

Small number of cells could be key enablers of cancer metastasis

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Just a small number of cells found in tumors can enable and recruit other types of cells nearby, allowing the cancer to spread to other parts of the body, report Georgetown Lombardi Comprehensive Cancer Center scientists. Working with their research collaborators, the scientists found that 'enabler cells' comprise about 20 percent or less of the cells in an aggressive tumor; their small numbers may account for why they are

often missed when bulk tissue analyses are used to inform therapeutic decisions.

The finding appears online June 16, 2021, in *Cancer Research*, a journal of the American Association for Cancer Research. "Our novel finding goes beyond the common understanding of cancer progression as one modeled on Darwinian selection where 'survival of the fittest' means the predominant type of cell in a [tumor](#) dictates its outcome," noted Anna Riegel, Ph.D., Professor of Oncology and Pharmacology at Georgetown Lombardi and the corresponding author of the study. "This could have major implications for our understanding of how best to diagnosis and treat certain cancers as blocking key cancer-promoting subpopulations of [cells](#) might be a way to defeat the cancer."

The advent of advanced gene sequencing technology coupled with the use of CRISPR, a tool that allows for easy gene editing, made this finding possible; it is a [collaborative effort](#) with researchers at The Ohio State University and Hackensack University Medical Center's John Theurer Cancer Center, a part of Georgetown Lombardi Comprehensive Cancer Center. These tools aided the scientists in building on their knowledge of alternative splicing, or cutting, of [genes](#) whereby a [single gene](#) can be spliced to code for multiple proteins.

The researchers' work using CRISPR in both zebrafish and mice zeroed in on cell subpopulations responsible for enabling metastasis. This led researchers to the discovery of a single RNA splicing event in the AIB1 (amplified in breast cancer 1) gene. One splice variant of the gene produced the AIB1-Delta4 protein, which was found to be responsible for promoting communication and recruitment of surrounding cells, eventually leading to metastasis.

"We propose that the detection of these enabler cells in early-stage breast cancers could predict which tumors are more aggressive and

destined to metastasize," said Ghada M Sharif, Ph.D., Research Assistant Professor at Georgetown Lombardi and first author of this finding. "Therapeutic targeting of vulnerabilities uncovered in the enabler cells, such as the splice variants, could represent a new approach to preventing malignant progression of [breast cancer](#)."

This finding is particularly relevant in triple-negative breast cancers which can be aggressive and hard to treat. These types of cancer usually start as non-malignant tumors, called ductal carcinoma in situ (DCIS), but in about 5 to 10 percent of women, they can quickly progress to malignant tumors. The investigators found that AIB1-Delta4 is found at increased levels in women with higher-risk DCIS.

The researchers' next step will be to conduct various single cell analyses in human tissue samples. "We are at a turning point in how we analyze tumor samples," said Riegel. "It was unthinkable and impractical just a few years ago to look at every single cell in a tissue sample. But technology is racing ahead and we believe that in the next few years, looking at each cell will allow us to determine which cells, even if they are small in number, are truly driving [cancer](#) progression."

More information: Ghada M Sharif et al, An AIB1 isoform alters enhancer access and enables progression of early stage triple-negative breast cancer, *Cancer Research*, (2021). [DOI: 10.1158/0008-5472.CAN-20-3625](#)

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