Study finds link between molecular mechanisms in prostate cancer and Ewing's sarcoma

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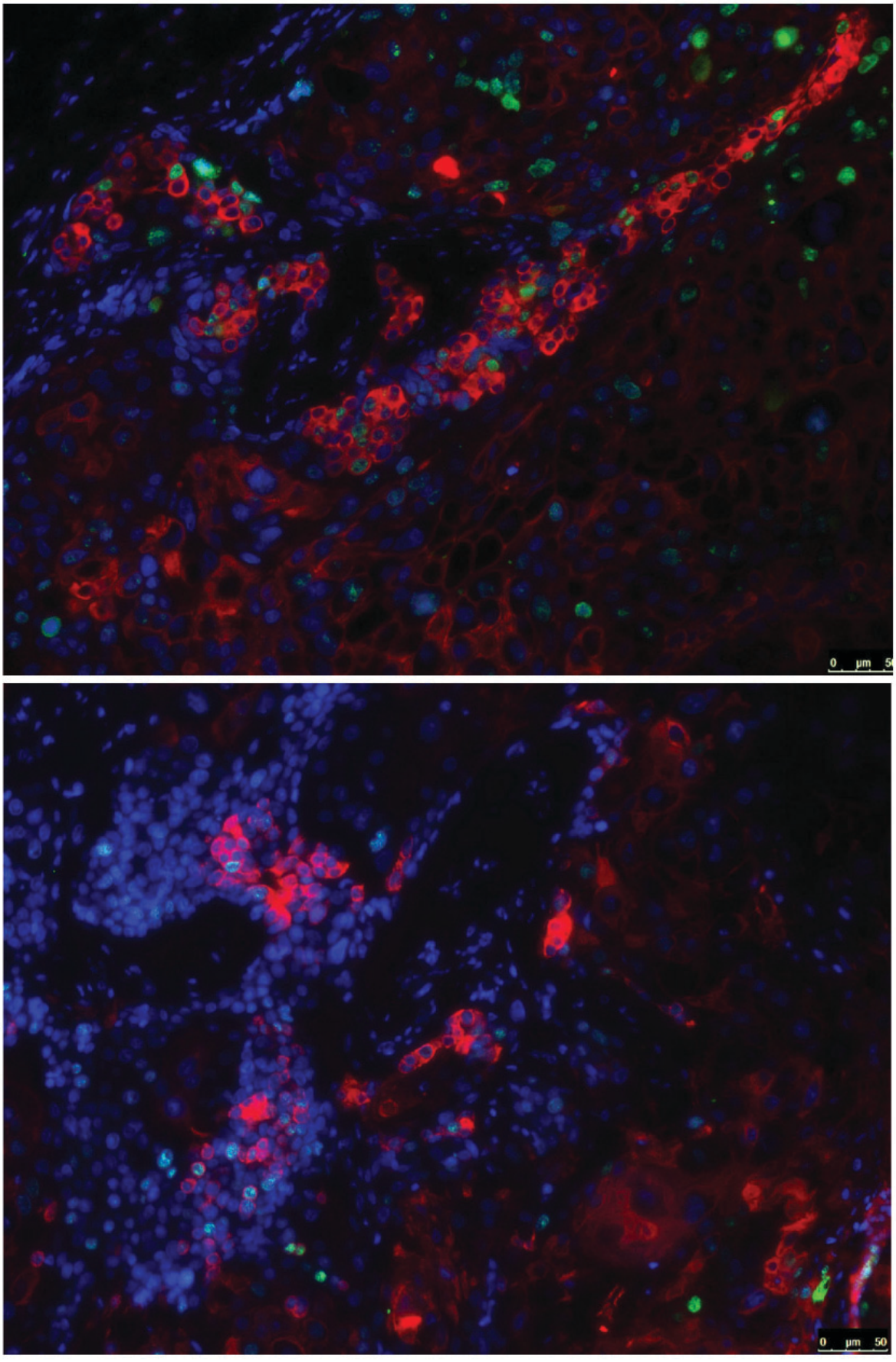
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These slides show tumor tissue where ERG and EWS genes interact normally, top, and tumor tissue where ERG has been modified to prevent interaction with EWS, bottom. The green sections indicate cellular proliferation, showing that tumors grow faster when ERG-EWS remains uninhibited. Credit: Indiana University

Medical researchers at Indiana University Bloomington have found evidence for a link between prostate cancer, which affects millions of men age 50 and older, and Ewing's sarcoma, a rare form of cancer that affects children and young adults.

