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Another building block for personalized medicine for lung cancer is discovered

University of Cologne researchers identify a specific genetic change that predicts whether patients can respond to targeted therapy / Publication in 'The Journal of Clinical Investigation'

Squamous cell lung cancer is a lung cancer subtype that is particularly difficult to treat. A new study now has revealed a novel genetic alteration that occurs in some cases in this type of tumour and that may expose a weakness of the tumor for therapeutic intervention. The University of Cologne researchers led by Professor Roman Thomas, director of the Department of Translational Genomics, was able to show that a certain genetic change occurs during tumour formation and that a previously unknown oncogene is produced. Oncogenes are genes that promote the growth of tumours. In some cases, they can be inhibited by targeted drug treatments. This approach is often accompanied by a higher success rate and lower side effects compared to conventional chemotherapy. The scientists' discovery could therefore be a first step toward a more successful therapy of this particular type of cancer. The current study was published in *The Journal of Clinical Investigation* under the title 'Somatic rearrangements causing oncogenic ectodomain deletions of FGFR1 in squamous cell lung cancer'.

The new discovery concerns a genetic modification that leads to the removal of the 'extracellular domain' of the FGFR1 protein (fibroblast growth factor receptor). This domain plays a crucial role in the activation and regulation of the FGFR1 protein. FGFR1 can be found in the cell membrane that separates the cell from its environment. Thus, the protein has both points of contact with the cell interior and with the environment. The study shows that the loss of the extracellular domain, i.e. the part that protrudes outwards, leads to sustained growth signals in the tumour cells. The receptor no longer receives stop signals and the tumour continues to grow. One

positive aspect is that FGFR inhibitors are already being used in clinical practice, for example for the treatment of bladder cancer. Such inhibitors are drugs that specifically bind to proteins and deactivate them. “Hopefully, the new results will enable a new therapy option for a specific group of patients with squamous cell carcinoma of the lungs,” said Dr Florian Malchers, first author of the current study.

Thirteen years ago, scientists in Professor Thomas’ laboratory described the amplification of FGFR1 in squamous cell carcinoma of the lung for the first time. Amplification is the multiple occurrence of gene copies in a tumour. Unfortunately, a first clinical study showed that the mere presence of amplification as a selection criterion for personalized FGFR therapy in patients is not yet sufficient. Only 11 percent of patients benefited from treatment with an FGFR inhibitor. In this group of patients, the team has now been able to demonstrate a link between the genetic modification of the FGFR1 protein, the removal of the extracellular domain, and a significant decrease in tumour volume. These findings could therefore offer a new avenue of treatment for this group of patients.

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Further Information:

Original Study: https://www.jci.org/articles/view/170217#

Commentary to Study: https://www.jci.org/articles/view/174171

Link to Laboratory: www.translational-genomics.de

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