-response–element binding protein (CREB) and repressor element 1-silencing transcription factor/neuron-restrictive silencing factor (REST/NRSF) (Buckley, N. J., et al. 2010).

The interaction of Htt with these transcriptional regulators has been examined for clues as

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to their potential importance in HD. Mutant Htt can interact with CBP (CREB binding protein) that has histone acetyltransferase activity, suggesting that histone modifications may be implicated in gene expression changes occurring in HD. The transcription factor Sp1 has been shown to interact with mutant Htt with a greater affinity than wild type Htt. Although levels of Sp1 are not decreased in HD, the association of Sp1 binding with its target genes is interrupted by mutant Htt (Cha, J. H., 2007).

Htt binds to two intermediate proteins that interact with the transcriptional repressor REST, which causes REST to sequester in the cytoplasm. Mutant Htt disrupts this process, and allows REST to enter the nucleus, where it represses BDNF expression. One hypothesis of the cause of striatal cell death in HD is due to the loss of trophic support provided by the growth factor brain derived neurotrophic factor (BDNF). Wild-type Htt protein can activate BDNF gene transcription, whereas mutant Htt represses BNDF gene transcription. Microarray studies of gene expression changes show a substantial number of REST target genes are altered in HD brains. REST acts to silence gene expression by recruiting histone deacetylases such as HDAC1 and HDAC2 as well as histone demethylases, histone methyltransferases and chromatin remodelling factors. Thus, REST has a large number of potential neuronal targets, and may exert a large influence on the neuronal transcriptome.

REST is also a regulator of noncoding mRNAs, including micro RNAs (miRNAs). Micro RNAs are short, noncoding RNAs that play a major role in post-transcriptional regulation. The expression of several miRNAs is decreased in HD, and in both mouse models of HD and in human tissue samples, predicted REST target miRNAs are dysregulated. Interestingly, their expression profiles show regional variation, suggesting regulation is differentially modulated across cell types, which may be related to the observation that Htt toxicity is localized, whereas

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Htt is expressed in many cell types. Htt protein stabilizes the interaction of Argonaut with processing bodies, two key players in the microRNA silencing pathway. Argonaut proteins sequester target mRNAs to cytoplasmic structures. In the presence of mutant Htt, microRNA silencing was shown to be greatly impaired (Savas, J. N., et al. 2008). The loss of miRNA silencing has been linked to degeneration of Purkinje neurons, and may suggest another means by which neurodegeneration occurs in HD. Further, microRNA dysregulation has been linked to a number of other disorders, including cancer, neurodegeneration and psychiatric disorders.

References

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