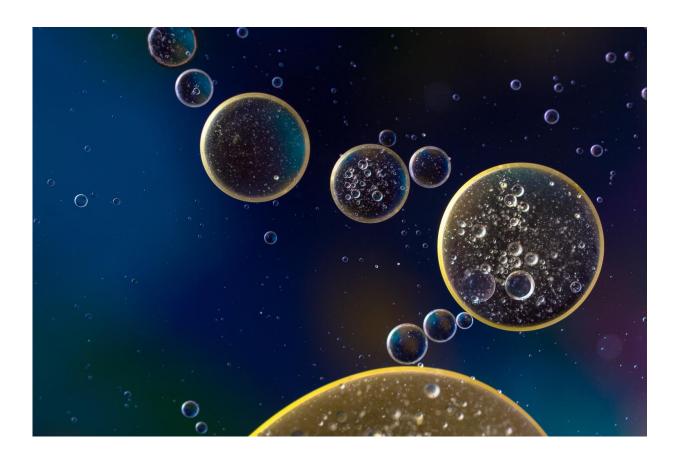


# Large-scale mapping of protein networks behind tumor growth in the lungs

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Researchers at the University of Copenhagen have used highly sophisticated molecular analyses to identify key proteins in the signaling pathways that cancers use to spread in the body. The study could help in



personalizing cancer treatment and developing new drugs.

Lung cancer is the biggest cause of cancer-related deaths in the world. There were 2 million new cases last year. After seven years of in-depth analysis of signaling networks in lung tissue, researchers at the University of Copenhagen are the first in the world to have mapped the networks of proteins that control the pathways used by <u>cancer cells</u> to spread in lung tissue.

The study, which has just been published in *Cell*, has also identified new proteins that are activated when cancer cells mutate and contribute to tumor growth.

"We have developed completely new methods to map the main signaling networks in lung tissue and the proteins that control the spread of cancer in lung tissue. We have done so to understand what is actually happening in cancer mutations. This may prove to be crucial, as we need to improve existing treatments to patients who often become resistant, and to develop new treatments that target newly identified proteins in the <a href="signaling pathway">signaling pathway</a> in tissue," says Professor Jesper Velgaard Olsen of the Novo Nordisk Foundation Center for Protein Research.

## Mapping cancer cell communication

The Novo Nordisk Foundation Center for Protein Research is an international leader in so-called mass spectrometric protein analysis, and in this study, researchers used the technology to quantify and map the signaling network of proteins in the lungs. They also compared their findings with analysis of cancer mutations from cancer patients in large databases.

Cell growth and division in tissues is controlled by a specific protein—a receptor—that sits on the outer membrane of cells. This so-called EGF



receptor acts as a communication channel between the environment outside the cell and its interior. The receptor transmits signals to the cell's "engine room" and dictates when the cell should grow or divide. In the case of cancer mutations, the cell receives an erroneous signal that leads to constant and unrestrained growth and division—and this can lead to tumor growth.

### Mapping is crucial in the fight against resistance

Several drug treatments, so-called <u>tyrosine kinase inhibitors</u>, are designed to inhibit the EGF receptor and thus slow down the activity of the receptor in cancer cells. Unfortunately, cancer cells can develop resistance to these treatments, hence the pressing need to take novel approaches in treating lung, liver and breast cancer, for example.

In normal cell growth, cells constantly receive signals from the EGF receptor that dictate whether a cell should grow or remain passive. However, cancers have a special ability to develop new mutations in the EGF receptor and other receptors that can evade existing cancer treatments with tyrosine kinase inhibitors that target the receptor. Now, scientists have succeeded in using the "cancer map" against the main protein networks to identify a particular mutation in the EGF receptor, which sends a constant signal to the cell about unrestrained growth and division.

The study has also shown that cancer cells can use tissue mutations to recruit other proteins that increase the cancer cell's growth potential. Using the cancer map will enable scientists in the future to see what happens when new cancer mutations occur. They can identify signaling pathways as well as the protein networks involved in the spread of cancer.

"Proteins act a bit like social networks, where they communicate with



each other on the basis of mutual interest and functionality. By revealing their communications, we can understand exactly what happens when a new mutation causes uncontrolled tumor growth. This type of mapping can enable us to determine and understand how the signaling or communication between proteins goes wrong in patients," says Associate Professor Alicia Lundby from the Department of Biomedical Sciences and Novo Nordisk Foundation Center for Protein Research.

#### Next step is to map all cancers

The signaling mechanisms in <u>lung tissue cells</u> are reminiscent of cellular communication in the rest of the body's tissues. The researchers have also looked into the <u>protein</u> networks that control the EGF receptors in liver <u>tissue</u> and the next step is to identify the rest of the body's tissues.

The results of the study are now publicly available and could have a major impact on cancer researchers worldwide who are working to crack the code of tumor growth for all kinds of <u>cancer</u>.

**More information:** Alicia Lundby et al, Oncogenic Mutations Rewire Signaling Pathways by Switching Protein Recruitment to Phosphotyrosine Sites, *Cell* (2019). DOI: 10.1016/j.cell.2019.09.008

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