NEURODEGENERATIVE DISEASE

Allies in the fight against neurodegeneration

Huntington's disease is caused by expanded polyglutamine (polyQ) repeats in the huntingtin protein (HTT). The build up of mutant HTT into intracellular deposits known as inclusion bodies as well as the selective death of striatal and cortical neurons are hallmarks of this disease. However, the effect of inclusion bodies on neurodegeneration — whether it is pathogenic, beneficial or incidental — has been much disputed. Now, Finkbeiner and colleagues provide some evidence to settle this debate with an innovative new approach, showing that these deposits are firm allies in the fight against neurodegeneration.

Finkbeiner and colleagues developed an ingenious robotic microscope imaging system that can follow the survival of individual neurons, intracellular levels of mutant HTT and the formation of inclusion bodies in the same cells over several days to help them to understand changes in the risk of cell death that occur over time.

The results showed that neuronal death was related to the length of polyQ expansions in HTT. This effect remained constant over time and was therefore not related to an increase in the size or number of inclusion bodies over the same time period, nor was it related to the formation of inclusion bodies. Instead, it seems that polyQ expansion causes toxicity in more diffuse forms of HTT, independent of its effect on levels of intracellular HTT, and this triggers an increased risk of cell death. Higher levels of this toxic diffuse HTT were associated with earlier formation of inclusion bodies.

Finkbeiner and colleagues went on to investigate the relationship between inclusion-body formation and neurodegeneration in more detail. They report that higher levels of these toxic diffuse forms of HTT were more likely to lead to the development of inclusion bodies in neurons. In a comparison of subpopulations of neurons that were closely matched for initial levels of expression of diffuse HTT, inclusion-body formation was associated with a decrease in the diffuse forms of intracellular HTT and, consequently, prolonged cell survival.

Therefore, these results support the idea that inclusion bodies protect neurons by decreasing the levels of toxic diffuse forms of mutant HTT, which, the authors speculate, prevents them from acting on crucial intracellular targets. Moreover, the method is just as noteworthy as the results, as it provides a valuable new tool that could be used to determine the nature of cellular changes in relation to the pathogenesis of other diseases.

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References and links

ORIGINAL RESEARCH PAPER Arrasate, M., Mitra, S., Schweitzer, E. S., Segal, M. R. & Finkbeiner, S. Inclusion body formation reduces levels of mutant huntingtin and the risk of neuronal death. *Nature* **431**, 805–810 (2004)

FURTHER READING Orr, H. T. Neuron protection agency. *Nature* **431**, 747–748 (2004)