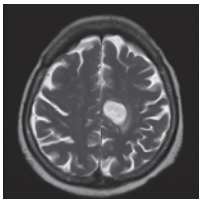
Metastasis

Major Finding: Brain-metastatic breast tumors depended on lipids produced by fatty acid synthase (FASN) for survival.

Concept: Pharmacologic inhibition of FASN reduced the growth of breast cancer brain metastases *in vivo*.

Impact: Depriving brain metastases of nutrients lacking in the brain microenvironment may be a useful strategy.

BREAST CANCER BRAIN METASTASES RELY ON FASN-MEDIATED LIPID BIOSYNTHESIS



Although metastases of HER2$^+$ breast cancers are sometimes treatable, brain metastases tend to be treatment-refractory. Because the brain microenvironment has been demonstrated to be deficient in several nutrients required by cancer cells, Ferraro, Ali, Luengo, and colleagues investigated metabolic differences between HER2$^+$ breast tumors growing in the brains and mammary fat pads of mice. This analysis revealed that the tumors growing in the brains exhibited higher expression of genes involved in fatty acid synthesis, a finding confirmed at the protein level, and had greater metabolism of glucose to produce fatty acids. *Ex vivo* experiments using organotypic slice cultures confirmed that metastases grown in the brain retained increased expression of lipid synthesis genes, whereas *in vitro* experiments revealed that there was no such increase in brain-metastatic cells removed from brain tissue; together, these experiments suggested that the brain microenvironment itself promoted increased tumor fatty acid synthesis. Notably, fatty acid synthase (FASN) and the mRNA encoding this enzyme were more highly expressed in breast tumors that had metastasized to the brain compared with primary breast tumors or tumors that had metastasized to other sites. Further analysis showed that, in the brain, extracellular fatty acids were available to breast cancer cells only in limited quantities, explaining the need for increased lipid biosynthesis. Experiments employing *FASN* knockout or pharmacologic FASN inhibition revealed that FASN played a critical role in fulfilling the need for lipids in breast tumors grown in the brain, but not the liver, further supporting the notion that lipid-limiting conditions in the brain must be circumvented for breast cancer cells to establish brain metastases. Importantly, treatment with a FASN inhibitor reduced the growth of breast cancer brain metastases but not tumors in the mammary fat pad. This work supports the notion that cancer cell lipid biosynthesis is key for breast cancer brain metastasis and suggests that FASN inhibition may be a strategy of interest in controlling this condition. ■

Ferraro GB, Ali A, Luengo A, Kodack DP, Deik A, Abbott KL, et al. Fatty acid synthesis is required for breast cancer brain metastasis. Nat Cancer 2021;2:414–28.

Epigenetics

Major Finding: Extrachromosomal DNA (ecDNA) molecules associated with transcriptionally active genes on linear chromosomes.

Concept: ecDNA molecules are independent circular DNA that may be tens to millions of base pairs long.

Impact: ecDNA-induced transcriptional activation may be a means by which ecDNA can promote oncogenesis.

EXTRACHROMOSOMAL DNA CAN PROMOTE ONCOGENE TRANSCRIPTION IN *TRANS*

The presence of high levels of extrachromosomal DNA (ecDNA), a type of circular, histone-packaged DNA that is separate from the canonical chromosomes and can range from tens to millions of base pairs in length, is a common feature of cancer cells. Zhu, Gujar, Wong, and colleagues investigated the spatial organization of ecDNA molecules in the nucleus and its potential functional impacts, finding evidence for extensive intra-ecDNA interactions along with interactions between ecDNA molecules and conventional chromatin in cancer cells. ecDNA molecules were more often found to be associated with sites bound by RNA polymerase II on ordinary chromosomes, mostly at or around chromosomal promoter regions, suggesting a possible role in transcriptional regulation. Notably, evaluation of the promoter regions of three oncogenes amplified on cancer cell ecDNAs revealed that these genetic regions preferentially formed contacts with regions of both canonical chromosomes and ecDNA molecules that had high levels of histone 3 lysine residue 27 acetylation (H3K27ac), a marker of active chromatin. Interestingly, ecDNA–linear chromosome contact regions were associated with actively transcribed genes, and further investigation revealed that these contacts were highly specific and may have functioned to connect superenhancer elements to target genes in *trans*. Experiments using synthetic ecDNA molecules further supported the notion that ecDNA molecules could serve as mobile transcriptional enhancers, increasing transcription of genes at chromosomal locations they bind. Due to observed spatial clustering of actively transcribed oncogenes interacting with these ecDNA molecules, it is possible that, in addition to their known oncogenic role of harboring multiple copies of oncogenes, ecDNA molecules may act epigenetically to enhance transcription of oncogenes in cancer. The previously unexplored concept that ecDNA can function as a mobile *trans* activator in a cancer-specific manner may have translational value. ■

Zhu Y, Gujar AD, Wong CH, Tjong H, Ngan CY, Gong L, et al. Oncogenic extrachromosomal DNA functions as mobile enhancers to globally amplify chromosomal transcription. Cancer Cell 2021; 39:694–707.E7.