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Making Visible How Genes React

What exactly happens when a signaling molecule binds to the cell surface? The complex cellular reactions resulting from such a bond have now been made visible for the first time at a genetic level by a team of researchers headed by PD Dr. Dr. Peter E. Huber of the Deutsches Krebsforschungszentrum (German Cancer Research Center).

The researchers chose a well-known molecule for their investigations: The endogenous protein endostatin, which inhibits the formation of new blood vessels (angiogenesis) by endothelial cells. Tumors bigger than one or two millimeters need a supply of blood from the bloodstream. Treated with endostatin, tumors stop growing or even shrink, as was shown in 1998 in mice.

Using a DNA chip representing about 90 percent of the human genome, the scientists have investigated which genes of the endothelial cells are silenced or activated under the influence of endostatin. They found that the signaling molecule strongly intervenes in the cellular metabolism: A surprising 12 percent of genes studied showed significant changes in expression. These were no random findings: Detailed evaluation of the results at the gene and protein levels have revealed that the activity changes are based on a purposeful scheme.Genes with a known angiogenesis-stimulating effect were blocked, while those inhibiting blood supply were activated.

“We were successful in taking the first ever ‘snapshot’ documenting how genes react to a signaling molecule. In the process, we were able to identify genes formerly unknown to be associated with angiogenesis, which may provide targets for innovative tumor drugs”, said Peter Huber, commenting on the result. Tumor cells actively cause blood vessels to sprout new branches into the cancerous growth. Blocking this blood supply has been regarded as a promising treatment concept since the nineties. The first drug working according to this principle (Avastin) has recently been approved in the US for colorectal cancer. The advantage of the approach is that angiogenesis inhibitors, unlike other cancer drugs, do not target the genetically unstable cancer cells, but healthy, genetically stable endothelial cells. Scientists hope that this will delay the development of drug resistance, which often restricts the effectiveness of conventional chemotherapy.

Amir Abdollahi, Philip Hahnfeldt, Christian Maercker, Herman-Josef Gröne, Juergen Debus, Wilhelm Ansorge, Judah Folkman, Lynn Hlatky, and Peter E. Huber: Endostatin’s Antiangiogenic Signaling Network. Molecular Cell, Vol. 13, p. 649, 2004

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