A new paradigm for treating transcription factor-driven cancers

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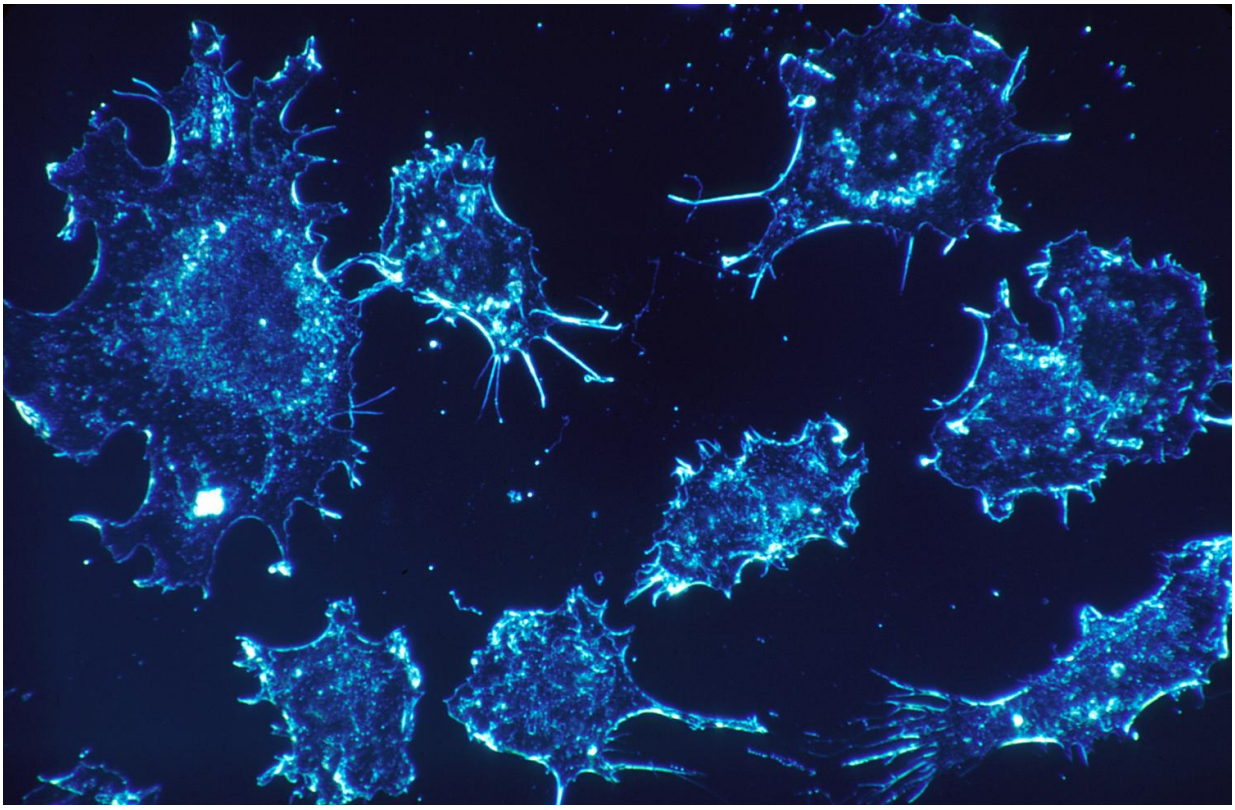

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In the current issue of *Proceedings of the National Academy of Sciences*, researchers from Nationwide Children's Hospital describe a new paradigm for treating transcription factor-driven cancers. The study focuses on Ewing sarcoma and how the EWS/FLI transcription factor

drives the malignancy – and suggests ways to disrupt the process.

Transcription factors are involved in the process of transcribing DNA into RNA, which is then translated into proteins. The EWS/FLI transcription factor is comprised of two domains, EWS and FLI. The FLI component has a well-defined structure with a surface that fits neatly into a groove in DNA. FLI binds to GGAA-microsatellites responsible for the regulation of many genes required for Ewing sarcoma development, such as the NR0B1 gene.

The presence and location of the GGAA-microsatellites are essential for the development of Ewing sarcoma. If microsatellites are not in the right place in the genome, and of the right sequence and length, it's likely not possible to get this particular type of cancer.

"This knowledge helps to explain some of the questions around susceptibility to Ewing sarcoma," says Stephen Lessnick, MD, PhD, director of the Center for Childhood Cancer and Blood Diseases in The Research Institute at Nationwide Children's and senior author of the study. "For example, Ewing sarcoma is 10 times more prevalent in people of European descent than in people of African descent. Also, humans are the only species that can get Ewing sarcoma. We believe that these patterns are directly related to microsatellite location and length. There appears to be a 'sweet-spot' microsatellite length where EWS/FLI is most effective at regulating gene expression."

The FLI subunit binds to GGAA-microsatellites, and it had been thought that the EWS portion regulates gene expression. However, the Lessnick team found that EWS also works with the FLI portion to help it bind GGAA-microsatellites of "sweet-spot" length. But how does EWS do this? According to Dr. Lessnick, this is one puzzle that the team is working to solve. One of the pieces of the puzzle is that EWS lacks a rigid structure. In fact, Dr. Lessnick says its structure is more akin a

strand of spaghetti.

Traditional cancer therapies are built on the lock and key construct. Enzymes have pockets that can be filled with a drug to block their function. Cells have receptors that can be blocked with a drug. With the EWS, there's no rigid structure, and therefore no apparent "lock" for the "key" to target.

"The theory is that the EWS component is interacting and communicating with FLI, helping it to bind DNA, and at the same time is interfacing with other cellular proteins to turn on gene expression that causes Ewing sarcoma," says Dr. Lessnick, who is also professor of Pediatrics at The Ohio State University College of Medicine. "The EWS portion may be locking together in some way or segregating cellular components to create neighborhoods – more work needs to be done to determine the mechanism."

Figuring out how EWS interacts with other EWS portions, and with FLI, could result in a clinical revolution for transcription factor-driven cancers. "If you can disrupt the function of the EWS component, you can stop cancer in its tracks. New cancer would be prevented, and the cancer that exists will die," says Dr. Lessnick. "Another target would be to block the binding of FLI to the microsatellites. Without this binding, Ewing sarcoma can't manifest."

Further research is still needed to bring applications of this discovery to the clinic, but the implications of understanding the interactions between transcription factors and microsatellites extends beyond Ewing sarcoma. "Other transcription factor driven cancers, and even potentially Alzheimer's disease, may have new treatments as we continue to learn more about these processes," Dr. Lessnick says. "As our understanding grows, it is exciting to consider the future of this area of research."

More information: Kirsten M. Johnson et al. Role for the EWS domain of EWS/FLI in binding GGAA-microsatellites required for Ewing sarcoma anchorage independent growth, *Proceedings of the National Academy of Sciences* (2017). DOI: 10.1073/pnas.1701872114