Researchers identify pathway that controls breast cancer metastasis to the brain

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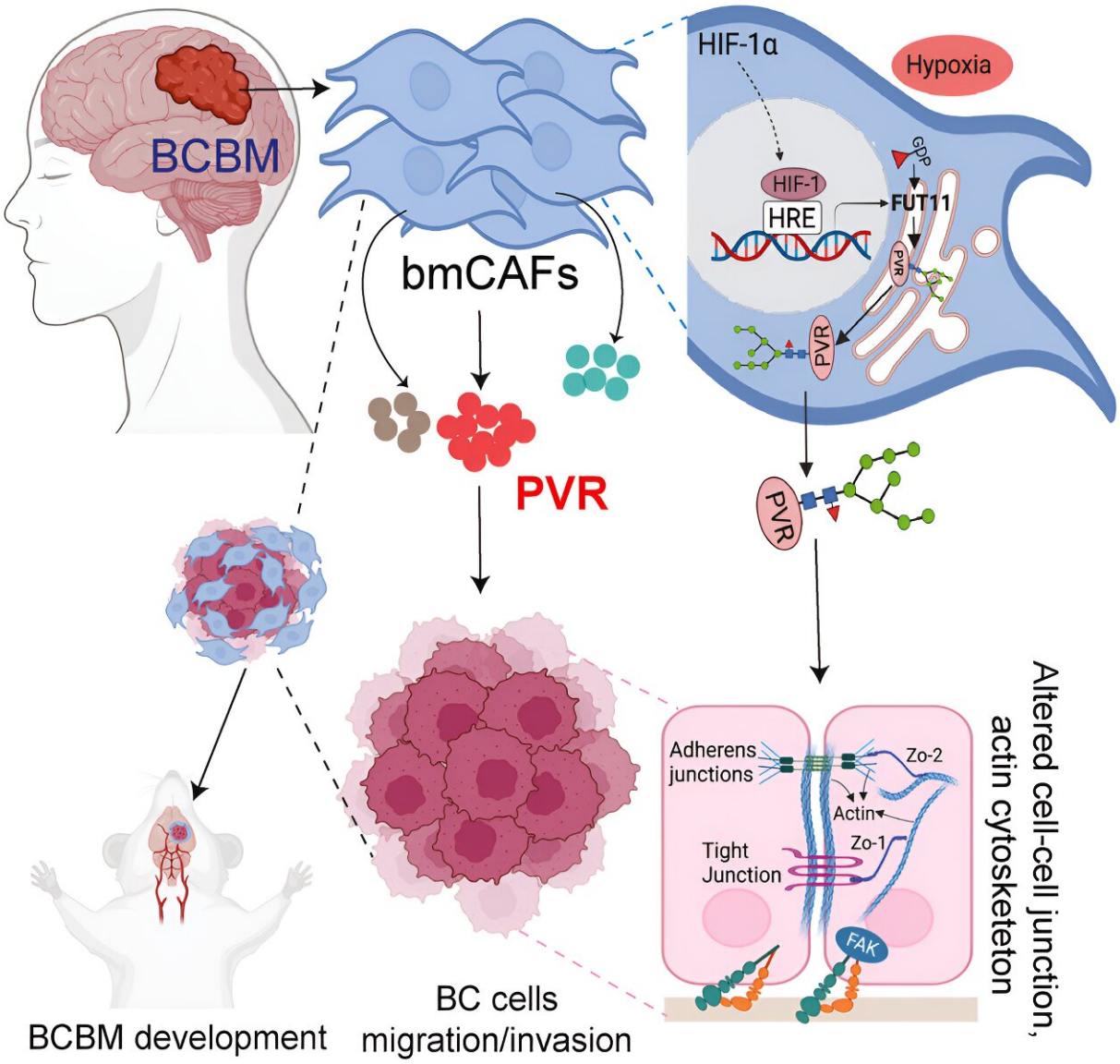

Graphical Abstract. Credit: *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.113463

Breast cancer is the second most common cause of brain metastasis, which occurs in 10% to 30% of patients with metastatic breast cancer. Breast cancer patients who develop brain metastasis have limited treatment options and poor survival. Moffitt Cancer Center researchers are working to better understand the molecular mechanisms that promote the development and progression of breast cancer brain metastasis to help improve diagnostics and treatments.

In a new study published in *Cell Reports*, they report on identifying a cell signaling pathway that controls breast cancer brain metastasis.

The Moffitt team focused their investigations on cancer-associated fibroblasts and the process of fucosylation. Cancer-associated fibroblasts are a type of cell in the tumor environment that can support and promote cancer development and progression.

Cancer-associated fibroblasts are well-established for their functional contributions to primary breast cancer development; however, their roles in brain metastasis are less defined. Fucosylation is a type of protein modification in which the sugar L-fucose is added to proteins, impacting their behavior and functions. Cell signaling pathways can be regulated by fucosylation, and high levels of fucosylated proteins appear to be associated with breast cancer progression.

"Emerging studies have highlighted mechanistic roles for fucosylation in the pathogenesis of multiple cancer types, including those within the brain; however, how aberrantly fucosylated proteins may alter tumor/cancer-associated fibroblast interactions to promote progression

of tumors in the brain is not known," said Eric Lau, Ph.D., associate member of the Department of Tumor Microenvironment & Metastasis at Moffitt.

In early laboratory experiments, the researchers discovered that breast cancer-associated fibroblasts have high levels of fucosylation that correlate with metastasis, suggesting that this process in cancer-associated fibroblasts may promote breast cancer progression.

A subsequent and comprehensive series of experiments revealed that cancer-associated fibroblasts from breast cancer brain metastases secrete the protein poliovirus receptor (PVR), which potently stimulates the migration and invasive capacity of metastatic breast cancer cells, increasing breast tumor invasion in the brain.

Importantly, the researchers determined that the secretion of PVR from the fibroblasts is triggered by its fucosylation, which is mediated by the hypoxia-induced protein FUT11. The researchers also confirmed in patient samples that levels of fucosylated PVR are higher in cancer-associated fibroblasts from breast cancer brain metastases than in breast cancer cells.

These combined observations suggest that fucosylation of PVR and its consequent secretion by cancer-associated fibroblasts is an important regulator of breast cancer metastasis and invasion in the brain. The researchers hope these findings will help scientists develop better diagnostic and therapeutic approaches for breast cancer brain metastasis patients.

"Our study provides important mechanistic insights into breast cancer brain metastasis pathogenesis, highlighting, for the first time, brain metastasis cancer-associated fibroblast-secreted/-fucosylated PVR and FUT11 as potential new therapeutic targets and biomarkers for breast

cancer brain metastasis," said Emma Adhikari, Ph.D., lead study author and recent Moffitt Cancer Biology Ph.D. graduate of the Lau lab.

More information: Emma Adhikari et al, Brain metastasis-associated fibroblasts secrete fucosylated PVR/CD155 that induces breast cancer invasion, *Cell Reports* (2023). DOI: 10.1016/j.celrep.2023.113463

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