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Self-regulating networks dictate the genetic program of tumor cells

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Scientists at Charité – Universitätsmedizin Berlin could explain a yet unknown regulatory network that controls the growth of tumor cells. Understanding such networks is an important task in molecular tumor biology in order to decode the relationships between the determinants defining which molecules are produced and in what quantities, in both normal and tumor cells. The study is published in the journal Molecular Systems Biology.

The growth of a tumor and its reaction to specifically targeted therapy is dictated by changes in its genetic material (mutations) encoding special signal molecules. These molecules activate the genetic program of tumor cells via branched signalingpathways and influence all processes needed for cell division, the mobility of cells and metastasis. Significant steering elements of these tumor-specific programs are called transcription factors. These are molecules that selectively control the transcription of the cell's genetic information (DNA) into messenger RNA and enable production of proteins . Altogether a complex network of mutually regulating transcription factors is activated.

Whereas the signal network in human tumors has already been characterized very well, it is hardly understood how transcription factors cooperate and regulate each other. In order to explain this transcription factor network, the scientists used a systems biology approach. A complex experimental data set—in which the transcription factors in tumor cells were systematically disrupted—was analyzed with the help of mathematical modeling. As a result, interactions within the network

could be reconstructed and the network controlling tumor growth clarified.

"Contrary to a current assumption, the results show that no superordinate transcription factor exists that controls the activity of other factors as a master regulator," explains Prof. Reinhold Schäfer, head of the Laboratory for Molecular Tumor Pathology and deputy director of the Charité Comprehensive Cancer Center. Instead, two hierarchical groups of interacting factors exist. Each of them activates gene sets needed for growth and cancer-specific properties of the cells. The results indicate that new therapeutic approaches against tumors must target multiple rather than singular factors and consider the network structures.

More information: Stelniec-Klotz I, Legewie S, Tchernitsa O, Witzel F, Klinger B, Sers C, Herzel H, Blüthgen N, Schäfer R. Reverse engineering a hierarchical regulatory network downstream of oncogenic KRAS. *Mol Syst Biol.* 2012 Jul 31;8:601. doi: 10.1038/msb.2012.32

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