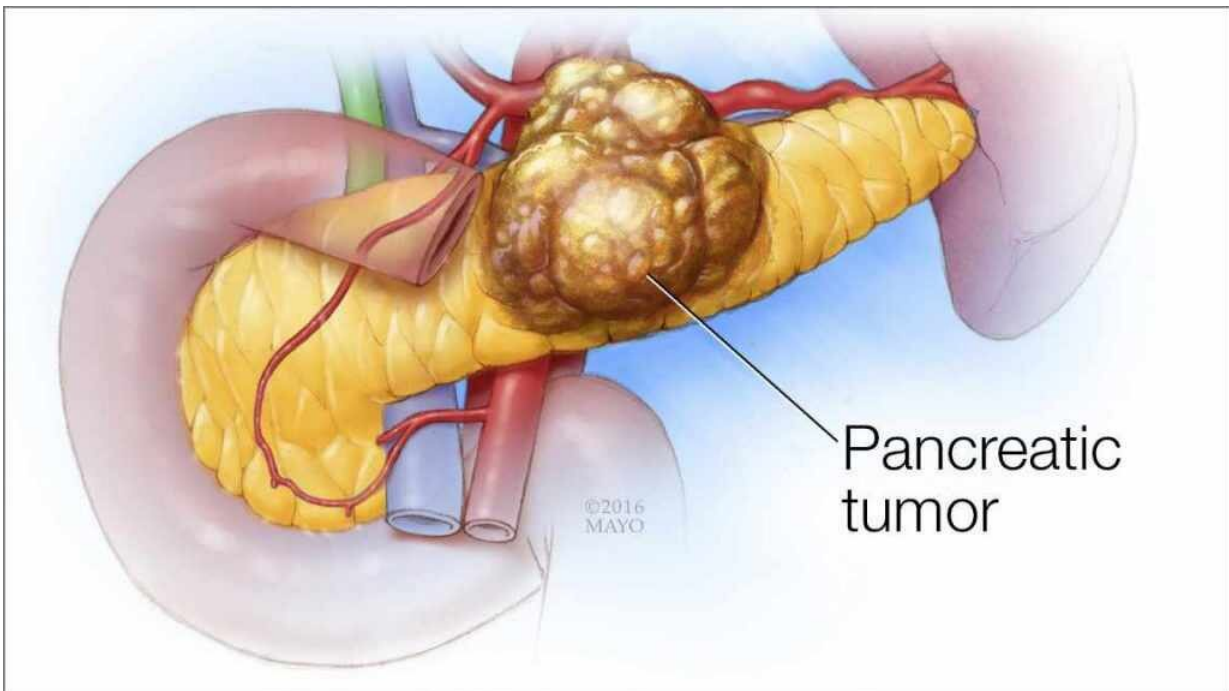


# Researchers identify potential gene marker for treating pancreatic cancer

September 22 2022, by Joe Dangor

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Credit: Mayo Clinic

Researchers at Mayo Clinic Comprehensive Cancer Center have identified a gene marker that may lead to a more effective, precision treatment for pancreatic ductal adenocarcinoma (PDAC). The researcher's findings are published in *Nature Cancer*.

"Pancreatic ductal adenocarcinoma is one of the most lethal cancers,"

says the paper's senior author Zhenkun Lou, Ph.D. Dr. Lou says while Poly-ADP-ribose-polymerase inhibitors (PARPi) are now an FDA-approved option for standard maintenance therapy for patients with metastatic PDAC who harbor pathogenic germline BRCA1/2 mutations, only about 10 percent of patients with PDAC harbor pathogenic mutations of the homologous recombination (HR) genes. "This leaves most patients missing out on this encouraging treatment strategy," says Dr. Lou.

In this study, Dr. Lou and his colleagues found that the protein METTL16 may be a new biomarker for PARPi treatment, and that PDAC with elevated expression of METTL16, may benefit from PARPi treatment.

"METTL16, belongs to a family of factors that regulate RNA methylation, whose function in DNA repair is unclear," says Dr. Lou. "We found that METTL16 expression was correlated with accumulated DNA damage in a PDAC microarray." He says elevated METTL16 may result in HR DNA repair defects, which may lead to accelerated aging, disease or increased risk of cancer. "Our research showed that METTL16 suppresses DNA repair via interaction with a key DNA repair nuclease called MRE11."

Dr. Lou and his colleagues found that METTL16 unexpectedly bound with MRE11 not through direct protein to protein interaction but through RNA. "Because METTL16 is highly expressed in a subset of PDAC and inhibits HR, PDAC cells with high METTL16 expression showed increased sensitivity to PARPi in both cellular and mouse models, especially when combined with gemcitabine," says Dr. Lou.

These findings may collectively reveal that in addition to PDAC with BRCA1/2 mutation, PDAC without BRCA1/2 mutation, but with elevated expression of METTL16, may also be a target for PARPi

treatment. "In addition, the treatment strategy of gemcitabine combined with PARPi may be more beneficial," says Dr. Lou. He believes immunochemistry-based METTL16 expression detection of tumors may eventually become a routine clinical practice for patients before starting treatment."

Dr. Lou says that his team unexpectedly found that METTL16 functions in DNA repair independent of its role in RNA m6A modification. "Prior to our study, all documents regarding METTL16 showed its role in cellular activity depending on the RNA m6A methyltransferase activity. Second, we strikingly revealed an inhibitory role of RNA and RNA binding proteins in DNA repair." Dr. Lou says the function of RNA on promoting DNA repair has been investigated in several studies. In this study his team showed that RNA mediates the formation of an inhibitory complex (METTL16-RNA-MRE11 complex) in DNA repair regulation, which suggests RNA could also be a negative regulator of DNA repair.

**More information:** Xiangyu Zeng et al, METTL16 antagonizes MRE11-mediated DNA end resection and confers synthetic lethality to PARP inhibition in pancreatic ductal adenocarcinoma, *Nature Cancer* (2022). [DOI: 10.1038/s43018-022-00429-3](https://doi.org/10.1038/s43018-022-00429-3)

Provided by Mayo Clinic

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