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Breast cancer brain metastases: patterns in immune cells could improve therapy decisions

Brain metastases are among the most serious complications of advanced breast cancer. Researchers at Heidelberg Faculty of Medicine at Heidelberg University, German Cancer Research Center (DKFZ), and Heidelberg University Hospital (UKHD) have concluded an in-depth investigation of the body's own immune cells in the brain tissue surrounding these breast cancer brain metastases (BCBM). Their findings show that specific spatial distribution patterns of immune cells are associated with prolonged patient survival. These findings, which have recently been pulished published in Cancer Cell (Cell Press), could in the future help to guide a more targeted use of immunotherapies immunotherapies for breast cancer patients in the future.

Whenever cancer cells detach from the primary tumor in the breast and form metastases on in the brain, treatment options for affected patients are currently limited. As a result, brain metastases are often associated with poorer prognoses than metastases in other organs. Therefore, there is a strong need for a better understanding of cellular interactions within brain metastases in order to develop more targeted therapeutic strategies. In the present study, the Heidelberg research team analyzed the cellular environment of brain metastases from a total of 156 breast cancer patients, focusing in particular on immune cells as well as other components of the tumor microenvironment. To achieve the most detailed analysis possible, they combined several methods to characterize both the cell types and their immune activity. Using spatial analysis, the researchers were also able to determine where highly active immune cells were located within the tissue.

Two "immune landscapes" with favorable outcomes

The researchers identified distinct patterns in the spatial distribution of immune cells, which they described as "immune landscapes." If only a small number of cancer-fighting immune cells were present around in the metastasis, these patterns were associated with an unfavorable prognosis. In contrast, the team identified two immune landscapes linked to more favorable patient outcomes. One of these patterns was characterized by a high number of tissue -resident-like memory T cells . These specialized immune cells are thought to remain in the tissue, recognize tumor cells upon re-encounter, and respond particularly rapidly. The second favorable pattern was defined by organized clusters of immune cells within the tumor tissue that resemble small lymph nodes in function and can support an immune response against the tumor.

Patient-derived models confirm the key role of T cells in tumor control

"It is remarkable that we were not only able to identify these patterns, but also to describe their biological function," says Dr. Dr. Lena Jassowicz, researcher at Heidelberg Faculty of Medicine in the Section of Experimental Neurosurgical Research at UKHD, the the study's lead first author. In order to validate experimentally their observations from metastatic tissuetheir observations from metastatic tissue experimentally, the team used patient-derived models. In these models, isolated tumor and immune cells from the same patient are brought together in the laboratory to study their interactions directly and without external interference. The results showed that the identified tissue -resident-like memory T cells attacked and destroyed the patient's tumor cells very effectively. "From these findings, we conclude that these cells indeed play an important role in tumor control," says Dr. Fangyoumin Feng, co-lead author of the study and member of the DKFZ Computational Cancer Genomics research group.

These T cells could serve as a starting point for targeted immunotherapy approaches. Immunotherapies enhance the body's own immune response against cancer cells. However, not all patients benefit equally from this treatment. Therefore, biomarkers are needed to predict which patients are likely to respond. The study provides important clues in this regard: in additional laboratory experiments, the researchers also showed that T cell activity could be further increased through immune checkpoint blockade.

Gene signatures as markers of immune landscapes

In a further step, the researchers derived characteristic patterns of active genes from their findings that define the previously identified favorable immune landscapes. In tests using external datasets of breast cancer patients, these gene signatures reliably indicated a better prognosis. In the future, these signatures could be used to more precisely classify tumors or metastases at the molecular level and support treatment decisions. For example, it may be useful to identify immunologically "cold" metastases that are unlikely to respond to immunotherapy. This could help avoid unnecessary burdens from treatments with little expected benefit. "To know that a patient is more likely to benefit from a different treatment than immunotherapy – that alone can be very valuable in a clinical setting," says PD Dr. Martina Seiffert, head of the Immune Modulation in Cancer research group at DKFZ.

"This work not only provides new insights into the biology of breast cancer brain metastases, but also offers specific starting points for the development of personalized therapies," says Prof. Dr. Sandro Krieg, Medical Director of the Department of Neurosurgery at Heidelberg University Hospital. One possible next step would be to develop therapeutic strategies to specifically enhance existing immune responses against tumor cells. "Our data clearly show that it is worthwhile to consider brain metastases as a distinct biological entity," says Prof. Dr. Christel Herold-Mende, Professor of Experimental Neurosurgery at Heidelberg University's Faculty of Medicine and head of the Section of Experimental Neurosurgical Research at UKHD. "Only by understanding these unique characteristics can we make therapies more precise. We hope they will also be more effective," Herold-Mende adds.

Publication::

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