Pediatric Glioblastoma Model Suggests Treatments

Mutations in the ATRX gene increase the aggressiveness and genetic instability of high-grade pediatric gliomas, but also leave tumors more susceptible to DNA-damaging drugs and radiation, according to a recently published study (Sci Transl Med 2016;8:328ra28).

ATRX, a histone chaperone protein, is inactivated by mutation in 30% of pediatric glioblastoma multiforme, tumors that progress rapidly, have no effective treatment, and are universally fatal. The study links ATRX to defects in DNA repair, and suggests that some children may benefit from treatments that induce double-stranded DNA breaks, including topoisomerase inhibitors—topotecan and inotinocan—and radiation.

“This paper helps not only to elucidate the biology of this histone protein, but also to lay the platform for deciding how to potentially treat patients who have ATRX mutations,” says Maciej Lesniak, MD, a neurosurgical oncologist and chairman of neurosurgery at Northwestern University Feinberg School of Medicine in Chicago, IL, who was not involved with the study.

In the new work, Maria Castro, PhD, of the University of Michigan School of Medicine in Ann Arbor, and colleagues created a mouse model of ATRX-deficient glioblastoma by knocking down the gene in neuronal stem cells in the lateral ventricles of newborn pups. The mice developed aggressive tumors that displayed microsatellite instability, an indicator of genomic instability.

ATRX mutations cause genetic instability in human tumors, too, the researchers showed. An analysis of publicly available genome sequencing data from 293 pediatric high-grade gliomas revealed a higher incidence of single nucleotide variation in ATRX-mutated tumors, compared to ATRX-wild-type tumors. ATRX status did not correlate with copy-number alterations or karyotypic changes. The effect of ATRX on mutation rate was unique to childhood tumors—an analysis of 290 adult glioblastomas revealed no effect of ATRX status on mutation rate.

In the mice, ATRX loss resulted in specific defects in DNA repair, mainly affecting nonhomologous end joining pathways responsible for mending double-stranded DNA breaks. Because of the repair deficit, the mouse tumors were more sensitive to agents that induce double-stranded DNA damage, including doxorubicin, topoisomerase inhibitors, and radiation.

The results suggest that ATRX loss results in tumors that are both more aggressive and more responsive to treatment. Recent studies have shown that in adults, lower-grade gliomas with ATRX mutations respond better to treatment. In the new study, the researchers showed that ATRX mutations give a survival advantage in treated high-grade pediatric gliomas as well.

“We found exactly the same as in the mouse tumor—the genome of the pediatric cancers with ATRX mutations was unstable, and the children responded better to therapeutics,” Castro says.

The model will be useful for testing novel chemotherapeutic agents, either as single agents or in combination with radiation therapy. The model has another benefit too: Because it uses immunocompetent mice, researchers can assess immunotherapies as well, Castro says. —Pat McCaffrey ■

Proposed NIH Budget Includes Mandatory Funding

President Obama recently unveiled his proposed budget for fiscal year (FY) 2017, which would increase the NIH’s total budget by $825 million to roughly $33.1 billion. To fund the increase, he suggested relying on mandatory dollars instead of discretionary funding, which is controlled by Congress. In addition, he proposed trimming the NIH’s base budget, funded through discretionary spending, by $1 billion, which would then be offset by $1 billion in mandatory funding.

The modest overall increase of $825 million would prioritize just three NIH programs: $680 million for the NCI’s recently announced cancer “moonshot” initiative; $100 million for the Precision Medicine Initiative cohort program; and $45 million for the BRAIN initiative.

Many in the medical research advocacy community have greeted the proposed budget with considerable skepticism. “It’s unrealistic, generally speaking,” says Lynn Marquis, director of the Coalition for the Life Sciences. “Thinking in terms of your household budget, you’d never add to your mandatory expenses—picking up a more expensive mortgage, for instance—without knowing you could pay for it.” The same concept applies to what the president has proposed, she says, because a funding source for a mandatory budget increase for the NIH has yet to be identified. Additionally, competition for such funding sources is fierce. Discretionary dollars are more favorably regarded, Marquis explains, because “the appropriations process allows for flexibility to add new programs or modify existing initiatives.” On the other hand, mandatory spending—once a federal revenue stream has been established—includes no such flexibility, which “could be problematic for a constantly evolving agency like the NIH.” Nonetheless, she acknowledges that this was the president’s workaround “to ensure that important programs continue to receive sufficient support,” given that spending caps agreed to last year by Congress and the administration “left things very tight, fiscally.”

Mandatory funding is “not a totally foreign concept,” says NIH Director Francis Collins, MD, PhD. Last year, the House of Representatives passed the 21st Century Cures Act, aimed at accelerating drug discovery and development, which if implemented would provide nearly $9 billion in
An international team of researchers—led by Susan Halabi, PhD, a professor of biostatistics at Duke University School of Medicine in Durham, NC—gathered information from nine phase III studies, encompassing 8,736 men with mCRPC. The patients in these trials had all received docetaxel as standard therapy. The researchers classified them into one of four groups corresponding to the site of metastases: bone, liver, lungs, and lymph nodes. Most (72.8%) had bone metastases; another 8.6% and 9.1% had metastatic lesions in the liver and lungs, respectively, while those with lymph node metastases made up the smallest group (6.4%).

