How does a heart know when it's big enough?

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A protein discovered in fruit fly eyes has brought a Johns Hopkins team closer to understanding how the human heart and other organs automatically "right size" themselves, a piece of information that may hold clues to controlling cancer.

The protein, named Kibra, is linked to a relay of chemical signals responsible for shaping and sizing tissue growth by coordinating control of cell proliferation and death, according to research published Feb. 16 in *Developmental Cell* by teams at Johns Hopkins and Florida State University.

In a series of experiments, the scientists manipulated Kibra's role in a signaling network called the Hippo pathway, which consists of several proteins working together as a braking system. Counterparts of the components in the Hippo pathway in flies are found in most animals, suggesting that this pathway may act as a "global regulator" of organ size control, according to Duojia Pan, Ph.D., a professor of molecular biology and genetics at Johns Hopkins University School of Medicine and an investigator of the Howard Hughes Medical Institute.

"People have always been curious about what makes a hippopotamus grow so much bigger than a mouse," says Pan, "as well as how our two hands, which develop independently, get to very similar sizes. Our studies show that Kibra regulates Hippo, which keeps organs characteristically sized, preventing my heart or your liver from becoming as hefty as those befitting a large African amphibious mammal," he adds, referring to the signaling pathway's name.

Pan's team identified the gene they named Hippo in 2003, showing that an abnormal copy of it led to an unusually large eye in a developing fruit fly. Two years later, the team established that Hippo lies in the middle of a signaling cascade: Its "stop growing" message is relayed along a molecular pathway of biochemically linked proteins, which limits the expression of genes that otherwise promote cell division and cell survival. In 2007, they showed that by manipulating the pathway in a mouse liver, the organ grew to five times its normal size and became cancerous.

The new experiments, Pan says, moved the investigation "slowly and methodically upstream" to find Hippo's trigger, where, he believes, "the key to size-control lies." The Hippo-Kibra link could be a key to understanding and treating cancer, Pan adds, because cancer is literally a disease of uncontrolled growth.

The Johns Hopkins and Florida State teams discovered Kibra by studying ovarian cells from adult flies and by using a gene-controlling technique called RNA interference (RNAi) to systematically turn off each of the approximately 14,000 genes in the fly genome, one at a time, in cultured fly cells. They then analyzed the function of Kibra in the developing fly larvae. Each of the specialized discs that develop into a fly's eyes starts out with approximately 30 to 40 cells and then grows by about a thousand-fold in the larval stage before stopping, making larvae the ideal place to catch the right-sizing process in action, Pan says. These studies told them that the Hippo pathway was not active in the absence Kibra.

Further studies on human cells measured the activity of the Hippo pathway while manipulating human Kibra and showed that like its fruit fly counterpart, human Kibra acts as a tumor suppressor protein that regulates Hippo signaling.

"The discovery of Kibra moves us an important step closer to identifying the initial signal that triggers Hippo's activation," Pan says. "We're making progress along the Hippo pathway, heading toward the cell surface, and believe we will find that elusive signal en route."

The name Kibra, a shortened combination of the words kidney and brain, is based on earlier evidence that Kibra is prominently expressed in those two organs. Kibra's role in memory performance in humans has already garnered interest.

More information: www.cell.com/developmental-cell/

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