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Discovery of Molecular Protection Linked to Kennedy’s Disease

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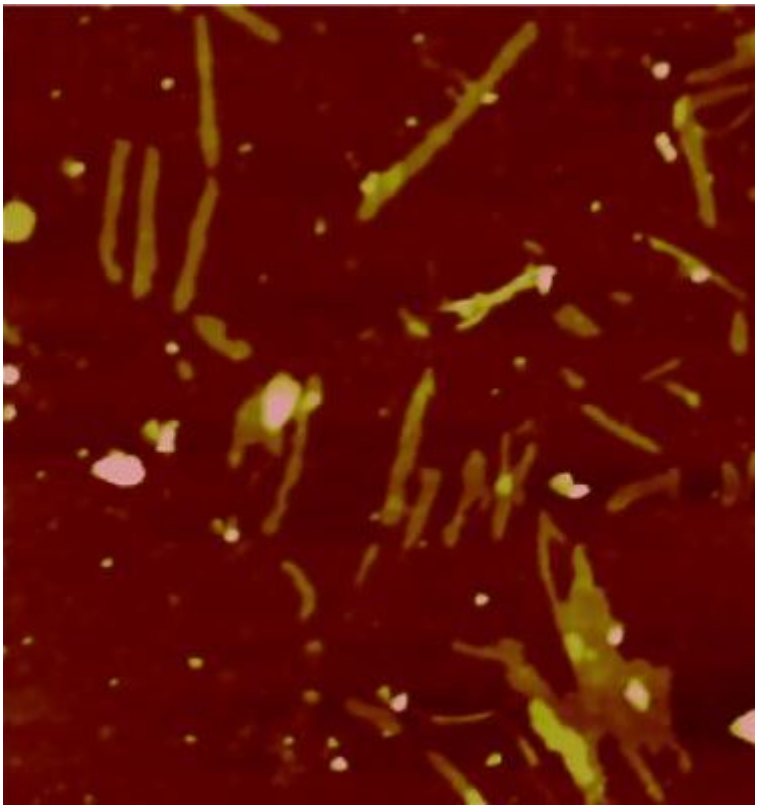

Protein Androgen Receptor forms aggregates that damage muscle and motor neuron cells in Kennedy's Disease. Credit: B. Eftekharzadeh, Institute for Research in Biomedicine Barcelona

Kennedy’s disease is a degenerative neuromuscular disease that leads to progressive muscle wastage, affects only men while appearing between 40 and 50 years of age.

In individuals with this disease, muscle cells and motor neurons die over the years because they accumulate a protein that is mutated.

Researchers have discovered that this protein has a self-protective mechanism through which the effects of the mutation are delayed.

In Kennedy’s disease, the muscle cells and motor neurons — the latter linked to muscle function, too — are damaged as a result of the accumulation of androgen receptor fibers, a process that causes them to die.

"Many aspects of diseases involving aggregates, such as Alzheimer’s and Parkinson’s, are unknown. In this regard, Kennedy’s disease is in a worse position because it is a rare condition,"

explains Xavier Salvatella, head of the Molecular Biophysics Lab at IRB Barcelona.

The onset of this genetically inherited disease occurs in late adulthood, affecting one in every 40,000 men and causing progressive deterioration of all muscles. Although not fatal, the condition is debilitating, and 20 percent of those affected eventually need a wheel chair.

Attacking the flanks of the protein

The mutation carried by those affected by Kennedy's disease causes a repeated and excessively long chain of a specific amino acid, namely glutamine, which impairs the activity of the androgen receptor. This protein, which activates the hormone testosterone, is responsible for triggering the genetic program that favor the differential characteristics of men: more hair, deep voice, larger hands, etc.

During adolescence, and depending on the extent to which they are affected, boys with the mutation do not fully develop the male phenotype, but this is often not diagnosed. In a second stage, in adulthood, muscle degeneration begins. It is known that the longer the polyglutamine chain, the earlier the onset of muscle atrophy. What we don't know and what this study helps us to understand is why the harmful effect is triggered when the length of the poly glutamine exceed 38 residues.

Using Nuclear Magnetic Resonance facilities in Europe, scientists have studied the protein in a test tube. They have observed that right next to the glutamine chain there is a region comprised by four leucine residues that allay the effects of the mutation. The leucine molecules favour the folding of the polyglutamine chain into a helix, a structure that prevents the chains from adhering to one another. However, the impact of the leucine molecule on the glutamine region is limited, and if there are many glutamine amino acids, the chains do not fold. Instead, they stretch out like rods, stick to each other, and end up forming a fibrous wall.

"We have seen that four leucine molecules delay this process. What would happen in the presence of six?" asks Salvatella. "Conceptually speaking, one clever way of delaying the aggregation could be to use drugs to strengthen the effect of the leucine residues that have so much influence on the mutation site that causes the protein to aggregate."
