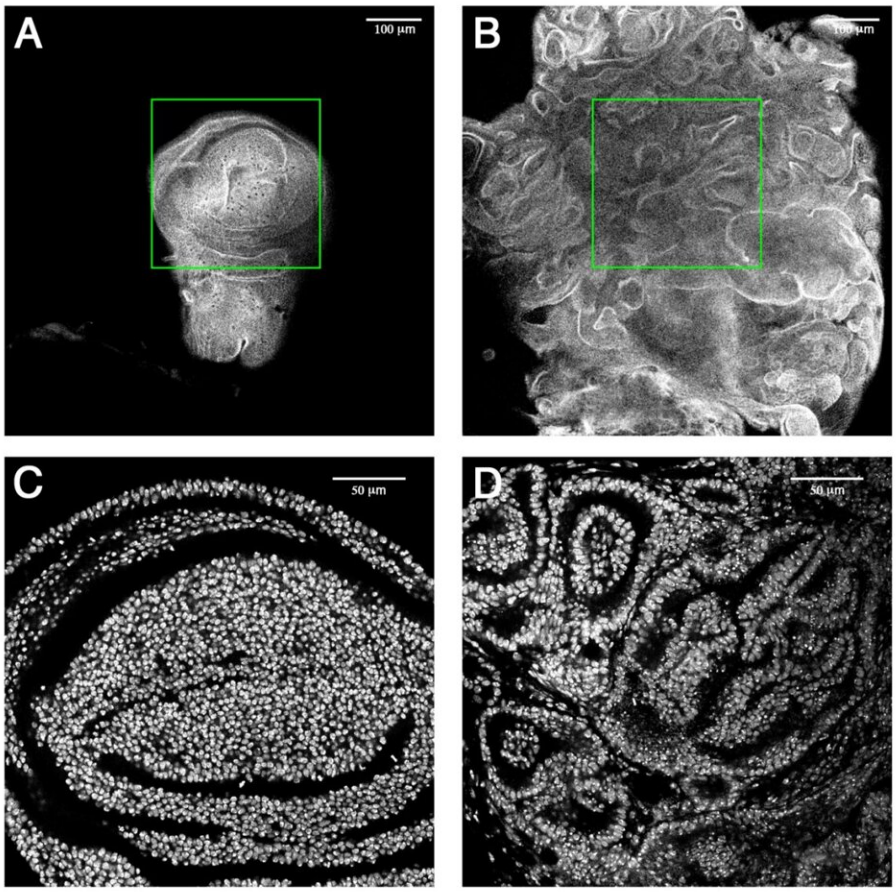
Researchers develop a study model for Ewing sarcoma in the Drosophila fly

October 7 2022



EWS-FLI$_{1FS}$ induces epithelial malignant tumors in the developing wing discs. Wing imaginal disc from a wild-type third instar larvae (A, C) and wing disc tumor after implantation in an adult host (B, D). Green squares in A and B represent the area shown in C and D. Scale bar=100 µm in A and B. Scale bar=50 µm in C and D. Credit: *PNAS Nexus* (2022). DOI: 10.1093/pnasnexus/pgac222

Ewing sarcoma is the second most frequent bone tumor in children, adolescents, and young adults. There is no specific treatment for this disease and current management is still limited to surgery, radiotherapy, and chemotherapy. The long-term survival of patients with metastatic or relapsed Ewing sarcoma is very low.

Ewing sarcoma is caused by a single oncogene that results from the fusion of two genes. Although a variety of genes may be involved, EWSR1 and FLI1 and the resulting cancer-driving oncogene, known as EWS-FLI, are found to be responsible in the majority of patients. Unlike most other types of cancer, all attempts to develop experimental animal models of Ewing sarcoma in mice (expressing the EWS-FLI oncogene) have failed.

Prompted by the need for a genetically tractable model that could be used to study the disease, researchers led by Dr. Cayetano González, ICREA research professor at IRB Barcelona, and Dr. Jaume Mora, scientific director at the SJD Pediatric Cancer Center Barcelona (PCCB), have engineered Drosophila transgenic strains that express a mutant variant of the human oncogene called EWS-FLIFS.

Remarkably, they have found that expression of the human EWS-FLIFS protein in certain types of Drosophila cells triggers the same oncogenic pathways known to account for EWS-FLI oncogenic activity in human patients.

Lighting up two oncogenic pathways

Building upon their new transgenic Drosophila line, the authors have rewired two oncogenic pathways used by EWS-FLI, such that when triggered by the presence of EWS-FLIFS, they result in the expression

of a fluorescent protein that would otherwise never be expressed. Thus, rather than tumor growth, the researchers use fluorescence as a read-out of EWS-FLI oncogenic activity.

"This simple genetic trick greatly facilitates the implementation of massive genetic and chemical screens to identify 'modifiers' that inhibit EWS-FLI's oncogenic activity as inhibitors of the appearance of fluorescence," explains Dr. Cristina Molnar, a postdoctoral researcher at IRB Barcelona and first author of the study.

Genetic screens based on this new model will make it possible to discover critical proteins required for EWS-FLI to exert its oncogenic function, hence expanding our knowledge of the molecular basis of the disease, as well as identifying new putative therapeutic targets. Chemical screens may identify compounds that could serve as lead molecules for the development of therapeutic drugs.

The research was published in *PNAS Nexus*.

More information: Cristina Molnar et al, Human EWS-FLI protein recapitulates in Drosophila the neomorphic functions that induce Ewing sarcoma tumorigenesis, *PNAS Nexus* (2022). DOI: 10.1093/pnasnexus/pgac222

Provided by Institute for Research in Biomedicine (IRB Barcelona)