

FUNCTIONAL MEDICINE UPDATE

December 2014

Vol. 34, No. 12

The Role of Insulin Signaling in Diabetes, Obesity, and Insulin Resistance

This issue concludes a three-part series on the topic of diabetes. In the previous two issues, Dr. Bland interviewed endocrinologist Dr. Phillip Kern about patient management and Dr. Osama Hamdy about the application of lifestyle intervention programs. This month, the focus shifts to the cellular and metabolic states of the body that influence the development of type 2 diabetes. Dr. Bland interviews renowned researcher C. Ronald Kahn, MD, Chief Academic Officer of the Joslin Diabetes Center. Dr. Kahn was a member of the team credited with the discovery that the insulin receptor is an insulin-stimulated receptor tyrosine kinase. Since that discovery, Dr. Kahn has focused on understanding how this event activates the complex signaling network that leads to the multiple actions of insulin.

Clinician/Researcher of the Month

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Dr. C. Ronald Kahn is a pioneer in the field of insulin signal transduction. He was the research director at the Joslin Diabetes Center from 1981 to 2000 and served as the president of Joslin from 2001 to 2007. He is currently the center's Chief Academic Officer. Dr. Kahn has authored more than 600 publications over the course of his career.

Tyrosine kinase activation within the insulin receptor and insulin receptor substrate activates the signaling network that leads to the multiple actions of insulin. This is a discovery Dr. Kahn and his team were credited with making in 1972, at a time when there was not a clear understanding of how or why individuals became diabetic. This discovery was a key event in moving the field of diabetes research forward, and Dr. Kahn has continued to be leading researcher in examining the mechanisms of insulin signaling.

The kinase signaling network is complex. During their discussion, Dr. Bland and Dr. Kahn attempt to provide clinicians with a better understanding of what takes place at the cellular level in patients who are diabetic and/or insulin resistant. They also discuss the role chronic inflammation can play in insulin signaling. Dr. Kahn explains the four most important tissues in insulin signaling: the liver, the fat cell, the beta cell, and—as demonstrated by emerging research—the brain. They discuss the concept of “type 3”

diabetes, which links insulin resistance to dementia and cognitive issues. Dr. Kahn provides his thoughts about the direction of this research.

In his recent published work, Dr. Kahn has focused on the cell physiology of different types of adipocytes (white, brown, and beige). Dr. Bland asks him to go into more detail about this work and the clinical ramifications. Dr. Kahn and his team are also doing research on the gut microbiome, trying to determine if there are microbiota that can promote more insulin sensitivity and others that would promote less insulin sensitivity. Research has shown that the gut microbiome can be influenced by environmental factors. The conversation turns to this area and the tools that are now available to study it. Dr. Kahn states that he sometimes calls the environment “the last frontier of medical research.” REF #1-5

Issue Synthesis

As he has now reached the end of this three-part series, Dr. Bland summarizes what has been elucidated through his interviews with these skilled clinicians and researchers. Diabetes is a consequence of multiple inputs from the environment sieved through the lens of multiple genotypes of individuals. Dysfunctions of metabolism arise clinically as altered parameters associated with glucose metabolism. There are multiple ways to end up with the diagnosis that is called type 2 diabetes. Because different pathways and connections between genes and environment are involved in this complex condition, the door opens for individualized therapy. Dr. Bland’s view is that “this is pretty excitingly complex.” He goes on to provide his own insights and recommendations about nutritional approaches to a personalized program. Ref #6-13

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