Researchers discover, manipulate molecular interplay that moves cancer cells

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Based on research that reveals new insight into mechanisms that allow invasive tumor cells to move, researchers at the Mayo Clinic campus in Florida have a new understanding about how to stop cancer from spreading. A cancer that spreads elsewhere in the body, known as metastasis, is the process that most often leads to death from the disease.

In the March 29 online issue of Nature Cell Biology, researchers say that a molecule known as protein kinase D1 (PKD1) is key to the ability of a tumor cell to "remodel" its structure, enabling it to migrate and invade. The researchers found that if PKD1 is active, tumor cells cannot move, a finding they say explains why PKD1 is silenced in some invasive cancers.

During metastasis, invasive cancer cells respond to biological signals to move away from a primary tumor. Multiple research groups at Mayo Clinic in Florida are especially interested in this process. One team, led by cancer biologist Peter Storz, Ph.D., has been investigating a process known as actin remodeling at the leading edge - the most forward point - of these migrating tumor cells.

"The events that reorganize the actin cytoskeleton at the leading edge are complex — a multitude of molecules act in concert," Dr. Storz says. "But it appears that PKD1 must be turned off if cancer cells are to migrate."

Actin filaments help make up the cytoskeleton of cells. For cancer cells

to move, the actin-based cell structure has to be continually reorganized, Dr. Storz says, and to do this, new actin filaments need to be generated to shift the cell forward.

Dr. Storz' group discovered that PKD1 was critical to this process. The researchers found that PKD1 inhibits another protein known as slingshot, which regulates the severing of existing actin structures so that new actin filaments can be synthesized, an event that is essential for cell movement.

The researchers used methods to deplete tumor cells of PKD1 and found that their motility increased. They then expressed activated PKD1 in tumor cells and found that movement was blocked. PKD1 is therefore a negative regulator of directed cell migration, and if PKD1 is not expressed in tumor cells, slingshot will become active and will contribute to the reorganization of actin, and a tumor cell will move, according to researchers.

"This makes sense, because other investigators have found that PKD1 is down-regulated, or turned off, in invasive forms of gastric, prostate, and breast cancer," says Dr. Storz.

So far, investigators have identified a number of players along the pathways that regulate cancer cell movement, from the molecule (RhoaA) that activates PKD1, to the well-known protein (cofilin) that disassembles actin filaments and which is regulated by slingshot. When PKD1 is activated, cofilin does not function and so the cell cannot move.

"Now that we have identified PKD1 as key regulator in processes regulating actin-based directed tumor cell movement, we can begin to think about designing treatments to stop invasive cancer cells from metastasizing," says Dr. Storz. "The basic mechanisms we have uncovered are key to developing those strategies."

Source: Mayo Clinic (news : web)

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