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Not a Relay Race, but a Team Game: New Model for Signal Transduction in Cells

Among the key communication systems within a cell is the Wnt signaling pathway, which regulates embryonic development and whose deregulation can also contribute to cancer development. Scientists at the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now been able to close one of the last remaining gaps in our knowledge of this well studied sequence of biochemical signals. In doing so, they discovered that signal transduction actually happens in a way that differs from previous concepts.

Following the docking of one of the numerous members of the Wnt protein family at its specific binding site on the cell membrane, a signaling cascade is triggered that transmits messages via the cytoplasm to the nucleus. The cell responds to the signals by switching on or off specific genes. The very first step of this signaling pathway had remained unknown: What happens immediately after the Wnt proteins have docked at their receptors at the cell surface, called “Frizzled” and “LRP6”?

Using confocal microscopy, scientists of the Division of Molecular Embryology headed by **Professor Dr. Christof Niehrs** at the DKFZ have suceeded in live imaging of this process. In an article published in *Science*, the researchers describe how the Wnt signal induces the formation of large protein complexes close to the cell membrane composed of phosphate-labeled LRP6 and adaptor protein axin. Another component of the Wnt signaling pathway, the Dishevelled protein (Dvl), is vital for the formation of these aggregates. The scientists have shown that these are real protein complexes, rather than chance assemblies in a transport vesicle of the cell.

Niehrs and co-workers have developed a model to explain the formation of the aggregates termed “LRP6 signalosomes”. Thus, Wnt binding leads to a clustering of receptor proteins LRP6 and Frizzled, which form polymers with the aid of Dvl. This leads to a high density of the LPR6 receptor, which, in turn, facilitates LRP6 phosphorylation by kinase CK1γ and promotes the binding of axin.

Up to now, signal transduction within the cell has been imagined as a kind of relay race in which a protein passes the message to the next partner. The findings by Niehrs and collaborators now provide a completely new concept of intracellular communication. Like in many other biochemical processes – such as protein degradation by proteasomes or apoptosis – here, too, large protein polymers, like molecular machines, are required to bring together the participating reaction partners in a confined space.

Josipa Bilic, Gary Davidson, Ya-Lin Huang, Timo Zimmermann, Cristina Cruciat and Christof Niehrs: Wnt induces LRP6 signalosomes and promotes Dishevelled-dependent LRP6 phosphorylation. Science 316:1619, 2007

This press release is available at www.dkfz.de/pressemitteilungen

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