UNIVERSITÉ DE GENÈVE

PRESS RELEASE

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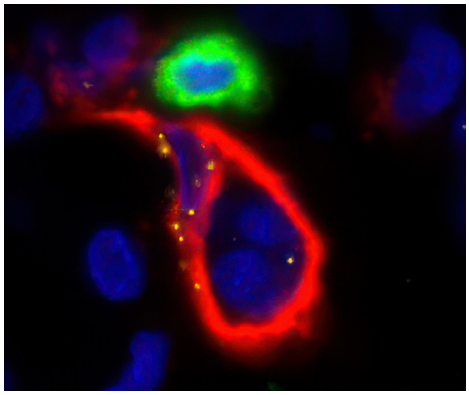
An enzyme to disarm tumours

UNIGE Scientists have discovered an enzyme in cancerous lymphatic cells whose properties enable the immune system to fight tumours more effectively.

When a tumour develops, it creates a structure around itself called the tumour stroma, within which blood and lymphatic vessels ensure nutritional and respiratory biological exchanges. Lymphangiogenesis, i.e. the development of lymphatic vessels, is generally associated with a poor prognosis, as it favours the spread of metastases to other organs. By studying the cells that make up the wall of lymphatic vessels, a team from the University of Geneva (UNIGE) has made an unexpected discovery: an enzyme they express appears to play a key role in supporting immune cells, particularly when they are activated by anti-tumour treatments. These results, published in *Nature Communications*, could pave the way for improving the effectiveness of immunotherapies.

Blocking lymphangiogenesis to limit the risk of metastasis? The idea seemed promising but turned out to be disappointing. "While it is true that lymphatic vessels promote metastasis, they are also essential for transporting immune cells and activating the anti-tumour immune response," explains Stéphanie Hugues, a full professor in the Department of Pathology and Immunology and at the Geneva Centre for Inflammation Research in UNIGE Faculty of Medicine, who led this research. "Their role is therefore more complex than we imagined, which is why we wanted to understand how the cells that make them up respond to the tumour microenvironment in order to influence the immune response."



Section of human melanoma showing the expression of the CH25H enzyme (in yellow) by lymphatic endothelial cells (in red, the lymphatic vessels), and their interaction with an anti-tumour immune cell (in green).

Pictures

An enzyme that blocks the tumour's defences

The research team measured the gene expression of lymphatic endothelial cells, the cells that make up the wall of lymphatic vessels, in melanoma and in healthy mouse skin. They detected an over-expression of an enzyme called CH25H in the lymphatic endothelial cells associated with the tumours, a result they confirmed in human beings: the more lymphatic vessels the melanomas contained, the more this enzyme was over-expressed. "What's more, patients with high levels of this enzyme had a better prognosis, an effect that was even more pronounced in those treated with a particular type of immunotherapy, the immune checkpoint inhibitors," explains Stéphanie Hugues.

This enzyme's function is to convert cholesterol into 25-hydroxycholesterol, a cholesterol metabolite important in antiviral immunity. In melanoma, this enzyme seems to also have an impact on the immune system, probably by undermining the tumour's defence mechanisms. Indeed, the tumour microenvironment naturally produces factors that inhibit the activation of immune cells. However, 25-hydroxycholesterol prevents this inhibition, and therefore enables better activation of anti-tumour immunity.

The multiple roles of lymphatic cells

Prof Hugues' team then deleted this enzyme in mouse lymphatic endothelial cells. Its absence led to a sharp drop in 25-hydroxycholesterol levels in the melanoma tumours, followed by a suppression of immune activity leading to a much less effective fight against the disease. In contrast, mice vaccinated with tumour antigens showed a clear increase in the expression of the CH25H enzyme and in the production of 25-hydroxycholesterol, leading to better activation of the immune cells. This is consistent with clinical observations: in patients undergoing immunotherapy, the level of expression of this enzyme gives an indication of the response to treatment. "Our discovery could therefore provide a biomarker for predicting the success of immunotherapy, enabling treatments to be adjusted according to the specific characteristics of each patient," adds Stéphanie Hugues.

Lymphatic vessels have long been regarded as simple transport routes. "Our work clearly shows the much more complex role of the cells that make them up. Highly malleable, they respond to the tumour microenvironment and to modulations by the immune system. The stroma is therefore not just a scaffold for the tumour but constitutes a highly complex microworld with both beneficial and pathological roles. We therefore recommend not targeting lymphangiogenesis as a whole but modulating specific functions to fight the disease more effectively," conclude the authors.

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