Protein found to control drivers of normal growth and cancer

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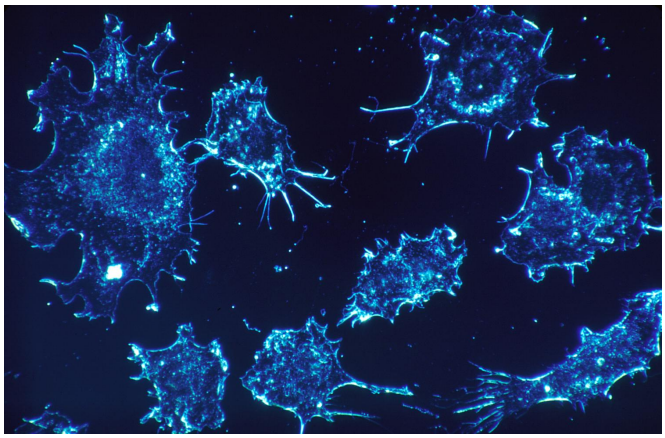

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Researchers have found a long-sought enzyme that prevents cancer by enabling the breakdown of proteins that drive cell growth, and that causes cancer when disabled.

Publishing online in *Nature* on April 14, the new study revolves around the ability of each human cell to divide in two, with this process repeating itself until a single cell (the fertilized egg) becomes a body with trillions of cells. For each division, a cell must follow certain steps, most of which are promoted by proteins called cyclins.

Led by researchers at NYU Grossman School of Medicine, the work revealed that an enzyme called AMBRA1 labels a key class of cyclins for destruction by cellular machines that break down proteins. The work finds that the enzyme's control of cyclins is essential for proper cell growth during embryonic development, and that its malfunction causes lethal cell overgrowth. Moreover, the study further suggests that an existing drug class may be able to reverse such defects in the future.

As in a developing fetus, restraints on cell division are central to the prevention of abnormal, aggressive growth seen in cancers, and the new study finds that cells have evolved to use AMBRA1 to defend against it.

"Our study clarifies basic features of human cells, provides insights into cancer biology, and opens new research avenues into potential treatments," says corresponding study author Michele Pagano, MD, chair of the Department of Biochemistry and Molecular Pharmacology at NYU Langone Health, and an investigator with the Howard Hughes Medical Institute.

New Tumor Suppressor

The current study addresses the three D-type cyclins, the subset that must link up with enzymes called cyclin-dependent kinases (CDKs), specifically CDK4 and CDK6, if cells are to divide. The authors found that AMBRA1, as a ligase, attaches molecular tags to all three D-type cyclins, labeling them for destruction. Previously proposed mechanisms for how D-type cyclins are eliminated by the cell could not be reproduced by the scientific community. Thus, prior to the new study, a central regulator of D-type cyclins had remained elusive for a quarter of a century, Pagano says.

The new work also revealed the role of AMBRA1 in development. Mice lacking the AMBRA1 gene, which codes for the AMBRA1 enzyme, developed uncontrolled, lethal tissue growth that distorted the developing brain and spinal cord. The researchers also found for the first time that treating with a CDK4/6 inhibitor pregnant mice carrying embryos without the AMBRA1 gene reduced these neuronal abnormalities.

In terms of cancer, the authors analyzed patient databases to conclude that those with lower-than-normal expression of AMBRA1 were less likely to survive diffuse large B-cell lymphoma, the most common form of non-Hodgkin lymphoma in the

United States. The causes of lower expression of AMBRA1 may include random changes that delete the gene or make its encoded instructions harder to read.

To confirm the role of AMBRA1 as a tumor suppressor, the researchers monitored cancer cell growth in mouse models of diffuse large B-cell lymphoma, in collaboration with study author Luca Busino, Ph.D., at the University of Pennsylvania. When human B-cell lymphoma cells were transplanted into mice, for instance, tumors without the AMBRA1 gene grew up to three times faster than those with the gene. While the NYU Langone-led study looked at diffuse large B-cell lymphoma, two other studies led by Stanford University and the Danish Cancer Society Research Center, published in the same issue of *Nature*, found missing or disabled AMBRA1 to be a key factor in lung cancer.

Further, D-type cyclins are known to assemble with CDK4 and CDK6 into enzymes that encourage both normal and abnormal cell growth. Drugs that inhibit CDK4 and CDK6 have been FDA-approved in recent years as cancer therapies, but some patients have a weaker response to the drugs. Providing insight into this problem, the current team found that lymphomas lacking AMBRA1 are less sensitive to CDK4/6 inhibitors. When the AMBRA1 gene is missing, levels of D-type cyclins become high enough to form complexes with another CDK (CDK2), which, due to its structure, cannot be inactivated by CDK4/6 inhibitors.

"This makes AMBRA1 a potential marker for the selection of patients best suited for CDK4/6 inhibitor therapy," says first author Daniele Simoneschi, Ph.D., a senior research coordinator in the Department of Biochemistry and Molecular Pharmacology at NYU Langone Health. As a next step, he says the team plans to study the effect of combining CDK4/6 inhibitors with CDK2 inhibitors in tumors with low AMBRA1, as well as in those with mutations in D-type cyclins that make them insensitive to AMBRA1.

More information: CRL4AMBRA1 is a master regulator of D-type cyclins, *Nature* (2021). DOI: 10.1038/s41586-021-03445-y

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