Activity of cancer inducing genes can be controlled by the cell's skeleton

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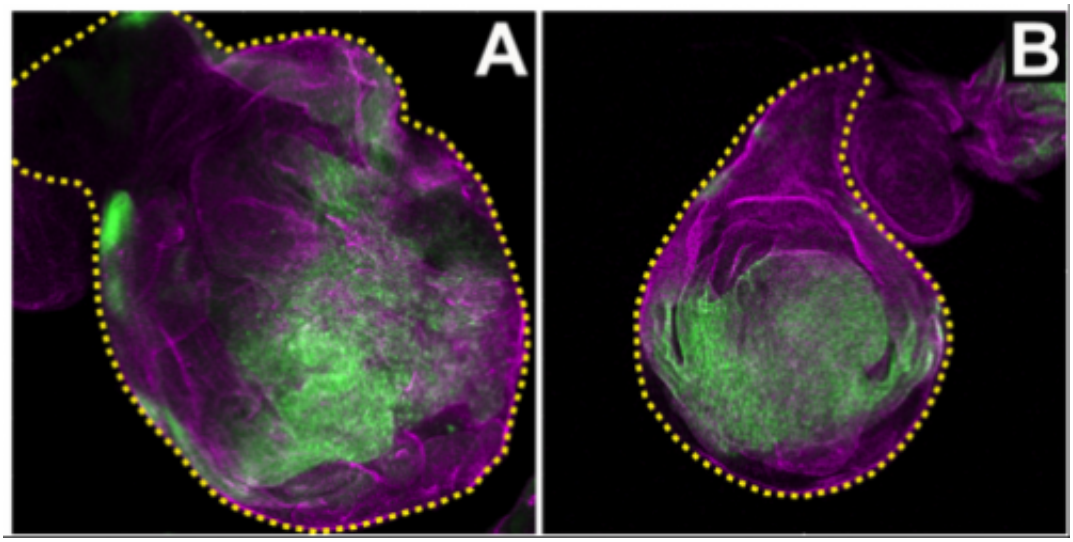

A) Tissue overgrowth is due to the presence of higher levels of Scr activity in the fruit fly wing disc (tissue that will generate the wings in the adult fly); B) This overgrowth is restrained due to a higher expression of the "tuner" actin Capping protein. Credit: Beatriz Gárcia Fernandéz, IGC.

Cancer is a complex disease, in which cells undergo a series of alterations, including changes in their architecture; an increase in their ability to divide, to survive and to invade new tissues or metastasis. A category of genes, called oncogenes, is critical during cancer progression, as they codify proteins whose activity favours the development of cancer. One of these molecules, Src, is implicated in a large number of human cancers. However, it is still not clear how healthy

cells constrain its activity not to become tumorous. In the latest issue of the journal *Oncogene*, Florence Janody and her team at the Instituto Gulbenkian de Ciência (IGC, Portugal), identified a novel mechanism by which the activity of Src is limited by the cell's skeleton (named cytoskeleton) limiting the development of tumours.

Using the fruit fly, *Drosophila melanogaster*, as a model, Florence Janody and her team were able to stop the tumour development induced by the high activity of Src through the genetic manipulation of the cytoskeleton in fly tissues. A major component of the cytoskeleton, the actin protein, form cables that crisscross the cell, creating a network, where molecules can move, inside the cell. These cables are constantly being elongated and shortened at their ends in a process tuned by molecules called actin-Capping Proteins. Florence Janody´s team showed that the development of tumours is stopped in the presence of high levels of the actin Capping Protein. This "tuner" restrains the activity of proteins that are usually activated by high levels of Src. Although the precise molecular mechanism is still unknown, the hypothesis raised by these scientists is that the "tuner" creates a tension in the cables of the cytoskeleton that impedes the action of these proteins. Conversely, the activity of Src is higher when the levels of the actin Capping Protein are lower, as the proteins activated by Src are able to escape the blocking effect of the network and act in the cell, resulting in the development of tumours. Thus, when the cytoskeleton network is not tightly regulated, the activity of oncogenes such as Src is not trapped and tumour development is observed.

Florence Janody says: "The cytoskeleton works as a "barbwire" network. The winner of the competition between molecules of the "barbwire" network and the Src oncogene, which fights against it, will determine whether the cell will stay healthy or become a cancer cell.

Beatriz García Fernández and Barbara Jezowska, first authors of this

work added: "Our work suggests that the appearance of mutations in molecules that regulate the skeleton may play a significant role in inducing cancer development during the early stages of the disease by releasing the activity of oncogenes."

Src was the first oncogene described in the 1950s as capable to induce cancer. This discovery was awarded with the Nobel Prize in Physiology and Medicine in 1989.

More information: García Fernández, B., Jezowska, B., and Janody, F. (2013) Drosophila actin-Capping Protein limits JNK activation by the Src proto-oncogene, *Oncogene*, May 6, doi:10.1038/onc.2013.155

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