For prostate cancer, study identifies how common mutation makes good cells go bad

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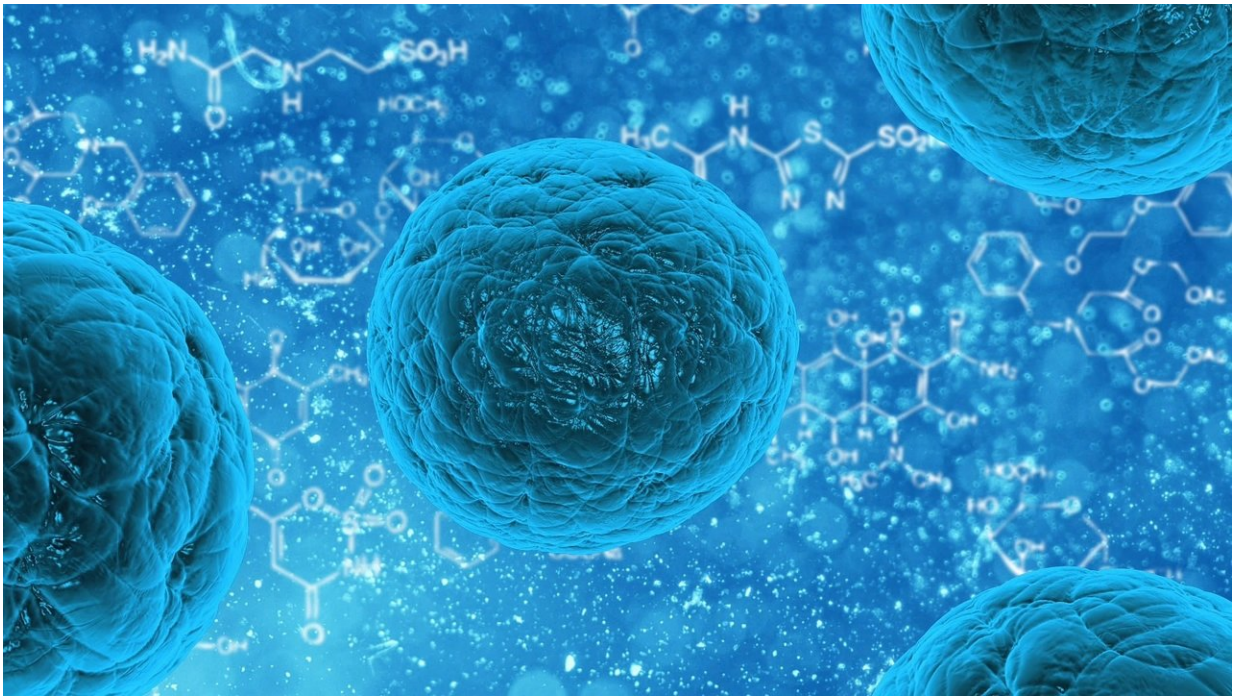

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In more than half of all prostate tumors, two genes—one for a transcription factor called ERG, the other a testosterone-triggered gene called TMPRSS2—become fused together, resulting in excess ERG expression. The TMPRSS2-ERG protein pushes prostate cells to become cancerous, but precisely how it does so, and what can be done about it, have been unclear.

In a paper in Molecular Cell, a research team led by Gabriel Sandoval, John Pulice, Broad institute member William Hahn, and institute member and Epigenomics Program co-director Cigall Kadoch (all also at the Dana-Farber Cancer Institute) showed that the fused protein engages in an act of molecular piracy, roping a cellular machine called the BAF complex into helping it boot up a gene expression program that would otherwise be silent in normal prostate cells. This, they found, encourages prostate cells' transformation into cancer cells, and may provide a new opportunity for prostate cancer drug development.

Transcription factors like ERG perform a variety of tasks that help a cell express the right genes at the right time. Cells are normally quite picky about which transcription factors they use, expressing certain ones only at certain times during their development and growth. Normal prostate cells, for instance, neither produce nor use ERG, but the TMPRSS2-ERG gene fusion pushes these cells to produce the factor constantly.

To understand the consequences of this untimely activity, the team joined several collaborators, including members of the Broad's Cancer Program and Proteomics Platform, to find out which proteins partner with the fused ERG factor in prostate cancer cells.

High up on the resulting list were several members of BAF, a complex of proteins that work together to open tightly packed DNA for transcription. Using a mix of cell line and organoid models of prostate cancer, the team found that the overexpressed TMPRSS2-ERG protein retargets BAF complexes, forcing them to open up regions of prostate cells' DNA they would otherwise not, turning on normally inactive genes, and driving the cells to turn cancerous.

The team also noted that ERG relies on BAF complexes to do its dirty work; in their experiments, suppressing members of BAF shut down the

gene program activated by TMPRSS2-ERG. This may present an opportunity: a drug that interferes with BAF and TMPRSS2-ERG's interactions, they think, could alter prostate cancer gene expression in powerfully therapeutic ways.

This is not the first case of BAF complex hijacking that Kadoch's lab has come across. Previously they reported that another fused protein, called SS18-SSX, similarly commandeers BAF complexes in a rare cancer called synovial sarcoma, and that the EWS-FLI1 fusion protein retargets BAF complexes in another tumor called Ewing sarcoma.

More information: Gabriel J. Sandoval et al. Binding of TMPRSS2-ERG to BAF Chromatin Remodeling Complexes Mediates Prostate Oncogenesis, *Molecular Cell* (2018). DOI: 10.1016/j.molcel.2018.06.040

Matthew J. McBride et al. The SS18-SSX Fusion Oncoprotein Hijacks BAF Complex Targeting and Function to Drive Synovial Sarcoma, *Cancer Cell* (2018). DOI: 10.1016/j.ccell.2018.05.002

Gaylor Boulay et al. Cancer-Specific Retargeting of BAF Complexes by a Prion-like Domain, *Cell* (2017). DOI: 10.1016/j.cell.2017.07.036

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