Mechanism facilitates brain metastasis from breast cancer and melanoma by inducing neuroinflammation

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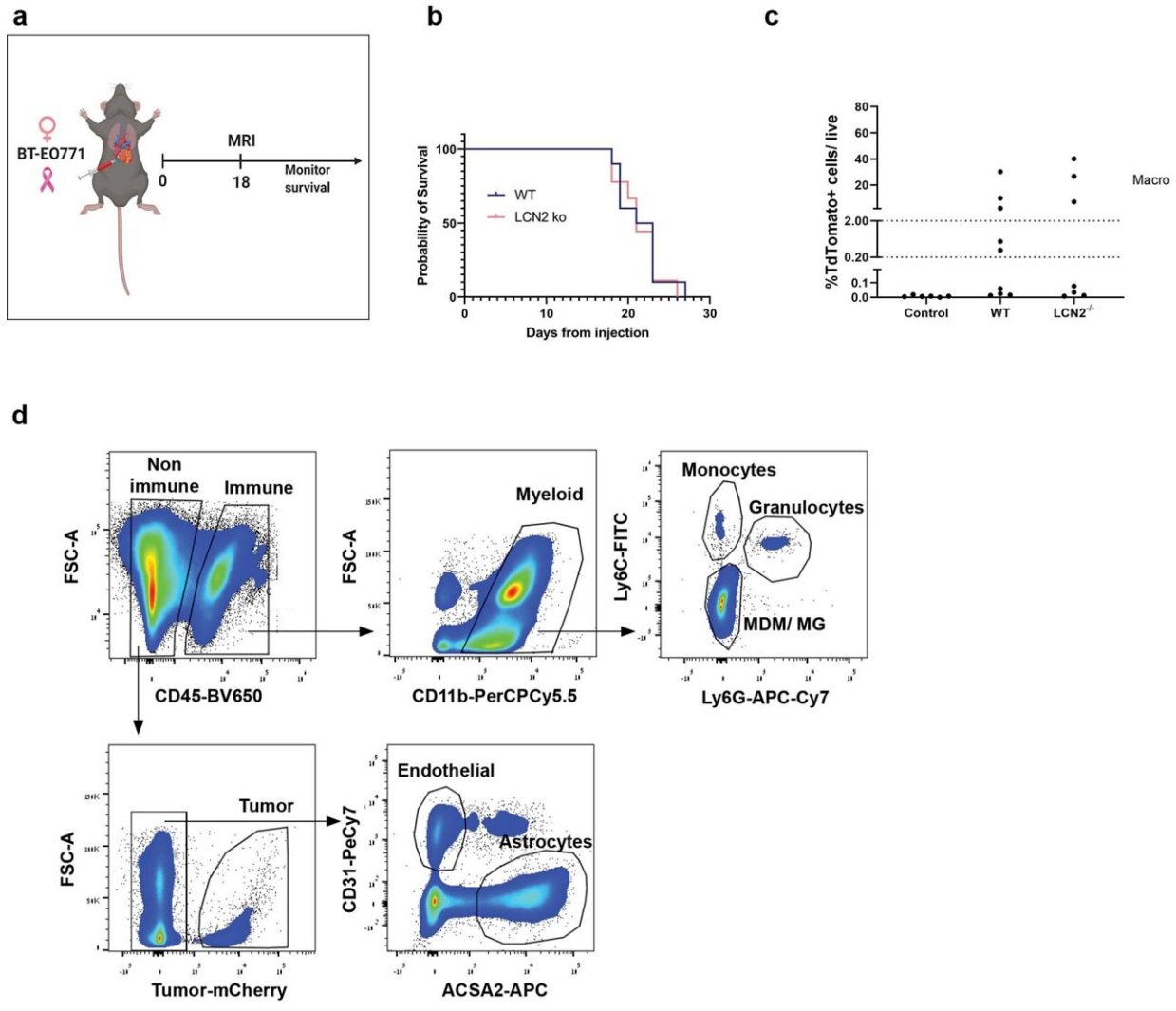

Brain metastatic burden and survival in mice injected with breast cancer cells. a.