The results of the study, reported today in the journal *Cell Reports*, suggest that the molecular mechanism that triggers the rare disease Ewing's sarcoma could act as a potential new direction for the treatment of more than half of patients with prostate cancer.

A form of bone and soft tissue cancer that affects about one in 1 million children and young adults age 10 to 19, Ewing's sarcoma is terminal in 44 percent of teens age 15 to 19 and 30 percent of children. Over 100,000 men are diagnosed with prostate cancer each year in the U.S, with more than 99 percent of cases occurring after age 50.

"This research shows that the molecular mechanism involved in the development of most prostate cancers is very similar to the molecular mechanism known to cause Ewing's sarcoma," said Peter Hollenhorst, an associate professor in the medical sciences program at IU Bloomington, a part of the IU School of Medicine. "It also suggests that this mechanism might be used to explore a common treatment for both diseases, one of which is not often pursued by drug companies due to its

rarity."

Hollenhorst is also a member of the Indiana University Melvin and Bren Simon Cancer Center in Indianapolis.

Other authors on the paper include Vivekananda Kedage, a graduate student in the IU Bloomington College of Arts and Sciences' Department of Molecular and Cellular Biochemistry, and Travis J. Jerde, an associate professor in the Department of Pharmacology and Toxicology at the IU School of Medicine in Indianapolis. Kedage is the first author on the study.

There are 28 genes in the human body known as ETS genes, four of which are known to produce proteins that cause prostate cancer. These four cancer-causing genes, or "oncogenes," are called ETV1, ETV4, ETV5 and ERG, the last of which has been implicated in over 50 percent of all prostate cancers. The other three combined play a role in about 7 percent of prostate cancers.

Ewing's sarcoma results from errors in the chromosome repair process that causes the merger of two separate gene segments into a mutant hybrid gene, also known as a chimeric or fusion gene. One of these genes is called EWS, the other is a gene that produces ETS proteins.

Hollenhorst's study is the first to show that the proteins produced by the EWS gene interact with all four ETS proteins known to trigger prostate cancer. Moreover, the EWS protein only interacts with proteins from these four harmful ETS genes, not the other 24 ETS genes not found to play a role in prostate cancer.

"A molecular mechanism that sets these four genes apart from the ones that don't trigger cancer has never been identified until now," Hollenhorst said. "This is significant because it suggests that any

compound that disrupts EWS-ETS interaction would specifically inhibit the function of the four oncogenes and not the others, which play important roles in the healthy function of the body."

The team also found the ETS genes implicated in prostate cancer interact with the un-mutated form of the EWS gene. In Ewing's sarcoma, the small blue tumors that characterize the disease do not occur unless mutation occurs.

IU scientists used a combination of laboratory experiments and mouse models to observe the interaction of EWS and ETS proteins in prostate cells. The majority of the experiments involved observing the behavior of ETS oncogenes in prostate cancer cell cultures to reveal interaction with EWS proteins.

In experiments at the IU School of Medicine, they also introduced the ERG gene into normal human prostate cells in mice, which triggered the formation of tumors. The scientists then introduced an artificial mutation in the ERG gene to disrupt interaction with the proteins produced by the EWS gene. In these mice, the tumors failed to form.

"Together, the results indicated that the interaction between ERG and EWS is important for tumor formation," Hollenhorst said. "We chose to focus our greatest efforts on the ERG protein since it is responsible for over 50 percent of all prostate cancers, and therefore the potential to benefit the greatest number of people."

More information: *Cell Reports*, DOI: 10.1016/j.celrep.2016.10.001 , www.cell.com/cell-reports/full … 2211-1247(16)31370-5

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