The researchers confirmed earlier studies identifying visceral disease—liver and lung metastases—as a negative prognostic factor of survival. Patients with liver metastases fared worst, with a median OS of just 13.5 months; those with lung metastases had a slightly longer median OS of 19.4 months. In contrast, patients with disease involving bone or lymph nodes had median survival times of 21.3 and 31.6 months, respectively.

Anthony D’Amico, MD, PhD, chief of genitourinary radiation oncology at Dana-Farber/Harvard Cancer Center in Boston, MA, suggests that particular variants of mCRPC could explain the poorer survival of patients with visceral disease. “Classic prostate adenocarcinomas have a penchant for bone-only metastases,” he explains. “Certain other prostate tumors, though, have a mixed histology that includes a neuroendocrine or small-cell component. These readily spread to internal organs like the liver and lungs and are associated with a worse prognosis.” Recent research has shown that even classic prostate adenocarcinomas can acquire neuroendocrine expression over time, he adds.

Distinguishing neuroendocrine and small-cell prostate cancer from adenocarcinoma is important, D’Amico says, because approved hormone therapies like abiraterone acetate (Zytiga; Janssen) and enzalutamide (Xtandi; Astellas) are not effective against these variants. Rather, “you want to consider chemotherapy that’s used in such histologies—platinum drugs, for instance, or etoposide.”

The study researchers think the significantly different outcomes seen with these four subgroups highlight the importance of reporting end points, including OS, by metastatic site—although this has yet to be widely implemented in phase III studies of mCRPC. D’Amico agrees, adding that “future trials should be directed based on the biopsy of a patient’s metastatic lesion, so we know exactly what we’re dealing with and can figure out the best treatment.” –Alissa Poh ■

**Inflammation May Activate Antitumor Mechanism**

Inflammation promotes colorectal cancer, but it may also trip a molecular switch that hinders tumor growth by stimulating stem cells to divide asymmetrically, a recent study reported (Cell Stem Cell 2016;18:189–202).

Many types of normal stem cells divide asymmetrically, typically producing another stem cell and a cell that goes on to differentiate; normal intestinal and colon stem cells divide symmetrically. Cancer stem cells can divide symmetrically or asymmetrically, and “the consensus is that asymmetric division limits or suppresses cancer,” says Xiling Shen, PhD, of Duke University in Durham, NC, because it caps the number of cancer stem cells.

Shen and his colleagues investigated what controls intestinal stem cells’ mode of division, focusing on the developmental genes Numb and Notch and the tumor suppressor miR-34a. Notch stimulates cell division and promotes colon cancer, whereas Numb and miR-34a cause cells to differentiate and develop normally.

To the team’s surprise, they found that in addition to directly inhibiting Notch, miR-34a inhibits Numb—which is also an inhibitor of Notch. This counterintuitive result made sense, however, because the researchers determined that Numb, Notch, and miR-34a interact to form an incoherent feed-forward loop, a control circuit that behaves like a switch, directing cells to one of two fates. Flipping the switch in one direction produces high levels of Notch and causes symmetric

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**Metastatic Sites Predict Prostate Cancer Survival**

According to a new meta-analysis of clinical trial data from patients with metastatic castration-resistant prostate cancer (mCRPC), overall survival (OS) is strongly influenced by where this disease spreads (J Clin Oncol 2016 March 7 [Epub ahead of print]). Previous reports had indicated as much but involved only small numbers of patients, warranting a more comprehensive investigation.

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**NEWS IN BRIEF**

**Researchers Clear Path Toward Using T cells in Metastatic Prostate Cancer**

Mary Andrew, MD, PhD, and colleagues at Memorial Sloan Kettering Cancer Center in New York City recruited 19 patients with metastatic prostate cancer and found that many of them expressed mutations in cancer-related genes that could be targeted by immunotherapy (Nat Med 2016;22:139–47). Many of the patients also had mutations in DNA repair genes, which could allow their tumors to avoid being attacked by the immune system. The researchers are now designing a clinical trial to test whether immune therapies can work in such patients.

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**Brain Tumor Cells Often Change Histology**

Brain tumors are notoriously difficult to treat, but a new study suggests that this may be partly because the tumors are capable of changing their histology. The research team at King’s College London, in collaboration with the University of Oxford and the National Institute for Health Research’s Neuroendocrine Cancer Research Centre, identified examples of brain tumors that had switched to neuroendocrine histology in 20% of patients. The findings could suggest a new approach to treating these patients (J Clin Pathol 2016;69:145–50).

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**News from the ASCO Meeting**

What’s new from the American Society of Clinical Oncology (ASCO) annual meeting? Here are some highlights.

- **COBRA** (Cancer Biomarker Research and Applications) is a new ASCO initiative that will encourage collaboration between basic and clinical scientists.
- **The ASCO Oncology Practice Guidelines Initiative** is expanding to include principles of care for patients with late-stage cancer, palliative care, and survivorship.
- **ASCO’s new ASCOtv channel** offers free, video-based continuing education credits.

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