Rhes and the HD protein: another pathological interaction

Researchers at Johns Hopkins have discovered that a protein called rhes binds to the HD protein and causes toxicity. Rhes is a protein found mostly in the striatum where brain damage is most extensive in Huntington's Disease. It plays an important role in dopamine signaling in the medium spiny neurons; these are the neurons most affected by the disease.

The research team lead by Dr. Solomon Snyder looked at the effect of over and under expressing rhes in various cell models of the disease. In a mouse striatal cell line, survival time was the same for wild type (normal) or HD (knock in) cells as long as rhes was absent. When rhes was overexpressed, survival time decreased by 60 percent in the HD cell but not the normal one.

The mechanism by which this occurs is sumoylation. SUMO is a Small Ubiquitin-like Modifying protein. The SUMO protein is attached or detached to another protein as part of a post-translational process which modifies the protein's function.

Sumoylation is known to contribute to HD pathology. In 2004, Dr. Joan Steffan and colleagues found that sumoylation decreases aggregation of the HD protein (the soluble HD protein is more toxic than the aggregates), masks a signal for the HD protein to stay in the cytoplasm, and promotes the dysregulation of gene transcription in the nucleus of the cell. Dr. Steffan and her team suggest that disrupting the sumoylation of the HD protein could result in a significant treatment and notes that "The E3 ligase specific for attachment of SUMO-1 to Htt may present a particularly attractive therapeutic target" (p. 103).

The John Hopkins researchers found that rhes induces sumoylation of the HD protein and that overexpression of rhes increases sumoylation. Sumoylation occurs at specific lysines on the protein. When those lysines are mutated so that sumoylation can't take place, aggregates continue to be formed and cytoxicity is reversed. Using RNA interference to reduce the expression of the SUMO1 gene produced the same results while overexpression of the gene increased disaggregation and decreased survival time.

Dr. Snyder and his team plan further research to determine the effect of removing rhes from the HD mice.

The binding of the rhes protein to the HD protein and the subsequent induction of sumoylation may explain why the damage is greatest in the striatum in the disease. Significant damage also occurs in the cortex but the authors note that rhes is also expressed in the cortex although to a lesser degree. Rhes is not the only source of pathology however; there is no area of the brain that is unaffected by Huntington's Disease. Still, preventing the sumoylation of the HD protein could be a significant treatment for the disease and blocking the binding of rhes and the HD protein offers another target to do that.

References:

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