A study of fruit fly genes reveals how molecules cooperate to induce tumor formation

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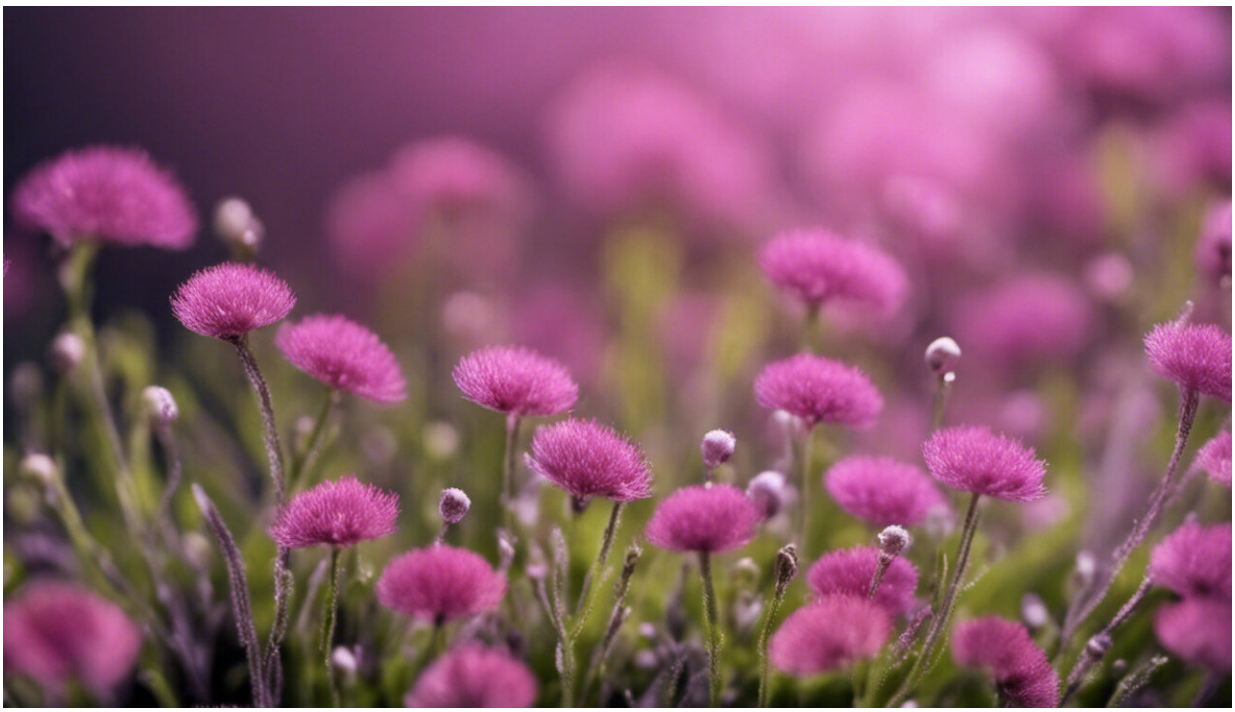

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Cancer biologists have known for decades that even the most potent cancer-causing genes do not act alone. Yet, identifying which combinations of genetic changes can cause a tumor to form and disease to progress remains a challenge. "The hope is that by understanding these

[combinations], it will be possible to design therapeutic strategies tailored to the genetic changes in different cancers," says Stephen Cohen of the A*STAR Institute of Molecular and Cell Biology (IMCB) and the National University of Singapore.

Sequencing the genomes of tumors from cancer patients is one approach to identifying cancer-causing mutations. The number of mutations can be so large, however, that researchers are left wondering which mutations are cancer 'drivers' and which are innocuous 'passengers', Cohen notes.

Taking an alternative approach, Cohen and his team in Singapore succeeded in identifying cancer-causing genes in the fruit fly, Drosophila melanogaster, based on function. The team set out to find genes that cooperate with known cancer drivers that promote tumor formation.

They began with a gene linked to breast and lung cancer, epidermal growth factor receptor (EGFR). Team member Hector Herranz developed a fly model in which activation of EGFR caused tissue overgrowth, but these overgrowths did not progress to form tumors. He then screened for secondary genetic changes that would enhance the ability of EGFR to produce tumors. Herranz found that co-expression of a microRNA called bantam with EGFR produced tumors that spread through the body and killed the fly.

As regulatory genes that produce small RNA molecules, microRNAs typically reduce the expression of other genes, decreasing their ability to produce proteins. The team therefore searched for a target of the microRNA whose absence increased the tumor-forming potential of EGFR. Team member Xin Hong was able to locate it: a gene known as Socs36E. In the team's fly model, Socs36E behaved like a tumor suppressor: the deletion of Socs36E enhanced EGFR-induced tumor

formation.

Hong then identified the corresponding human gene as SOCS5. He found that it also behaved as a tumor suppressor; SOCS5 cooperated with EGFR in an experimental model of human cancer.

Studies on human SOCS5 are ongoing, Cohen explains, but early indications point to a breast cancer link. Further work by the team will determine whether SOCS5 could be a useful biomarker.

More information: Herranz, H., Hong, X., Hung, N. T., Voorhoeve, P. M. & Cohen, S. M. Oncogenic cooperation between SOCS family proteins and EGFR identified using a Drosophila epithelial transformation model. *Genes & Development* 26, 1602–1611 (2012). genesdev.cshlp.org/content/26/14/1602

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