RNA mystery solved in triple negative breast cancer

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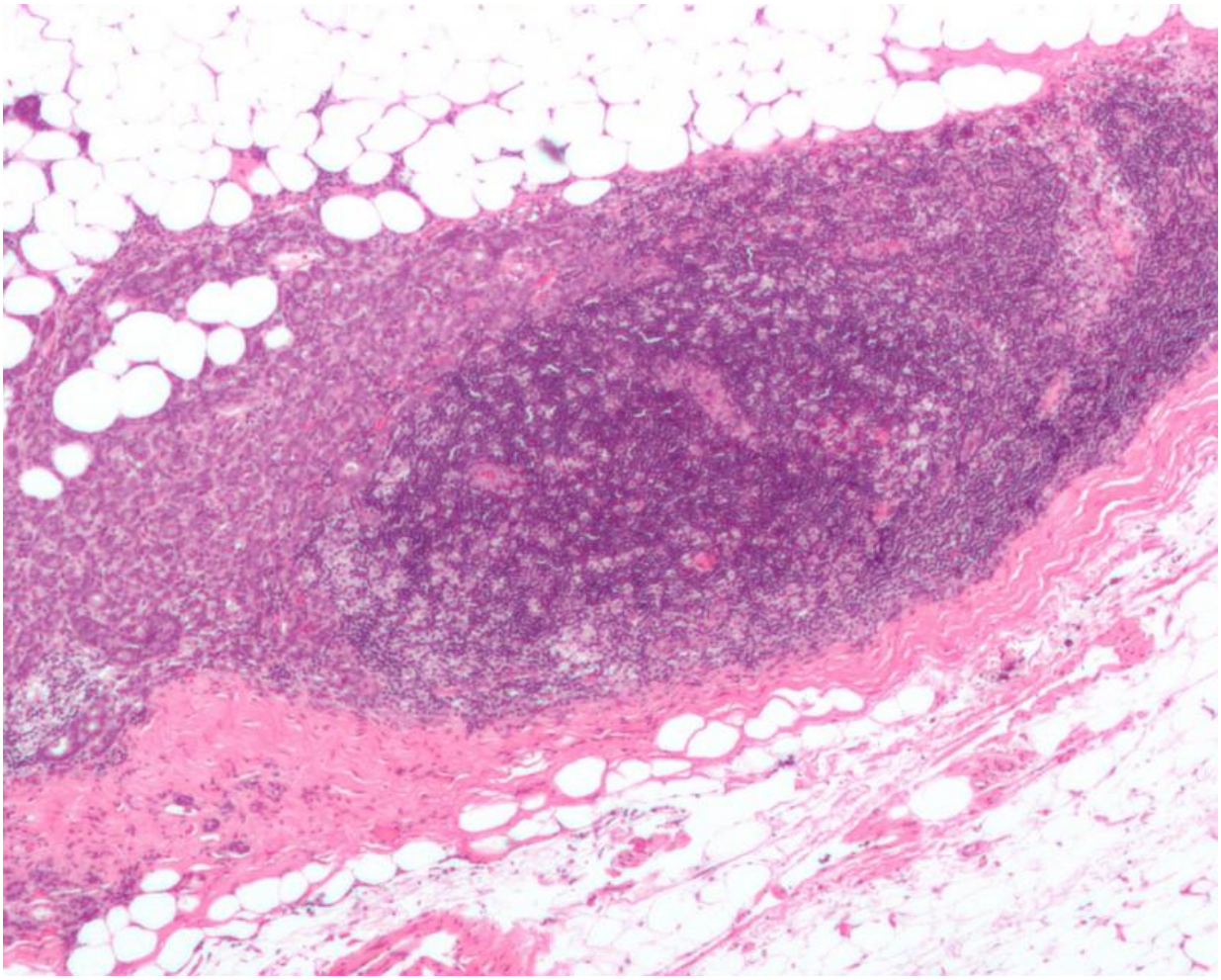

Micrograph showing a lymph node invaded by ductal breast carcinoma, with extension of the tumour beyond the lymph node. Credit: Nephron/Wikipedia

Researchers at Thomas Jefferson University have discovered why conventional efforts to block a tiny strand of ribonucleic acid, called microRNA, in triple negative breast cancer cells failed. In a study published December 2nd in the journal *PLOS ONE*, the new insight enables effective design of RNA blockers against previously intractable microRNAs.

"Triple negative breast cancer is one of the most aggressive forms of breast cancer, and there's been a lot of excitement in blocking the microRNAs that appear to make this type of cancer grow faster and resist conventional treatment," says senior author Eric Wickstrom, Ph.D., a Professor in the Department of Biochemistry and Molecular Biology at the Sidney Kimmel Medical College at Thomas Jefferson University. "However blocking microRNAs hasn't met with great success and this paper offers one explanation for why that might be the case."

"Triple negative breast cancer strikes younger women, tragically killing them in as little as two years," says first author Yuan-Yuan Jin, Ph.D. candidate in the Department of Biochemistry and Molecular Biology. "Only chemotherapy and radiation are approved therapies for triple negative breast cancer. We want to treat a genetic target that will keep patients alive with a good quality of life."

The researchers targeted a microRNA called miR-17 that is known to spur triple negative breast cancer growth by interfering with genes that would normally signal a diseased or early-cancerous cell to die. Specifically, miR-17 blocks the tumor suppressor genes PDCD4 and PTEN.

However, when Jin tried to diminish miR-17 levels in triple negative cancer cells, rather than increase the levels of the tumor suppressor genes, as they had expected, they saw an even greater decrease in these

genes than when the miR-17 was left untouched.

The current dogma in the field states that microRNAs, which are double stranded, only silence genes using one of their two strands. The matching, so-called passenger strand is thought to be discarded and degraded by the cell.

Although there have been some instances of both strands actively suppressing gene targets, researchers commonly use a method to silence microRNAs that involves flooding the cell with modified RNA sequences that mimic the passenger strand and bind to the single-stranded microRNA before it reaches its target.

When Jin used this method to block miR-17, she saw more silencing of the PDCD4 and PTEN genes, not less. Using bioinformatics and folding-energy calculations, the lead author realized that both strands of miR-17 were active in suppressing PDCD4 and PTEN genes in triple negative breast cancer cells. Jade Andrade, then an undergraduate at Haverford College, calculated a structural explanation for the success of the tiny microRNA passenger strands in modulating gene activity.

"Rather than blocking miR-17, we were inadvertently boosting its levels, and therefore boosting the cell's cancerous potential," says Jin. The experimental results open a pathway to design specific blockers of one microRNA strand without imitating the opposite strand. "We are now testing new miR-17 blocker designs made possible by these results," says Dr. Wickstrom, who is also a researcher at the Sidney Kimmel Cancer Center at Thomas Jefferson University.

More information: Y Jin, et al., "Non-specific blocking of miR-17-5p guide strand in triple negative breast cancer cells by amplifying passenger strand activity," *PLOS ONE*, DOI: 10.1371/journal.pone.0142574 , 2015.