Martin Frederik Dietrich
Dr. med.

The tumor suppressor LRP1b regulates cellular signaling and development through its extracellular domain

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Promotionsfach: Innere Medizin
Doktorvater: Professor Dr. med. Christof von Kalle

Lung cancer constitutes the single most lethal cancer entity worldwide. The positional cloning of chromosome 2q21 revealed *LRP-DIT*, a 600 kDa gigantic receptor and member of the Low-Density Lipoprotein receptor protein (LRP) gene family. This family of receptors has major physiological involvement in cargo transport and signal transduction in a variety of cellular and organ functions. *LRP-DIT* has been initially reported to be a major deletion in non-small cell lung cancer, and was further confirmed as a site of mutations in glioblastomas, cervical cancer, and other malignant diseases. The frequency of deletion and the combination of epigentic and genetic changes within the gene locus led to an assumed role as a tumor suppressor.

To understand the function of the different receptor domains, we created *LRP-DIT* deficient mice using a gene targeting approach. While mice expressing a truncated receptor covering exclusively the extracellular, but not intracellular or transmembrane domains, are phenotypically normal with regards to aging, fertility, and lack of tumor development, we describe the embryonic lethality in a model of a Lrp1b null mice. The observation of a rescuing effect of the extracellular domain has equally been made in other members of the LDL receptor gene family.

We could further demonstrate that the extracellular domain of the receptor is being secernated after cleavage by metalloproteases. With four ligand binding domains and a broad variety of known ligands, our work suggests that Lrp1b is processed and secreted into the extracellular space. It might serve then as a decoy or scavenger receptor to preserve a critical threshold in embryonic development. Given the similarities with cancer, further investigations should exploit whether this processing has physiological implications in cancer and other diseases.