Kennedy's Disease Association
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Good morning. My name is Jean-Marc Gallo, I work at King's College in London, England. I became interested in Kennedy's Disease because my department has a long standing interest in motor neuron diseases, especially amyotrophic lateral sclerosis, known in the US as Lou Gehrig's disease and Kennedy's disease was the first motor neuron disease for which a genetic defect had been identified. More specifically, what we are looking at is what could be common between Kennedy's Disease and other motor neuron disorders. We started by looking at aggregation and what we are doing now is to look at how the way neurons communicate with muscle can be disrupted in Kennedy's disease.

Unlike Dr Ellerby, I do not have a picture of where I work, but it is in rainy London, and certainly not as nice as California. The general idea of our approach is to find out what could be common between Kennedy's disease and other neurological diseases specifically affecting motor neurons. There are a number of such diseases have been well charactized to date. Apart from Kennedy's disease, of course, which is caused by a CAG repeat expansion in the androgen receptor gene, motor neuron diseases include Amyotrophic lateral sclerosis (ALS), known as Lou Gehrig's disease in the US. Most cases of ALS are sporadic, but abut 20% are familial. Within these familial cases, about 10% are caused by mutations in the gene coding for an enzyme, Cu/Zn superoxide dismutase. Since their discovery, the mechanisms by which Cu/Zn superoxide dismutase cause motor neuron disease has been a very active area of research, but this is still an unresolved question.

Other examples of motor neuron disease include Hereditary spastic paraplegias (HSP), that can have multiple genetic causes and spinal muscular atrophy, that mainly affects children. A first common feature of motor neuron diseases is abnormal protein aggregation in motor neurons. For instance, expanded androgen receptor forms inclusions in motor neurons in Kennedy's disease, and the formation of inclusion in the nucleus is a characteristic feature of all diseases caused by CAG expansions in the disease gene, such as Huntington's disease. Similarly mutant forms of superoxide dismutase associated with familial ALS also form inclusions in motor neurons. Aggregates are found in the nucleus and the cytoplasm of motor neurons, but also in axons. Axons are the long projections connecting motor neurons in the spinal cord with muscles and they can reach up to one meter. Signal from the motor neuron cell bodies in the spinal cord are transmitted through axons. Reciprocally, factors necessary for the survival of motor neurons, called neurotrophic factors are produced by muscle and transported to the cell bodies of motor neurons, also along axons. Therefore, communication between neurons and muscle requires a very sophisticated system to transport cargoes in both directions. This system is known as axonal transport. In axons, cargoes move along tracks made of filamentous organelles called microtubules and the movement is provided by a set of proteins collectively referred to as motor proteins.

For example, a protein called kinesin moves cargoes from the cell body towards muscle and another motor protein, called dynein move cargo in the opposite direction, form muscle to the cell body. This is called retrograde transport. **In the case of Kennedy's disease, a large aggregate of the androgen receptor in axons can physically block transport, and cargoes are actually stuck in traffic and cannot move.** This was originally shown by Angelo Poletti in neurons in culture. This leads us to a second general feature of motor neuron diseases, namely defects of axonal transport. As we have seen, axonal transport in motor neurons can be impaired by the presence of aggregates, but also as a consequence of genetic defects, in particular genetic defects affecting motor proteins. For example, Dr Fischbeck's laboratory has recently found that a disease resembling Kennedy's disease was caused by a mutation in the gene coding for a protein involved in retrograde transport, that is the transport of cargoes from muscles back to motor neurons. Similarly a chemically induced mouse mutant with motor neuron disease also bears a mutation in a retrograde transport protein. Finally, abnormalities of axonal transport have been shown demonstrated in animal models of ALS.

To come back to Kennedy's disease, in addition to the presence of axonal aggregates, axonal transport in Kennedy's disease could be perturbed by protein

changes secondary to the androgen receptor mutation. This could occur because of specific changes in gene expression, or because the expanded androgen receptor interferes with the binding of motor proteins to their cargoes or to microtubules. What we are doing is to identify such changes. For this, we are using two types of models, neurons cultured in vitro from normal animals in which we express the normal and Kennedy's disease version of the androgen receptor and tissue and cultured neurons from transgenic mice created by Dr Al La Spada. The first thing is to show that axonal transport is actually impaired. For this, we will follow and measure the movement of particles using high resolution computer-assisted microscopy in normal neurons and neurons carrying the Kennedy's disease mutation. To identify defects at the molecular level, we will use a modern approach, termed proteomics. For this purpose, we will isolate proteins binding to microtubules in motor neurons from normal and Kennedy's mice and identify proteins that are changed. This will be achieved using a technique called mass spectrometry that can actually 'weight' individual proteins. Based on this mass information, databases can be searched, so that proteins can be identified.

Dr Sobue has shown that high levels of testosterone, as found in men, as opposed to women are necessary for the disease to develop. Thus identifying changes that are regulated by testosterone will help identifying those protein changes that are particularly significant for Kennedy's disease.

Diane Merry, Ph.D.

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Thank you, Dr. Gallo, that was lovely. And perhaps while we're setting up Dr. Poletti's, talk, does anyone have any questions for Dr. Gallo? This idea of the axom, which is part of the nerve cell in the spinal cord and connects that nerve cell to the muscle, the idea that how molecules and important factors for nerve cells go back and forth between the muscle and the nerve cell is going to…be. You'll certainly probably hear more about it even this morning, and we'll be discussing it in fact this afternoon. Certainly a very provocative idea for one of the mechanisms in Kennedy's Disease.

Audience Question

Would spinal stenosis aggravate this? Make it worse?

Answer: Jean-Marc Gallo, Ph.D.

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I think anything that is having an impact on the overall function of the spinal cord would tend to make things worse.