Experimental scheme analyzed in (b,c). b. Survival curve analysis of WT and $Lcn2^{-/-}$ mice injected intracardially with BT-EO771 cells, (WT n = 10, $Lcn2^{-/-}$ n = 9 mice) (Kaplan–Meier curve, log-rank test). c. Quantification of brain metastatic burden for mice in (a), quantified as % CD45- mCherry+ tumor cells/live cells, (ctrl n = 9, WT n = 9, $Lcn2^{-/-}$ n = 7 mice) (one-way ANOVA). d. Gating strategy for isolation by FACS of different cells populations from WT and $Lcn2^{-/-}$ BrM mice injected intracardially with BT-RMS or BT-EO771 cells 18 days after injection. Credit: *Nature Cancer* (2023). DOI: 10.1038/s43018-023-00519-w

In a new study from Tel Aviv University published in the journal *Nature Cancer*, a team of researchers led by Prof. Neta Erez, head of the laboratory for the biology of tumors from the Department of Pathology at the Sackler Faculty of Medicine, identified and characterized a new mechanism that facilitates the formation of brain metastases and found that impairing this mechanism significantly reduced the development of brain metastases in mice.

Brain metastases are one of the deadliest forms of cancer metastasis. They are 2–10 times more common than tumors of the central nervous system (CNS). Despite the progress achieved in recent years in the development of novel treatments for melanoma and breast cancer, brain metastasis remain highly lethal with grave survival rates of less than one year in many cases.

The recorded incidence of brain metastases has been increasing in recent years, probably as a result of improvements in diagnostic methods as well as progress in the treatment of metastases in other organs. Therefore, developing better therapeutic strategies for brain metastasis is an urgent need.

In this new study from the Tel Aviv University, the researchers show

that Lipocalin-2 (LCN2) is a key factor in inducing neuroinflammation in the brain. Moreover, the researchers found that high LCN2 levels in patients' blood and brain metastases from several types of cancer are associated with disease progression and reduced survival.

LCN2 is a secreted protein that functions in the innate immune system and was originally discovered due to its ability to bind iron molecules and as part of the inflammatory process in fighting bacterial infection. LCN2 is produced by a large variety of cells and was shown to be involved in multiple cancer-related processes.

Prof. Neta Erez says, "Our findings reveal a previously unknown mechanism, mediated by LCN2, which reveals a central role for the mutual interactions between immune cells recruited to the brain (granulocytes) and brain glial cells (astrocytes) in promoting inflammation and in the formation of brain metastases. The findings establish LCN2 as a new prognostic marker and a potential therapeutic target."

In the study, the researchers used models of melanoma and breast cancer brain metastases in an effort to reveal the mechanism by which neuroinflammation is activated in the metastatic niche in the brain.

Prof. Erez says, "We show that signals secreted into the blood from the primary tumor stimulate pro-inflammatory activation of astrocytes in the brain. The astrocytes promote the recruitment of inflammatory cells from the bone marrow (granulocytes) into the brain, and they in turn become a main source of signaling by LCN2.

"We demonstrated the importance of LCN2 for the development of metastases by genetically inhibiting its expression in mice, which resulted in a significant decrease in neuroinflammation and reduced brain metastases. Moreover, in blood and tissue samples from patients

with brain metastases from three types of cancer, blood LCN2 levels were correlated with disease progression and with shorter survival , which positions LCN2 as a potential prognostic marker for brain metastases.

"We analyzed the LCN2 protein levels in the blood and cerebrospinal fluid (CSF) of mice with brain metastases, and found that LCN2 levels increased greatly in mice with melanoma and breast cancer metastases compared to healthy mice. Importantly—an increase in blood LCN2 preceded the detection of brain metastases by MRI. Furthermore, the mice in which LCN2 levels were very high developed brain metastases later, further establishing LCN2 as a predictive marker for brain metastases."

The researchers also examined whether LCN2 is elevated in the blood of melanoma patients at the time of initial diagnosis, and whether it can be a prognostic factor. The findings indicated that patients with melanoma had significantly higher levels of LCN2 in their blood compared to samples from healthy individuals. Strikingly, patients who developed brain metastases displayed significantly higher levels of LCN2 even before the diagnosis of the metastases, and high levels of LCN2 in the blood correlated with worse survival.

Prof. Erez says, "We have identified a new mechanism in which LCN2 mediates the communication between immune cells from the bone marrow and supporting cells in the brain, activates inflammatory mechanisms and thus helps the progression of metastatic disease in the brain, and demonstrated its importance. The functional and prognostic aspects of LCN2 that we have identified in brain metastases in mouse models as well as in cancer patients suggest that targeting LCN2 may be an effective therapeutic strategy to delay or prevent the recurrence of brain metastases."

More information: Omer Adler et al, Reciprocal interactions between innate immune cells and astrocytes facilitate neuroinflammation and brain metastasis via lipocalin-2, *Nature Cancer* (2023). DOI: 10.1038/s43018-023-00519-w

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