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Signaling Pathway in Cancer Cells Needs Acid:
New Targets for Tailor-Made Therapy?

What is known as the Wnt signaling pathway plays an important role during embryonic development and also in diseases such as cancer. When the Wnt protein binds to its receptor on the cell surface, this triggers several steps within the cell which ultimately lead to tumor suppressor genes being switched off and, thus, cell division is started. Not all of the individual steps of this signaling pathway are known in detail yet. In particular, the mechanism by which the Wnt protein activates the Wnt receptor when binding to it was still unclear. Scientists of the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have now made a substantial contribution to uncovering this mechanism. Their results have been published in the renowned specialist journal *Science*.

To find out which other components play a role in the Wnt signaling pathway, the research group headed by Christof Niehrs of the Division of Molecular Embryology studied human renal cells. Into these cells, the scientists transfected the luciferase gene, which emitted a light signal whenever the Wnt signaling pathway was activated by adding Wnt. Collaborating with colleagues from Michael Boutros' group of the Division of Signaling Pathways and Functional Genomics and using a whole-genome approach, they subsequently silenced 18,500 genes one after the other by adding small RNA molecules called small interfering RNAs. In those cells that no longer emitted light after adding Wnt, a crucial gene of the Wnt signaling pathway had apparently been switched off.

Taking a closer look at the cells which no longer showed a light signal, the researchers discovered two "old acquaintances". The first one is the prorenin receptor, which mediates the signal of the hypertension hormone renin. Children who have mutations in this receptor are often affected by mental retardation or epilepsy. This receptor also appears to mediate the Wnt signal together with the Wnt receptor. Another surprise has been the discovery that a "proton pump", which provides an acidic environment in cellular organelles, seem to be required to mediate the Wnt signal. It is known that this pump plays a role in various processes such as viral entry into cells, the onset of metastasis in cancer or left-right axis formation during embryonic development. Absence of this pump leads to premature death in many organisms.

"Our results raise further questions," says Christof Niehrs, looking ahead, "such as the role of the prorenin receptor in mental retardation. And the proton pump might be a promising target for therapy, such as by specific interference in the Wnt signaling pathway in cancer."

A picture for this press release is available at:
www.dkfz.de/de/presse/pressemitteilungen/2010/images/Fresh_Yellow_Lemon.jpg

Requirement of prorenin receptor and vacuolar H+-ATPase-mediated acidification for Wnt signaling.
Cruciat CM, Ohkawara B, Acebron SP, Karaulanov E, Reinhard C, Ingelfinger D, Boutros M, Niehrs C.
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The German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) is the largest biomedical research institute in Germany and is a member of the Helmholtz Association of National Research Centers. More than 2,000 staff members, including 850 scientists, are investigating the mechanisms of cancer and are working to identify cancer risk factors. They provide the foundations for developing novel approaches in the prevention, diagnosis, and treatment of cancer. In addition, the staff of the Cancer Information Service (KID) offers information about the widespread disease of cancer for patients, their families, and the general public. The Center

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