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Brain metastases hijack neuron-supporting cells to resist chemotherapy

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Cancer that spreads to other organs finds a particularly inviting hideout in the brain, where these metastases are usually far harder to treat than they are in other locations. Two researchers from The University of Texas M. D. Anderson Cancer Center discussed ways to more successfully target these tumors in their "sanctuary" at the American Association for Cancer Research 100th Annual Meeting 2009 in Denver.

Professor of Cancer Biology Isaiah J. Fidler, D.V.M., Ph.D., presented a novel theory about why brain metastases are resistant to chemotherapy.

"Astrocytes are spider-like cells that normally play the important role of providing oxygen and nutrients to neurons, and protecting neurons from naturally occurring toxins," Fidler said. "We show that brain metastases subvert astrocytes, tricking them into protecting the tumors, and that this is the important factor in resistance to chemotherapy."

Professor and Chair of Neurosurgery Raymond Sawaya, M.D., reviewed when and how to conduct surgery to remove metastatic tumors, including evidence that removing a tumor piecemeal raises the risk of cancer irretrievably spreading to the spinal fluid.

Fidler and Sawaya were among five speakers at "Invading the Sanctuary: New approaches to Brain Metastasis." Metastatic cancer causes the vast majority of cancer deaths. There are more than 100,000 new cases of metastatic brain cancer each year. By comparison, primary malignant brain tumors account for about 17,000 new cases annually.

Not all cancers spread to the brain. Sawaya lists lung, breast, melanoma, kidney and colon cancer as the most common. "It's common for us to operate on patients who no longer have known disease except for the metastasis in the brain," Sawaya said. Such patients have a better prognosis than those with heavier tumor burden elsewhere.

Research Shows Astrocytes Negate Chemotherapy

"The only way metastases can grow in an organ is to exploit the host organ's microenvironment," said Fidler, who with a series of experiments revived the seed-and-soil theory of metastasis first suggested by British physician Steven Paget more than 100 years ago. Paget argued that metastasis was not a random process, but that specific cancers spread only to certain organs - those who served as welcoming "soil" for specific cancer "seeds."

Fidler and colleagues examined alternate hypotheses for chemotherapy resistance. The blood-brain barrier, a tightness to brain vasculature that blocks blood-born toxins from entering the brain, was a prime suspect. They found that the barrier remains intact outside a metastasis, but breaks down inside metastases, which generally have leaky vasculature.

Another theory is that the P glycoprotein (PGP), a membrane protein that expels drugs from a cell's cytoplasm, blocks chemotherapy. "Our work and others' showed that using drugs that are totally resistant to PGP, or blocking PGP itself, did not improve survival," Fidler said.

The team turned to astrocytes, which are extremely sensitive to activation by hypoxia and inflammatory cytokines. "Every single metastasis in the brain and primary tumors are surrounded by activated astrocytes," Fidler said.

In a mouse with lung cancer or breast cancer brain metastases, astrocytes

surrounded and infiltrated the lesions. "The tumor kept growing, so they obviously were not killing it," Fidler said.

Fidler and colleagues separately introduced the drug Taxol and the PGP-resistant drug fluorouracil to cultures of metastatic breast cancer. Both drugs induced apoptosis, or programmed cell death. When the cells were collected with astrocytes, cell death dropped to levels seen when there was no drug applied to the cancer cells at all. Cultures treated with fibroblasts, another type of supportive cell, derived no protection against chemotherapy.

These results held for metastatic lung cancer and melanoma as well.

To better understand the mechanisms involved, the team cultured human breast and lung cancer cells with mouse astrocytes and fibroblasts.

Culturing either type of cancer with astrocytes increased the expression of six survival genes in the cancer cells. Additional research showed the astrocytes must be touching cancer cells to protect them, much like they physically touch neurons with one arm and tap a capillary with another arm.

Fidler and colleagues are investigating ways to inhibit astrocytes in tumors without affecting those that protect neurons. "To treat brain metastasis we must pay attention to the organ microenvironment, otherwise there is no way chemotherapy can work," Fidler said.

When surgery is warranted, en bloc removal is best

Brain metastases in the lower back portion of the brain - the posterior fossa - tend to escape irretrievably to the spinal fluid. Sawaya and colleagues at M. D. Anderson compared treatment of 379 such tumors with either surgery or noninvasive stereotactic radiosurgery. Of the 260

tumors that were surgically removed, 123 were completely intact (en bloc) and 137 were taken out in pieces.

They reported in the Journal of Neurosurgery last year that the cancer spread to the spinal fluid 6 percent of the time for those receiving the highly targeted radiation and also for those who had their tumor removed en bloc. Tumors removed piecemeal spread 14 percent of the time.

"This is the first time anybody has shown that the way you remove a brain tumor, in this case a metastasis, affects the likelihood of containing it or of spreading the tumor in the central nervous system," Sawaya said. "The good news is that surgery done en bloc does not add to that risk, which has drawn a great deal of interest in that study."

A number of important factors go into deciding whether a patient with metastatic brain tumors is a good candidate for surgery, Sawaya said.

Tumor size, location and origin are important, as are a patient's age, neurological status and general condition. The extent of metastatic cancer elsewhere in the body is crucial. "Those with evidence of extensive systemic disease don't do well," Sawaya said. Past or potential response to therapy and the number of metastases in the brain, are determining factors.

Patients used to be ineligible if they had more than one brain metastasis, but Sawaya and colleagues demonstrated in a 1993 paper that median survival of patients with two metastases removed was 14 months, identical to the survival of patients after surgery to remove only one metastasis. Now surgery can be considered for up to three metastases.

Improved techniques and better surgical guidelines have reduced surgical mortality - death from surgery, not cancer - from more than 30 percent to 2 percent over the last 50 years.

Studies show survival after surgery for melanoma, lung, renal cell, breast and colon cancer metastases ranges from a median of seven months for melanoma patients to a year for breast and lung cancer. Four studies showed that no patients with metastatic colon cancer survived for two years.

"Colon cancer goes first to the liver, then the lungs and then to the brain, so patients already have extensive cancer by the time it grows in the brain," Sawaya said.

Metastases tend to find a spot in the brain and grow without invading brain tissue. "They push on the brain, and cause swelling," Sawaya said. Before and after images of a large melanoma show the tumor, then a gap after surgery where the tumor had been, and then two years later no sign of tumor or gap.

"You take the tumor out, and the brain and white matter expand over time until you see no sign of the resected tumor," Sawaya said. The patient lived for more than five years.

Careful mapping of functional areas of the brain before surgery and new approaches that include reaching deeper tumors by going down into the folds of the brain rather than cutting through brain tissue have reduced side effects from surgery. A study of surgical results in 194 patients showed that the tumor was completely removed 94 percent of the time with neurological side effects in only 6 percent of cases.

Source: University of Texas M. D. Anderson Cancer Center (news : web)

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