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The Genetics of APOL1: How Does It Cause Disease?

Announcer:
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Dr. Pollak:
Hello, I'm Martin Pollak. I'm a Professor of Medicine at Harvard Medical School and Beth Israel Deaconess Medical Center in Boston. And I'm speaking about the genetics of APOL1-associated kidney disease and how it causes disease. So how do these two APOL1, what we call risk alleles, cause increased susceptibility to kidney disease in humans? So here is a schematic diagram, just a linear diagram of the APOL1 protein and its domains. APOL1 to the N-terminus, depending on the splice variant, it has or does not have a signal peptide. This is followed by what's known as the pore-forming domain, then a membrane-addressing domain, and then what's called the SRA-binding domain.

The SRA-binding domain is named because it binds to a protein made by African trypanosomes called SRA. The APOL1 kidney disease risk alleles are typically referred to as G1 and G2. Both are located in the C-terminal portion of the encoded protein. G1 refers to a pair of single nucleotide polymorphisms that change the coding sequence, and these two variants almost always inherited together. So a serine to glycine have risen to 342 and isoleucine to methionine at 384. Again, these are shared. They're basically inherited as a haplotype. There are very rare people with the first variant, but not the second, but 99% of the time they travel together.

The other variant that's relevant here is what we call G2. G2 refers to a deletion of two amino acids. It's an in-frame deletion, so we simply end up with a protein missing two amino acids, but then it continues to the C-terminus. What is the mechanism of disease? So one really important question regarding mechanism is whether these APOL1 risk alleles are loss of function or gain function. If I go back to the bottom of the slide, you can see here that what we call a high-risk APOL1 genotypes are those genotypes where a person inherits a risk variant from both mom and from dad. So you can have G1 from mom and G1 from dad, or G2/G2, or G1/G2. If you have 0, or just one of these risk alleles, then you're not at increased risk of kidney disease. So what's interesting here is that disease inheritance essentially follows a recessive pattern. People who inherit two of these risk alleles are at increased risk of kidney disease of various sorts.

So, are these risk alleles loss of function or gain of function? And this is an important question. Are these G1 and G2 variants somehow doing something bad to the kidney? Are they toxic? Or in the recessive state? If you have two of these variant forms of APOL1, are people losing some essential kidney function? And that has implications for how we might want to treat disease. Certainly, I think most of the community, including me, thinks that these risk variants are largely gain of function. When we express risk variant forms of APOL1 in cells and culture, we see toxicity. G0 is a little bit toxic to cells, the risk variant form is more toxic.

This is just one of many similar experiments that have been done by many people. In this case, this is an experiment we did in HEK293 cells. On the right is from a paper by Beckerman, et al, published in Nature Medicine fairly recently, in which APOL1, either G0 or the risk variant forms G1 or G2, are expressed in the podocyte of mice. Overexpression of G1 and G2 forms of APOL1 in mice cause a

glomerulosclerosis and podocyte phenotype, whereas overexpression of G0 did not in this study.

People have used a lot of different animal models to try to investigate APOL1 and APOL1 biology over the past several years. These include studies in fruit flies, in zebrafish, in yeast, and in a bunch of studies in mice as well. And for the most part, these are all, I think, consistent with the notion that these variant forms of APOL1 cause cell toxicity.

This is a picture showing an experiment that my colleagues and I performed. We developed BAC transgenic mice. So, we took the whole human gene in its normal human genomic context and put it into mice in the form of a transgene. And we made these in the G0 form, the G1 form, or the G2 form. These mice that have their transgenic for APOL1, none of them have any kidney phenotype at all in the normal state.

But, what happens when we expose these mice to interferon gamma? The interferon gamma is known to greatly upregulate the expression of APOL1 at the RNA level. When we cause these mice to express high levels of interferon gamma, we get essentially no phenotype in control mice, the black line, the G0/G0 transgenic mice, but we get considerable albuminuria in the G1/G1 mice and the G2/G2 mice. So the only difference between these mice, between the G0/G0 mice, and either the G1/G1 or G2/G2 mice are simply the differences that define these different alleles. And the mice with the risk variants have dramatic proteinuria compared to the mice without these variants. And this is true, not just in terms of proteinuria, but at the histologic level. You can see in the upper right that there's severe glomerulosclerosis in the G2/G2 mice, two weeks after interferon treatment, not in the G0/G0 mice.

So we believe APOL1 is toxic to cells. But how are they toxic? How do the G1 and G2 forms of APOL1 differ from the G0 form? There are a lot of hypotheses that are out there in the literature. These include possibility that the risk variant APOL1 forms a pore at the cell membrane or at other intracellular organelle membranes, and this altered pore, in the presence of risk variants, causes cell lysis. There's also some evidence that APOL1 risk variant forms enter the mitochondria and they open a pore in the inner mitochondrial membrane. Others have suggested that the risk variant forms of APOL1 misfold the endoplasmic reticulum and caused what's known as ER stress. It's also been suggested that APOL1 risk variant forms alter the structure of the podocyte, and may cause podocyte de-differentiation. These hypotheses are not mutually exclusive, and this is the subject of intensive investigation by many investigators. I'll wrap up now with that very short overview of APOL1 and how it causes kidney disease. And I thank you all for your attention.

Announcer:
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