Loss of cell's 'antenna' linked to cancer's development

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Cartoon showing HEF1 and Aurora A proteins dismantling cell's "antenna." Credit: Debbie Foster, Fox Chase Cancer Center

Submarines have periscopes. Insects have antennae. And increasingly, biologists are finding that most normal vertebrate cells have cilia, small hair-like structures that protrude like antennae into the surrounding environment to detect signals that control cell growth. In a new study published in the June 29 issue of *Cell*, Fox Chase Cancer Center researchers describe the strong link between ciliary signaling and cancer and identify the rogue engineers responsible for dismantling the cell's antenna.

Cilia-based sensing has important roles in sight, smell and motion detection and in helping an embryo develop into a normal baby. Defects in cilia can produce a range of disorders, including kidney cysts, infertility, respiratory problems, reversal of organs (for example, heart

on the right) and a predisposition to obesity, diabetes and high blood pressure. In each case, cells fail to appropriately detect growth-controlling signals and develop abnormally. Now, researchers are adding cancer to this list.

“Many cancers arise from defects in cellular signaling systems, and we think we have just identified a really exciting signaling connection,” Fox Chase Cancer Center molecular biologist Erica A. Golemis, Ph.D., points out. In the new study, Golemis and her Fox Chase colleagues found that two proteins with important roles in cancer progression and metastasis, HEF1 and Aurora A, have an unexpected role in controlling the temporary disappearance of cilia during normal cell division, by turning on a third protein, HDAC6. This action causes the “antenna” to be dismantled in an untimely way.

Why cilia come and go on normal cells is not entirely understood, but scientists increasingly suspect that it may play a role in timing the cell division process. Commonly, cancer cells have entirely lost their cilia, and this absence may help explain why tumors fail to respond properly to environmental cues that cause normal cells to stop growing. Hence, the discovery that too much HEF1 and Aurora A cause cilia to disassemble provides important hints into what may be happening in cancers.

Defects in cilia have already been identified in one disease that represents a significant public health burden. Polycystic kidney disease, or PKD, arises from genetic mutations that cause flawed kidney-cell ciliary signaling. PKD is the most common serious hereditary disease, affecting more than 600,000 Americans and 12.5 million people worldwide.

In this incurable syndrome, patients develop numerous, fluid-filled cysts on the kidneys. For many patients, chronic pain is a common problem. PKD leads to kidney failure in about half of cases, requiring kidney

dialysis or a kidney transplant.

The proteins involved in dismantling the cilia are no strangers to Golemis and her team. Golemis has been studying HEF1 for over a decade, since she first identified the gene. She first discovered that HEF1 has a role in controlling normal cell movement and tumor cell invasion. Golemis' laboratory has also shown that Aurora A and HEF1 interact to initiate mitosis (chromosome separation) during cell division.

Suggestively, many cancers produce too much of the Aurora A protein, including breast and colorectal cancers and leukemia. In 2006, excessive production of HEF1 (also known as NEDD9) was found to drive metastasis in over a third of human melanomas, while HEF1 signaling also contributes to the aggressiveness of some brain cancers (glioblastomas).

"Now there's a new activity for these proteins at cilia," said co-author Elizabeth P. Henske, M.D., a medical oncologist and genetics researcher who studies the genetic basis of kidney tumors. This complex HEF1 and Aurora A function may mean the increased levels of these proteins in cancer affect cellular response to multiple signaling pathways, rather like a chain reaction highway accident.

Clinical Application

The research has significant implications for the understanding and treatment of cancer. The experiments leading to the new paper showed that "small-molecule inhibitors of Aurora A and HDAC6 selectively stabilize cilia," the authors concluded, "suggesting a novel mode of action for these clinical agents." Clinical trials of such inhibitors have already begun, so learning more about the mechanisms of their targets is important in understanding how these agents work and who might benefit from them.

“It is also tantalizing to consider that closer connections exist between dysplastic disorders leading to cysts and cancer than have previously been appreciated,” the authors wrote. “Overall, deregulated Aurora A/HEF1/HDAC6 signaling may have broad implications for studies of human development and disease.”

The authors are now investigating possible roles for HEF1 and Aurora A in PKD. They are intrigued by the fact that a study published last year showed that important gene, PKHD1, commonly mutated in PKD has also been found as a target of mutation in colorectal cancer.

Source: Fox Chase Cancer Center