The case of a chase for the kinase

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We all acknowledge that a “syndrome” remains a “syndrome” until we understand the constellation of its clinical features well enough to link them together biologically and biochemically at the cellular level—then the syndrome graduates into a disease. At a distance, all cardiac surgeons can recognize the chunky patient waddling toward the hospital with a highly predictable catalog of problems. His or her obesity is “causing” hypertension, insulin resistance resulting in type II diabetes, hyperglycemia, hypertriglyceridemia, and low protective high-density lipoprotein levels. We reason that this “metabolic syndrome” must have something to do with dysfunctional cellular energy use and energy storage. But, we call it a “syndrome” because we really don’t know what is going on.

Potz and colleagues,¹ in the important accompanying article, have postulated that glycogen synthase kinase 3 β (GSK-3 β) is the culprit. GSK-3 β is a serine/threonine kinase, and like all the other hundreds of enzymatic kinases, GSK-3 β phosphorylates a signaling protein while phosphatases lop off that phosphate.^{2,3} The cellular signaling system is like a digital computer—you’ve either got a phosphate or you don’t. However, GSK-3 β is a likely offender, with a long criminal record of associations with type II diabetes, obesity, retinal ischemia, coronary artery disease, myocardial fibrosis, and exaggerated oxidative stress/inflammation. So, locking this guy up would seem logical. But, like all evolutionarily conserved enzymes, there must be some good buried down deep, and, indeed, GSK-3 β knockout is lethal—so we need to have some GSK-3 β activity.

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Central Message

We are now decoding the cellular signaling culprit of the “metabolic syndrome” as a kinase that controls the energy and inflammatory response to stress.

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The authors of the accompanying article¹ are to be commended for attempting to uncover the metabolic source of this “syndrome” that they reference as affecting 24% of the US population.⁴ But, dialing in just the right amount of GSK-3 β will likely prove a challenge. This problem is not biologically or sociologically unique, however. Like a nice glass of red wine or a cardiothoracic surgical residency, if it doesn’t kill you, it will make you tougher.

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