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Study identifies gene critical to development and spread of lung cancer

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A single gene that promotes initial development of the most common form of lung cancer and its lethal metastases has been identified by researchers at Mayo Clinic in Florida. Their study suggests other forms of cancer may also be driven by this gene, matrix metalloproteinase-10 (MMP-10).

The study, published in the journal PLoS ONE on April 24, shows that MMP-10 is a growth factor secreted and then used by cancer stem-like cells to keep themselves vital. These cells then drive lung cancer and its spread, and are notoriously immune to conventional treatment.

The findings raise hope for a possible treatment for non-small cell lung cancer, the leading cause of U.S. cancer deaths. Researchers discovered that by shutting down MMP-10, lung cancer stem cells lose their ability to develop tumors. When the gene is given back to the cells, they can form tumors again.

The power of this gene is extraordinary, says senior investigator Alan Fields, Ph.D., the Monica Flynn Jacoby Professor of Cancer Research within the Department of Cancer Biology at Mayo Clinic in Florida.

"Our data provides evidence that MMP-10 plays a dual role in cancer. It stimulates the growth of cancer stem cells and stimulates their metastatic potential," he says. "This helps explain an observation that has been seen in cancer stem cells from many tumor types, namely that cancer stem cells appear to be not only the cells that initiate tumors, but also the cells

that give rise to metastases."

Dr. Fields says the findings were unexpected, for several reasons.

The first is that the cancer stem cells express MMP-10 themselves, and use it for their own growth. Most of the known members of the matrix metalloproteinase genes are expressed in the tumor's microenvironment, the cells and tissue that surround a tumor, he says. The enzymes produced by these genes are involved in breaking down the microenvironment that keeps a tumor in place, allowing cancer cells to spread, which is why other genes in this family have been linked to cancer metastasis.

"The fact that a gene like MMP-10, which codes for a matrix metalloproteinase that has been linked to metastasis, is actually required for the growth and maintenance of cancer stem cells is very surprising. One would not have predicted that such a gene would be involved in this process," Dr. Fields says.

The researchers also did not expect to find that cancer stem cells produce much more MMP-10 than do the rest of the cells that make up the bulk of the tumor.

"MMP-10 acts to keep these cancer stem cells healthy and self renewing, which also helps explain why these cells escape conventional chemotherapy that might destroy the rest of the tumor," Dr. Fields says. "That is why lung cancer often recurs after treatment, and why its spread to other parts of the lung, as well as nearby lymph nodes, the brain, liver and spinal cord can't be stopped."

Researchers say their study suggests that MMP-10 overexpression may also be crucial to the survival of other human cancer stem cells. They observed a similar link between MMP-10 expression and the metastatic

behavior and stem-like properties of human colorectal cancer, melanoma, breast, renal, and prostate cancers.

The researchers are now looking for the mechanism by which MMP-10 stimulates the growth of cancer stem cells, and are investigating the design of inhibitors that could be used to inhibit MMP-10 activity.

"Given its dual role in cancer stem cells and metastasis, targeting MMP-10 may be especially effective in treating these tumors," Dr. Fields says.

More information: dx.plos.org/10.1371/journal.pone.0035040

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