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Press information

Metastatic Lung Cancer: A Targeted Therapy to Improve Treatment Efficacy

When faced with the most aggressive forms of lung cancer, how can the efficacy of chemotherapy be increased? Teams from Inserm, Université Paris Descartes and the Paris public hospitals system AP-HP have maybe hit on a solution. They have developed a targeted therapy which aims to improve the response to platinum salts - the standard chemotherapy used in lung cancer - by neutralizing the activity of a receptor that contributes to its aggressiveness. This research, published in *Cancer Letters*, shows that in mice this therapy restores the response to chemotherapy and reduces the risk of metastasis by one half to two thirds.

In metastatic lung cancer, life expectancy remains very limited, with death occurring within 5 years in 85 % of patients. The new treatments available for some patient populations present genuine efficacy, but this is of limited duration and successive relapses are common. Increasing the efficacy of existing treatments and finding new ones therefore remains a priority.

A priority that is being addressed by the team of Inserm researcher Patricia Forgez who, in collaboration with teams from the Paris public hospitals system AP-HP (Cochin, Lariboisière and Saint-Antoine hospitals) and Université Paris Descartes is developing a targeted therapy to increase the sensitivity of the most aggressive tumors to platinum salts, an essential chemotherapy in lung cancer.

In previous research, Forgez and her co-workers had shown that lung tumors and especially those at a metastatic stage overexpress the neurotensin receptor. Neurotensin is a small molecule produced in the intestines and brain that is also found to be abnormally overexpressed in tumors where, by binding to its receptor it triggers the continuous cascade of signals stimulating tumor cell growth, survival and migration. This renders them much more aggressive and with little or no sensitivity to platinum salts. By correlating the neurotensin receptor overexpression with the poorer prognosis observed in patients, the researchers had demonstrated that this receptor has a role to play in tumor progression.[1]

In this new study, the research team has developed an antibody to specifically

[1] This discovery has been protected by a patent filed by Inserm Transfert, the co-owners of which are Inserm and AP-HP. This patent claims that the neurotensin receptor is a marker of tumor aggressiveness and that neurotensin is a potential therapeutic target.

neutralize the form of neurotensin produced by the tumors.[2] When tested in multiple experimental mouse models, the researchers observed a 40 to 65 % regression in tumor size and a decrease in aggressiveness. The treated mice presented half as many lymph-node and lung metastases as their untreated counterparts. The researchers also showed that concomitant administration of the antibody with a platinum salt restored or improved treatment efficacy by improving the access of the therapeutic molecule to its target.

The long-term objective is to develop a targeted therapy to block the neurotensin receptor in order to weaken the tumor cells and improve their sensitivity to platinum salts.

"Almost all patients diagnosed with lung cancer receive platinum salts at some point in their treatment, reiterates Jean Trédaniel, study co-author and head of the Paris Saint-Joseph Hospital Group thoracic oncology unit, *whether as first-line treatment or following the failure of a targeted therapy or immunotherapy. However, platinum salts are toxic to the body, making it impossible to increase the doses in the event of resistance. Administering this antibody would render the tumor more sensitive to the treatment. What is more, it has been shown in mice to be very well tolerated over the long-term. "*

In collaboration with Inserm Transfert, French technology transfer acceleration company SATT Ile-de-France INNOV, and Fair Journey Biologics, the research team is now working on the development of anti-neurotensin antibodies for use in humans, the objective being to embark on a clinical trial. Encouraging results in lung cancer would enable the extension of this therapy to include the other cancers that express neurotensin and its receptor, such as those of the breast, ovary, endometrium, prostate, pancreas, stomach and colon.

Sources

Modulation of lung cancer cell plasticity and heterogeneity with the restoration of cisplatin sensitivity by Neurotensin antibody

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[2] This antibody has been the subject of several patent applications filed by Inserm Transfert on behalf of Inserm and Université Paris Descartes; one of these patents was issued in the USA at the end of 2018.

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