Scientists uncover role for cell scaffold in tumor formation

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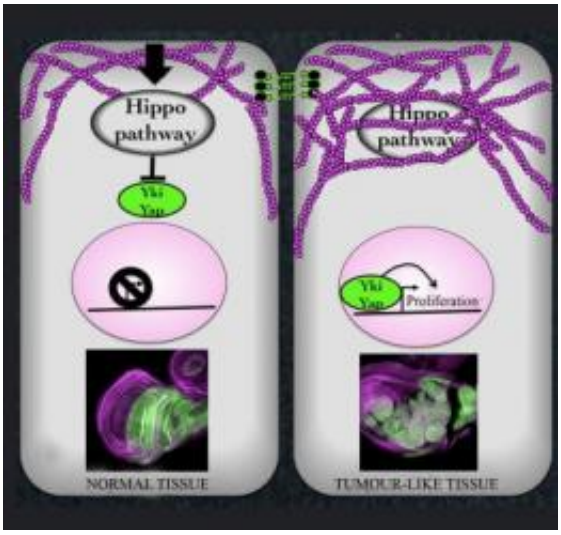

In normal tissue, with an intact cytoskeleton (in purple), the Hippo complex blocks the Yorkie protein (Yki, in green) from activating proliferation genes in the nucleus (image on the left). When the cytoskeleton is deregulated, Yorkie is free to enter the nucleus and activate proliferation of the cell (image on the right). Credit: Florence Janody, IGC

A group of scientists at the Instituto Gulbenkian de Ciencia, in Portugal, have uncovered a surprising link between the cell's skeleton and organ size. The team, led by Florence Janody, show in the journal *Development*, that one of the proteins that regulates the skeleton of the cell also acts to blocks activation of genes that promote cell survival and proliferation. Their findings have implications for cancer research, as

they add to the puzzle of understanding how proliferation genes are abnormally activated, often leading to tumours.

During development of an embryo, cells proliferate and organs grow. This process is tightly regulated, at several levels, to ensure that organs do not outgrow the body they are in. One of the key regulators in this process is the Hippo complex of proteins - first identified in the fruit fly Drosophila melanogaster. Mutant flies, in which this complex is defective are larger than their counterparts - they are hippopotamus-like. A search for analogous genes uncovered a similar role for the Hippo complex in mammals - organs grow larger than they should. In adults, this abnormal and untimely growth often leads to tumour formation.

A flurry of papers has shown that the Hippo complex itself is regulated by a range of signaling inputs within the cell. Florence Janody's group identified a new, and unexpected input: the cell skeleton (called cytoskeleton), in particular one of its proteins, the actin-capping protein.

Using Drosophila larvae, the IGC team showed that when the actin-capping proteins are inactive, there is overgrowth of tissue in the area that will become the adult wing. This growth is reminiscent of tumour formation. The researchers dissected the different steps in the process that lead to abnormal growth. Inactivating actin-capping proteins leads to accumulation of actin, a major component of the cytoskeleton; this reduces the activity of the Hippo complex, leaving another protein, Yorkie, free to act on the DNA in the nucleus, turning on proliferation genes.

The cytoskeleton serves several functions in a cell: it provides structure, motility (allows cells to move, change shape and divide) and membrane traffic (transport of proteins and other large molecules within the cell). The actin protein forms cables that crisscross the cell. The cables are constantly being elongated and shortened at their ends. The actin-

capping proteins are involved in this process.

In Florence's words, ' What we've revealed is that the cytoskeleton needs to be very tightly regulated within the cell, to prevent abnormal growth in the larvae. Since Hippo is also turned on in the adult and in mammals, we believe these findings provide insights into how this process may be manipulated in human cells, with a view to preventing tumour formation, or blocking its progression'.

Provided by Instituto Gulbenkian de Ciencia