Friedreich's Ataxia: From Molecular Biology to the Quest for Therapies

Friedreich's ataxia (FA) is the most common hereditary recessive ataxia, affecting 4-5 in 100,000 among the population of Indo-European origin, and there is currently no effective cure or treatment. FA is predominantly (but not exclusively) a neurodegenerative disease, mainly affecting the deep cerebellar nuclei, spinal cord, dorsal root ganglia and cardiac tissue. FA results from a deficiency of the protein frataxin brought about in most cases by a repeat expansion in intron 1 of the FXN gene. Frataxin is a nuclear genome-encoded protein which is largely localized to mitochondria where it may play major roles in the regulation of iron-sulfur cluster biogenesis and the response to oxidative stress. FA has usually a very early onset, and it may serve as a very useful model for other neurodegenerative diseases in which mitochondrial dysfunction also plays a crucial role.

We have developed distinct neural cell models to study the molecular mechanisms underlying the degenerative process triggered by the frataxin deficiency. These cell models are also being used to test potential therapeutic strategies, particularly those focused on identifying molecules (drugs or genes) capable of compensating for the functional defects induced by the loss of frataxin, or that are capable of efficiently increasing the expression of frataxin.

The techniques of gene transfer constitute a promising therapeutic possibility to treat FA and other neurogenetic diseases. Our group has also considered a gene therapy approach for FA that involves introducing correct copies of the entire genomic frataxin "locus". We are now attempting to optimize the route of administration and the delivery and distribution of both viral and non-viral vectors in the spinocerebellar system. Furthermore, we are also investigating the possible application of vectors that may carry other neuroprotective genes with a particular emphasis on neurotrophic factors.

References
