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IN FOCUS

Seeing the insulin receptor in action

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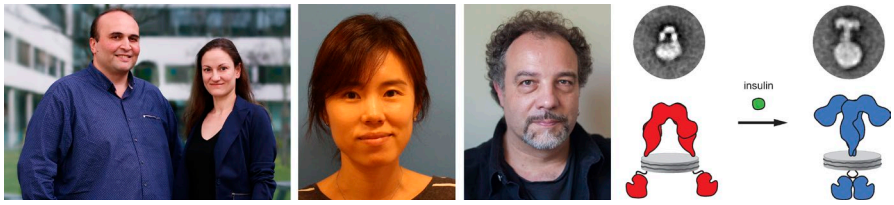
Researchers use single-particle electron microscopy to visualize an insulin-induced conformational shift that leads to receptor activation.



Focal Point (Left to right) Ünal Coskun, Theresia Gutmann, Kelly Kim, Thomas Walz, and (not pictured) Michal Grzybek perform single-particle electron microscopy on full-length human insulin receptors embedded in lipid nanodiscs and identify an insulin-induced conformational shift that brings together the receptor's intracellular kinase domains, enabling autophosphorylation and receptor activation. In the absence of insulin (left), the dimeric receptor's ectodomain adopts an inverted U-shape that separates the two transmembrane domains. In the presence of insulin (right), the ectodomain converts to a T-shaped conformation, bringing the receptor's transmembrane and intracellular domains together. COSKUN AND GUTMANN PHOTO COURTESY OF FRANZISKA CLAUSS. WALZ AND KIM PHOTOS COURTESY OF THE AUTHORS.

The insulin receptor has a central role in controlling cell metabolism and growth, and defects in insulin signaling are linked to a variety of diseases, including diabetes, cancer, and Alzheimer's disease. Despite its biological and medical importance, however, surprisingly little is known about how the receptor is activated in the presence of insulin. In this issue, Gutmann et al. use single-particle electron microscopy to visualize how the full-length insulin receptor changes its conformation in response to insulin binding so that it can initiate downstream signaling (1).

Most receptor tyrosine kinases dimerize in response to ligand binding, allowing the intracellular kinase domains to autophosphorylate and activate themselves. But, even in the absence of their ligand, insulin receptors exclusively exist as covalently-linked homodimers of two α and two β subunits, suggesting that insulin binding induces some sort of conformational change that results in receptor activation. Structural studies have largely focused on the ligand-binding ectodomain (2–4) or kinase domain fragments (5, 6). "But not much is known about how the full-length receptor behaves, particularly within membranes," explains Ünal Coskun, from the Paul Langerhans Institute in Dresden, Germany.

Indeed, previous attempts to visualize the full-length insulin receptor by electron microscopy failed to reveal any differences in receptor structure in the presence or absence of insulin (7). "So, the activation mechanism has remained elusive," says Theresia Gutmann, a graduate student in Coskun's laboratory. "I decided to try incorporating the full-length receptor into lipid nanodiscs to directly visualize the activation process."

Gutmann and colleagues reconstituted glycosylated, full-length human insulin receptors into lipid nanodiscs composed of phosphatidylcholine, sphingomyelin, and cholesterol, and then, with Thomas Walz and Kelly Kim at The Rockefeller University in New York, analyzed the receptor's structure by electron microscopy. "It was really important for us to collaborate with Tom because his lab has a long-standing expertise in studying growth factor receptors in nanodiscs," explains Coskun.

> "The [insulin receptor's] activation mechanism has remained elusive."

The researchers found that, in the absence of insulin, the receptor's ectodomain adopts an inverted U-shape, similar to the structures seen in previous studies of receptor fragments. In the presence of insulin, the ectodomain shifted to a T-shaped conformation that brings the transmembrane domains and in turn the intracellular kinase domains into close proximity. "The transition to the T conformation restricts the mobility of the kinase domains and appears to correlate with autophosphorylation and receptor activation," Coskun says.

These structural studies answer the basic question of how insulin activates its receptor, but the ability to observe nanodisc-embedded receptors by single-particle electron microscopy should allow the researchers to investigate the process in more detail. "One of our aims is to study how the membrane lipid composition will influence the structure and function of this and other receptors," says Coskun, whose laboratory has long been interested in how protein–lipid interactions modulate cell signaling.

The researchers also plan to examine how protein interaction partners influence insulin receptor activity and to investigate whether there are any differences between the two distinct isoforms of the receptor generated by alternative splicing. Finally, Coskun notes, the nanodisc system will enable researchers to optimize and screen for new drugs capable of modulating insulin receptor activation for potential therapeutic interventions.

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