Potential marker for success of immunotherapy in the treatment of lung cancer

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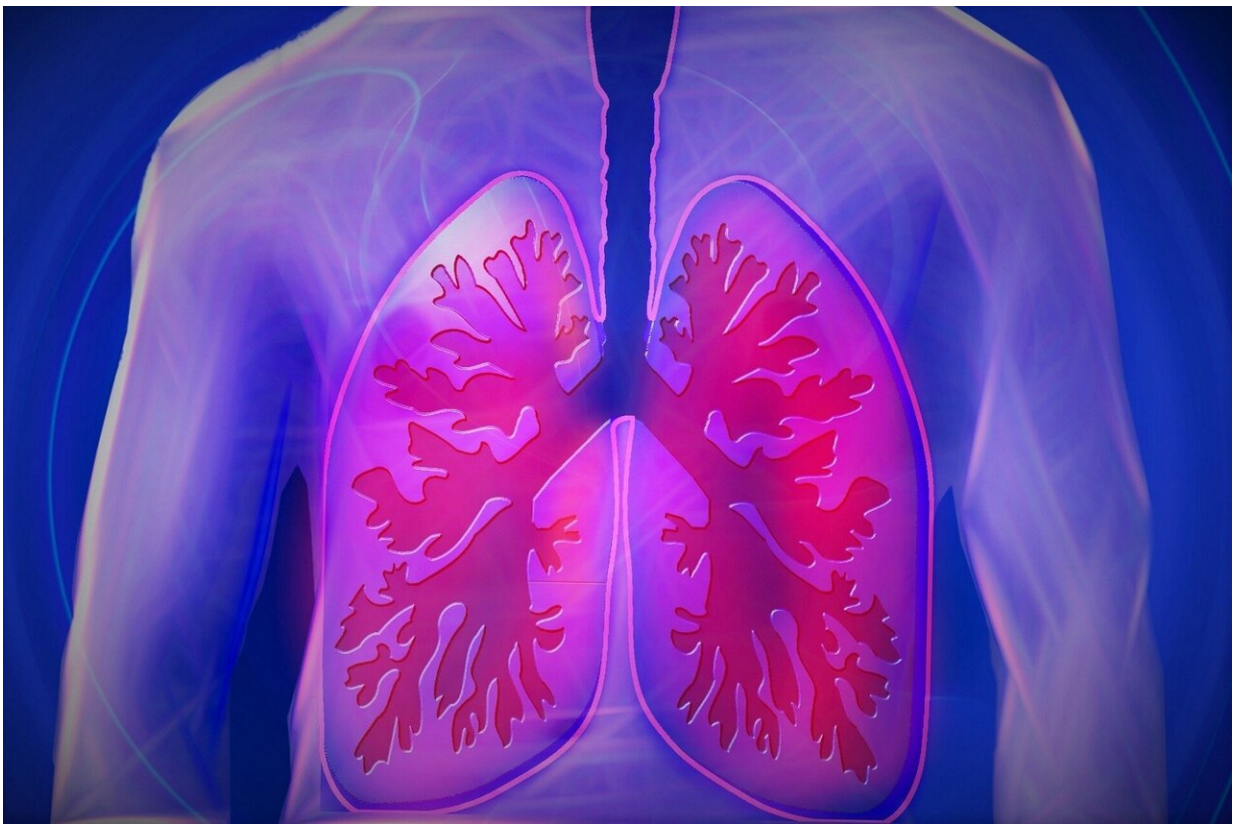

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Lung cancer has the highest mortality rate of all cancers, and treatment options are extremely limited, especially for patients with oncogenic

mutations in the KRAS gene. A great deal of hope was invested in the licensing of immune checkpoint inhibitors, but the reality is that some patients respond very well to this treatment while it is completely ineffective in others. In a paper just published in *Science Translational Medicine*, a MedUni Vienna research group led by Herwig Moll (Center for Physiology and Pharmacology) identified a potential marker for the success of immunotherapy in lung cancer patient and explained the underlying molecular processes.

KRAS it is a monomeric G protein that plays a key role in the growth of malignant tumors. KRAS-mutated lung carcinomas frequently occur in chronically inflamed lungs, particularly in heavy smokers. The inflammatory processes promote the growth of cancer cells. The research group has now shown that the expression of the highly anti-inflammatory protein A20, formed in the body itself, is often very low in these malignant cells and that there is a direct correlation between a patient's life expectancy and the expression of this protein. Moll explains: "Both in humans and in the animal model, the loss of A20 leads to downgraded immune surveillance of cancer cells. Cancer cells with low levels of A20 are able to escape detection by the immune system." This results in significantly faster tumor growth.

During the course of this study, which was co-funded by MedUni Vienna's Cancer Research Initiative and associated with the Comprehensive Cancer Center Vienna, the research team discovered that it is primarily an enhanced sensitivity of the cancer cells to the immunomodulatory cytokine interferon gamma that is responsible for this. Moreover, tumor cells with downregulated A20 responded particularly well to immune checkpoint inhibitors, in the same way as patients suffering from melanoma (skin cancer) with a similar gene expression structure.

"In A20 we have discovered a previously unknown tumor suppressor in

lung cancer, the loss of which as an immune checkpoint contributes to the development of this malignant disease," explains co-author Emilio Casanova from the Institute of Pharmacology. Since patients with low A20 expression have few tumor-fighting immune cells and so, in the advanced stage, express little of the important immune checkpoint molecule PD-L1, these patients could be excluded from immunotherapies directed against PD-L1. Indeed, the strength of expression of this molecule is currently regarded as an aid for deciding whether or not they should be treated with immune checkpoint inhibitors. "Based on our results and the data available from melanoma patients, we are convinced that we have identified a group of lung cancer patients who would really benefit from this immunotherapy. Exclusion from such treatment would significantly reduce the survival rate of such patients."

In a further study, the researchers want to find out whether it is possible to manipulate the expression of A20 in the cancer cells, in order to intensify the effect of immunotherapies. "However, smoking is still the most easily avoided risk factor for lung cancer. We must therefore support laws to protect the general public from inhaling harmful smoke, while at the same time appealing to people's personal responsibility to refrain from smoking altogether," says Moll. According to the MedUni Vienna experts, it is nevertheless important to continue to investigate new therapeutic approaches to improve the quality-of-life and chances of survival of those affected.

More information: Kristina Breitenecker et al, Down-regulation of A20 promotes immune escape of lung adenocarcinomas, *Science Translational Medicine* (2021). DOI: 10.1126/scitranslmed.abc3911

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