Cancer Researchers Describe Gene That Halts Spread of Aggressive Childhood Cancer

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Findings confirm new 'metastasis suppressor' gene

A team of cancer researchers has shown that a gene commonly lost during neuroblastoma tumor formation, one of the most aggressive cancers in babies and children, is in fact a "metastasis suppressor" gene. The researchers, from the Moores Cancer Center at the University of California, San Diego (UCSD) Medical Center and St. Jude Children's Research Hospital in Memphis, also describe how the gene, caspase 8, works.

The findings, published in the January 5 issue of the journal *Nature*, provide important new insights into the biology of metastatic disease and lay the necessary groundwork for developing targeted therapies designed to halt the spread of neuroblastoma, and possibly other cancers.

"A major problem with cancer is not necessarily the primary tumor formation, but the ability of some tumor cells within that primary tumor to metastasize, or travel to distant sites, where they develop new tumors," said David Cheresh, Ph.D., senior author on the paper and Associate Director for Translational Research at the Moores UCSD Cancer Center. Cheresh is also a professor of pathology at the UCSD School of Medicine.

Caspase 8's normal role is to act as a suicide gene, killing the cell it is housed within in response to cues from the immune system. The UCSD group had previously shown, in normal human cells, that caspase 8 can be activated even without signals from the immune system, particularly when the cell is present in a foreign location. This acts as a mechanism to ensure the cells would survive only in appropriate tissues; for example, liver cells in liver tissue and skin cells in skin tissue.

"The exciting point of the new research is that we are finding that even tumor cells will try to make sense of their location, and when they cannot, they will often activate this suicide pathway," said Dwayne Stupack, Ph.D., first author on the paper and assistant professor of pathology at UCSD.

The team showed that when a neuroblastoma cell attempts to migrate away from the primary tumor and encounters new tissues, cell-surface molecules called integrins detect that the cell is in "foreign territory" and send "death" signals into the cell. These signals activate caspase 8, which then instructs the cell to commit suicide. The researchers have coined this mechanism "integrin-mediated death."

Some cancer cells, however, have found a way to escape the normal death-promoting machinery the body has developed. These cells may suppress or even delete caspase 8, freeing themselves to become much more aggressive and survive in distant sites in the body.

"We've shown now in animals and human tissue that as soon as the neuroblastoma cells lose caspase 8, suddenly you have a much more aggressive disease," said Stupack. "This explains why we see the loss of caspase 8 in 70 percent of aggressive neuroblastomas in children."

Neuroblastoma is a solid tumor cancer that usually originates in the abdomen near the kidneys. In the majority of cases (about 70 percent), by the time of diagnosis the disease has already metastasized. The average age at diagnosis is two years old.

"It is clear this gene is a deciding factor in whether or not a cancer cell becomes metastatic, yet, surprisingly, it does not appear to be involved at all in the initial formation of the cancer," said Stupack. "As such, it is one of only a handful of true metastasis suppressor genes currently known."

A number of other cancers may use this same mechanism for regulating their metastatic properties, which the researchers are now studying. Caspase 8 loss or suppression is seen in about 70 percent of small cell lung cancer, about 10 percent of colon cancer and about 35 percent of medulloblastoma. While genetic mutation will sometimes delete both copies of the caspase 8 gene, typically the gene is simply silenced.

This paper opens up a new way of thinking about cancer therapy.

"Now we have a roadmap for attacking not just the primary cancer but the metastatic cascade, the metastatic disease process, as well," said Cheresh. "That is new, and very exciting. We now know the Achilles heel of the metastatic tumor cell. If we can develop drugs targeted at restoring caspase 8, we may be able to stop metastasis. That now appears feasible."

The study was co-authored by a team from St. Jude that included Tal Teitz, Ph.D., Peter Houghton, M.D., and Jill Lahti, Ph.D., as well as by UCSD scientists Matthew Potter, Ph.D., and David Mikolon. Lahti, the senior scientist in the St. Jude group, has collaborated with Stupack for several years.

The work was funded by grants from the National Cancer Institute awarded to Cheresh, Lahti, Houghton and Stupack. Additional local funding was provided by a grant from the San Diego

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Founded in 1979, the Moores UCSD Cancer Center is one of just 39 centers in the United States to hold a National Cancer Institute (NCI) designation as a Comprehensive Cancer Center. As such, it ranks among the top centers in the nation conducting basic, translational and clinical cancer research; providing advanced patient care; and serving the community through outreach and education programs.

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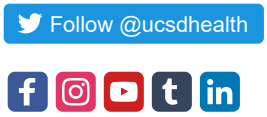
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