the DISEASE THEY CALL FAT

SCIENTIST/RESEARCHER
PATRICK TSO, PHD

Transcript of Scientist/Researcher Video Episode 4

SCIENTIST/RESEARCHER

PATRICK TSO, PHD

Research in Intestinal Lymphatics

I was training in Australia with one of the masters of lymphatic system. So our lab was instrumental in setting up the conscious lymph fistula rat model. And the beauty of that is you actually have all the lymph from the intestine, continuously, free of anesthesia, and then you can put anything into the stomach or into the duodenum. And then looking at the transport, how the gut handles the lipid meal, where do they go, and all that.

In the lymphatics, it's a wonderful place to sample things produced by the intestine, and the intestine is one of the major organs that secretes two of the body's major incretins. Now, what incretins are – these are gastrointestinal hormones whose production by the gut is stimulated by nutrients. So by having these incretins, and then if you have elevated blood sugar, the pancreatic beta cells secrete insulin and then take care of the blood sugar.

So the incretins are secreted, and most people measure blood incretin in the blood. Only problem in the blood is, you can imagine, the blood dilutes at many fold very quickly, and secondly, the blood has a protease. It's called DPP4, which hydrolyzes it very rapidly. So you have a double disadvantage: more dilution, great rate of degradation. So that's probably not the best place for you to study them.

> **How does the lymphatic vessel change as a result of the arrangements in lipid metabolism? Until we begin to understand that process, you can physically remove fat, or it may even be lymphatic vessels. Only problem: that's going to come back. You have not cured the problem.**

So we came up with the idea that maybe the lymphatic system is a much better system to study them, and lo and behold, when we studied that, that's absolutely the case. In the case of the glucagon-like polypeptide one, GLP-1, the concentration is about ten-fold higher in lymph than in the portal blood, and in the case of GIP [gastric inhibitory polypeptide], it's about three to four-fold higher.

One of the things you may wonder is: so what, it's higher. The reason why this is important is because the concentration is higher in lymph; you do not need so much to measure them. And our lab is one of the only labs that I know of that can sample the lymph in the mouth, in a conscious mouth. So as a result, you can actually measure the lymph from the mouth in a conscious state, and whenever their gene is being manipulated.

Now, normally it's very difficult to measure them because the assay is just simply not sensitive enough, but because it's lymph, it actually allows these hormones to be measured. And now you open up a whole new research area, and that is you can now actually look at how manipulation of certain genes affects the incretin secretion by the gut?

The neurons and the dendritic cells, and other cells in the lamina propria, are exposed to that. So the lymphatic concentration is more of a refraction of the actual concentration that these cells and neurons are exposed to, not the very low concentration that you measure in the portal blood, nor in the systemic blood, which is even lower. So that is really one of the major research areas that we are engaged in. We're very excited about it, because through our work, we now may have actually discovered a third incretin.

> **Not until we get a better handle on first of all, lipid derangement, and secondly, lymphatic function, then I think we will probably be in a better position to tackle this very difficult problem and debilitating problem.**

Now, this third incretin is an incretin made by the small intestine. It's called Apolipoprotein A-IV. It's got a number of unique characteristics. It's a long-acting incretin, with very long half-life. Instead of few minutes, it's actually few hours, so it acts a long time, and it has a lot of other properties as well. And we think that there may be three incretins that work together to maintain blood sugar, but A-IV plays another important role. And that is Apo A-IV is made by the small intestine, and is only stimulated by fat absorption. So we think A-IV is the protein that links lipid and carbohydrate metabolism together.

And this research is quite exciting, and we published that research, and the concept of A-IV being an incretin has excited a company in Boston called Healthcare Ventures. They've actually licensed the technology, and are in the process of testing out whether it can be a potential diabetic drug for the treatment of Type 2 diabetes mostly, may even have applications in Type 1.

A lot of the research will have to be probably in vitro, because it's easier to do and you can control the experimental conditions so much better. However, we may want to also take advantage in the in vivo situation of baby rats, because they are very young. Everything in their body is working very well. And that may offer us a window to look at lymphatic function, and how actually, lipoprotein, lipids, excessive lipid, how does it affect the lymphatic function? What about lymphatic permeabilities? Lymphatic transport?

The Need to Understand Lymphatic Function

I think, Catherine, not until we get a better handle on first of all, lipid derangement, and secondly, lymphatic function, then I think we will probably be in a better position to tackle this very difficult problem and debilitating problem.

Our lab is mostly involved in the in vivo. We're one of the only groups that studies intestinal lymphatics quite regularly. Now that actually opens up a new area in the sense that there is fat tissue that is close by to the lymphatic vessels, and there are lot of fats in the gut. And people call them bad fat. They cause metabolic syndrome, a lot of that.

But I think there is not enough work done in vivo. When you take those fat cells out of their environment and study them, it's very different from when they're in their natural environment, you see them much better. The intestine and the stomach, they're talking to each other.

So when you get the nutrients by [passing] the stomach, and going directly to the small intestine, then it secretes the incretins, which stimulate, in turn, the secretion of insulin. That secretion of insulin is much higher than if you go through the stomach. So one of the first instincts is you say, "Well that's normal. Why are you so surprised?"

> **The problem is, first of all, what causes the derangement of lipid metabolism? And secondly, how does this lipid derangement affect lymphatic function? And I think once we begin to have a handle on these two problems, then you are in a much better position to be able to deal with this rather sticky problem.**

Because if you go directly to the small intestine, it's going to be empty faster, and by emptying faster, you're going to get a bigger incretin response, bigger insulin response. But the story is not so simple. Because what we find is that the stomach actually plays a very important role in regulating the amount of incretin and insulin secreted by the small intestine.

And at the end of the day, voila! Interesting, the regulation of blood sugar is perfectly normal, with less insulin being secreted. So we think the stomach has a very big role. Very tempting to speculate. People are doing a lot of gastric bypass surgery. Maybe what they're doing is they're making the incretins respond much faster and bigger, because now you take away the stomach factor as much, and so it corrects the blood sugar. But in the long run, is that, so to speak, without liability? I'm not sure. Only time can tell.

One of the things that I'm very interested in is to actually begin to properly culture the lymphatic vessels, and just to see in a culture system what they do. The beauty of it is that we actually will be able to correlate the data, from both in vivo as well as in vitro, to look at what's going on here. And then coupled with our strong background in lipid biochemistry, I think we may have a chance to crack a problem, this big problem. We have some clues, some insights.

How does the lymphatic vessel change as a result of the arrangements in lipid metabolism? Until we begin to understand that process, you can physically remove fat, or it may even be lymphatic vessels. Only problem: that's going to come back. You have not cured the problem.

The problem is, first of all, what causes the derangement of lipid metabolism? And secondly, how does this lipid derangement affect lymphatic function? And I think once we begin to have a handle on these two problems, then you are in a much better position to be able to deal with this rather sticky problem.

About Patrick Tso, PhD

Dr. Patrick Tso, a research scientist, is Professor, Director of the Mouse Metabolic Phenotype Center in the Pathology and Laboratory Medicine Department, Director, Physician Scientist Training Program in the Metabolic Diseases Institute at the University of Cincinnati, Ohio.

AMA citation

Tso, P. *Research in Intestinal Lymphatics.* [video interview]
http://DiseaseTheyCallFAT.tv/shop/lipedema/obesity/fat-cells/patrick-tso
The Lipedema Project; 2015.