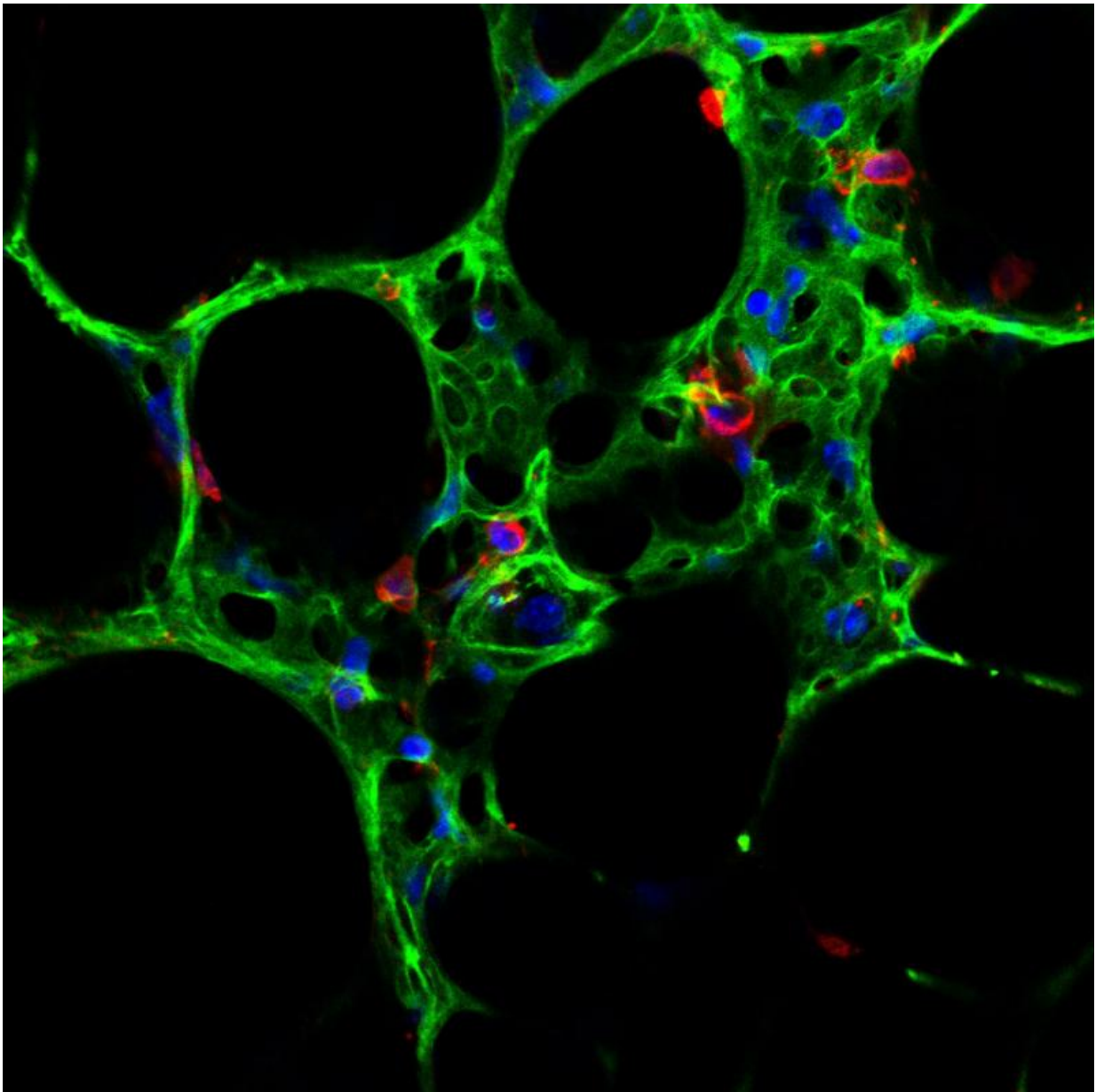


COPD – what causes the lungs to lose their ability to heal?

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The molecule Wnt5a prevents the repair of structures in the lung of COPD patients. Shown here are the alveolar epithelium (green) and immune cells (red). Credit: Helmholtz Zentrum München

In chronic obstructive pulmonary disease (COPD), the patients' lungs lose their ability to repair damages on their own. Scientists at the Helmholtz Zentrum München, partner in the German Center for Lung Research (DZL) now have a new idea as to why this might be so. In the *Journal of Experimental Medicine*, they blame the molecule Wnt5a for this problem.

The first indication of COPD is usually a chronic cough. As the disease progresses, the airways narrow and often pulmonary emphysema develops. This indicates irreversible expansion and damage to the alveoli, or air sacks. "The body is no longer able to repair the destroyed structures," explains Dr. Dr. Melanie Königshoff, head of the Research Unit Lung Repair and Regeneration (LRR) at the Comprehensive Pneumology Center (CPC) of Helmholtz Zentrum München. She and her team have made it their job to understand how this happens.

"In our current work we have been able to show that COPD results in a change in the messengers that lung cells use to communicate with one another," Königshoff continues. Specifically, the scientists discovered increased production of the Wnt5a molecule, which disrupts the classic (or canonical, as the experts call it) Wnt/beta-catenin [signaling pathway](#) that is responsible for such repairs.

The Wnt signaling pathway is one of many pathways for forwarding signals in order to allow cells to respond to external changes. The signaling pathway is named after its main player "Wnt", a signaling protein that takes on a key function in the development of various

animal cells as a local mediator. Numerous proteins are involved in the canonical (classic) forwarding of the signals, including beta-catenin as the central cellular messenger. A pathway in which Wnt acts through other messengers, as described here, is called a non-canonical signaling pathway; this can have a negative impact on the canonical signaling.

"Our working hypothesis was that the relationship between different Wnt messengers is no longer balanced in COPD," reports Dr. Hoeke Baarsma, LRR scientist and the study's first author. The team correspondingly searched for possible interference signals. "In both the pre-clinical model and the tissue samples from patients, we found that in COPD tissue particularly the non-canonical Wnt5a molecule is increased and occurs in a modified form." According to the authors, stimuli that typically cause a reaction in COPD, such as cigarette smoke, additionally lead to increased production of Wnt5a and consequently to impaired lung regeneration.

In the next step, the researchers were able to show where the misdirected signal originates: "It is produced by certain cells in the connective tissue, the so-called fibroblasts," Baarsma says. When pulmonary epithelial cells were treated with the Wnt5a derived from the fibroblasts, the cells lost their healing ability. The scientists were also able to use antibodies directed against Wnt5a in two different experimental models to slow down the lung destruction and better maintain the lung function.

"Our results show that the classic Wnt/beta-catenin signal cascade is disrupted by the Wnt5a ligand. This is a completely new mechanism in association with COPD and could lead to new therapeutic approaches, which are urgently needed for treatment," study leader Königshoff explains the importance of the results.

More information: Non-canonical WNT-5A signaling impairs 1 endogenous lung repair in COPD. *Journal of Experimental Medicine*,

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