Study reveals how transcription factor EVI1 contributes to cancer development and tumor invasion

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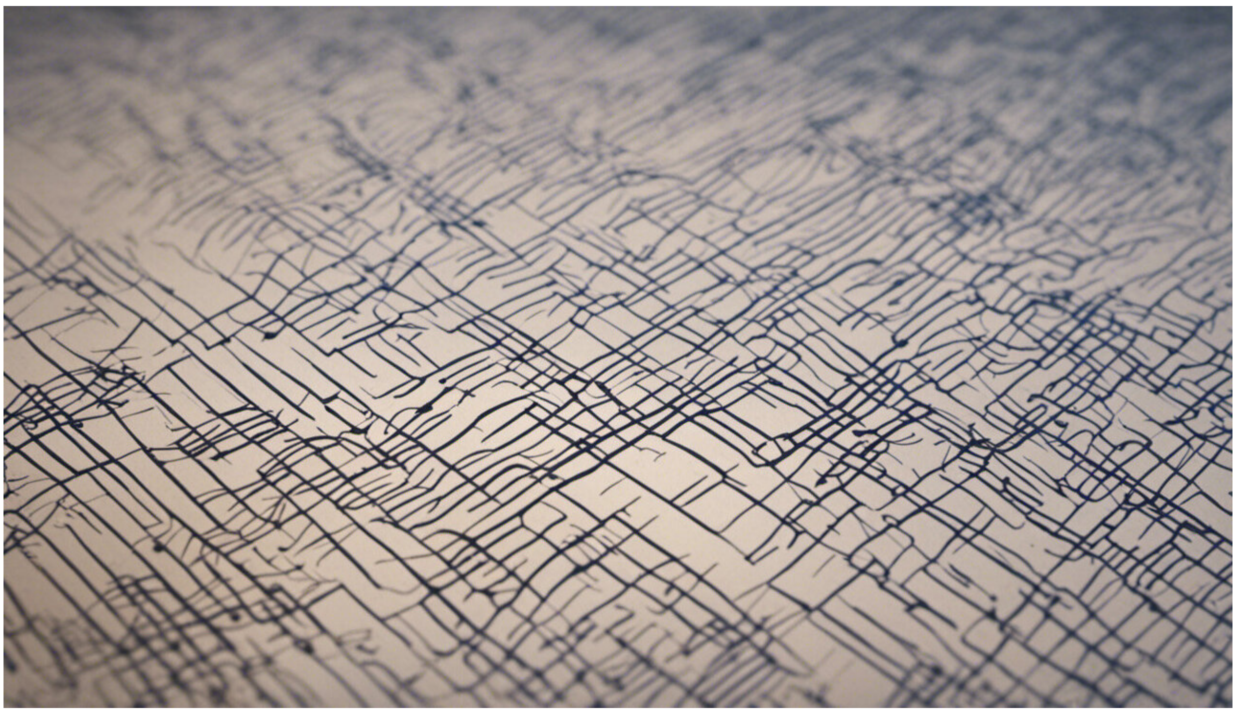

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Since its discovery close to 25 years ago, the EVI1 gene has emerged as a major player in many different types of cancer, including leukemia and tumors of the breast, prostate and colon, among other organs. In the US, for example, there is a company called NanoOncology that was founded to develop drugs for blocking this oncogene. Yet, despite all the interest in EVI1, very few of the gene's downstream targets are known.

Emilie Bard-Chapeau at the A*STAR Institute of Molecular and Cell Biology and co-workers1 have now used a systems biology approach to identify a slew of tumor-associated genes that are controlled by EVI1. The discovery could lead to new therapeutic drug strategies to combat various forms of cancer.

The EVI1 gene — short for 'ecotropic viral integration site 1' — encodes a zinc-finger transcription factor with two distinct DNA binding domains. When overexpressed, this oncogene leads to aggressive forms of cancer and poor patient survival. To better understand the biochemical functions of EVI1, Bard-Chapeau and co-workers searched for gene promoters and cooperating transcription factors that are actively bound by EVI1 in human ovarian cancer and chronic myeloid leukemia cell lines.

Systems biology uses a palette of analytical and computational techniques to study the complex interactions in biological systems. Using microarrays, ChIP-sequencing and immunoprecipitation assays, the researchers found that the two different zinc-finger domains of EVI1 activate unique sets of target genes, many of which are involved in cell adhesion, proliferation, colony formation and other aspects of tumor growth.

Notably, the researchers documented a strong association between EVI1 and FOS — the latter being one of the main components of the activator protein 1 (AP1) transcription factor complex that is known to drive tumorigenesis. Experiments in cell lines showed that EVI1 and FOS interact to co-regulate many hallmarks of cancer, and follow-up analyses in late-stage ovarian cancers taken from patients revealed an enrichment in expressed genes linked to both EVI1 and AP1. Taken together, the findings suggest that EVI1 expression might serve to fully elicit FOS oncogenic potential through a feed-forward regulatory loop that drives abnormal tissue changes.

"Our study has provided new mechanistic insights into the regulatory mechanism of EVI1, and revealed how EVI1 can function as a central player in many types of late-stage cancers," says Bard-Chapeau. "Disruption of the interaction between EVI1 and FOS may be a very interesting way to prevent cancer progression."

More information: Bard-Chapeau, E. A. et al. Ecotopic viral integration site 1 (EVI1) regulates multiple cellular processes important for cancer and is a synergistic partner for FOS protein in invasive tumors. Proceedings of the National Academy of Sciences 109, 2168–2173 (2012).

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