Press Release

Tumor-associated macrophages as therapeutic targets in brain metastases

Frankfurt am Main, 10/19/2021 – Researcher at the Georg-Speyer-Haus, Institute for Tumor Biology and Experimental Therapy and the University of Lausanne developed a novel combination therapy that prevents the acquisition of adaptive resistance and thereby results in improved efficacy in experimental brain metastasis.

Brain metastases represent the most common intracranial tumors in adults. Despite considerable advances in the treatment of primary tumors, the development of brain metastases is associated with poor patient prognosis and limited therapeutic efficacy. Therefore, the development of novel and effective therapeutic avenues is urgently needed to overcome obstacles to treatment success and to prevent the development of adaptive resistance. To achieve this goal, a major focus has been directed to therapies that target the tumor microenvironment in brain metastases. In this context, tumor-associated macrophages (TAM) are emerging as a highly abundant and promising therapeutic target.

The Max-Eder Junior Group led by Dr. Lisa Sevenich (Georg-Speyer-Haus) demonstrated in collaboration with researchers and clinicians at the University of Lausanne and the Institute of Neurology (Edinger Institute, University Hospital Frankfurt), that TAM-targeted therapies by colony stimulating factor 1 receptor (CSF1R) inhibition result in tumor stasis and even regression of established brain metastases. "These results show that depletion of TAMs by blockade of a central survival pathway impairs brain metastatic outgrowth", explains Dr. Florian Klemm, first author of the study and postdoctoral fellow in Prof. Johanna Joyce's lab, the co-senior author of the study that was published in October this year in Nature Cancer. "However, we noticed that the observed effects were only transient and that tumors rapidly rebound. Therefore, we sought to dissect mechanisms that drive therapy resistance and to exploit this knowledge for improved strategies that overcome this limitation", explains Dr. Lisa Sevenich. In the present study, the authors unraveled a compensatory activation of the CSF2Rb-STAT5 signaling axis in TAMs that were localized within the vascular niche and were thereby protected from cell death induced by CSF1R inhibition. However, the remaining TAM population showed pro-inflammatory activation which likely induced tissue damage and triggered repair mechanisms that ultimately fostered tumor growth. "We were able to block this effect by combined CSF1R and STAT5 inhibition which resulted in improved treatment efficacy. To our surprise, we did not observe a complete loss of the TAM population. Instead, the population was restored and showed morphological normalization. Most importantly, this TAM population was now able to control tumor growth", explains

Dr. Lisa Sevenich. Collaboration of the researchers at the Georg-Speyer-Haus and the University Hospital Frankfurt, who also work closely together within the Frankfurt Cancer Institute (FCI) and the German Cancer Consortium (DKTK), as well as collaboration with the team led by Prof. Johanna Joyce at the University of Lausanne allowed successful completion of the study. "We now seek to unravel the underlying mechanisms that drive the observed effects in response to combined CSF1R-STAT5 inhibition. We hope to develop novel and effective treatment options for brain metastases patients by inducing specific anti-tumor responses in TAMs. This will help to prevent damage of adjacent tissue and block the induction of the vicious cycle that leads to tumor promoting wound healing responses", concludes Dr. Lisa Sevenich.

Publication

Klemm F, Möckl A, Salamero-Boix A, Alekseeva T, Schäffer A, Schulz M, Niesel K, Maas RR, Groth M, Elie BT, Bowman RL, Hegi ME, Daniel RT, Zeiner PS, Zinke J, Harter PN, Plate KH, Joyce JA* and Sevenich L*. Compensatory CSF2-driven macrophage activation promotes adaptive resistance to CSF1R inhibition in breast-to-brain metastasis. Nature Cancer, October 18, 2021. Read the online paper. *Corresponding authors

About the Georg-Speyer-Haus

The Georg-Speyer-Haus, Institute for Tumor Biology and Experimental Therapy, aims to decipher the molecular and cellular basis of tumorigenesis. A particular focus is placed on the analysis and the interaction of various cell types within the tumor, the tumor microenvironment. New therapeutic concepts are being tested in valid pre-clinical tumor models. In close collaboration with the University Cancer Center (UCT) and the LOEWE Center Frankfurt Cancer Institute (FCI) as well as a member of the German Cancer Consortium (DKTK) these concepts are translated into early clinical trials. Visit our website georg-speyer-haus.de.

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