New therapeutic target discovered for a number of aggressive cancers

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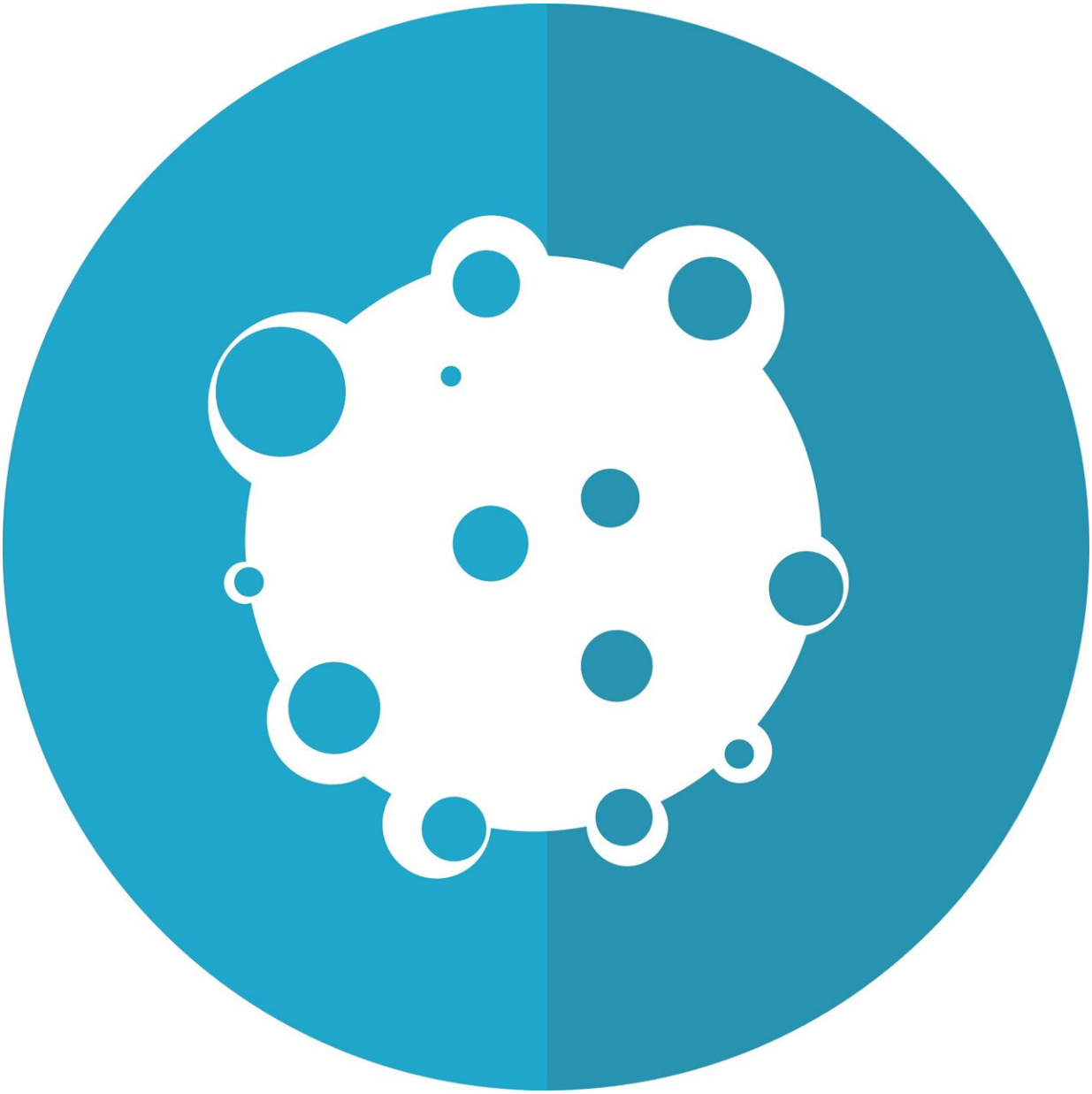

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A protein in tumor cells could be targeted to treat some types of aggressive cancer including brain, blood, skin, and kidney, new research has shown.

The scientists, from the Wellcome Sanger Institute, University of Cambridge and Harvard University, have identified a protein that plays a key role in transforming normal tissue into cancer, as a possible target for drug development. Inhibiting this protein effectively destroys cancer cells in laboratory models, including in cell lines and mice, while leaving healthy cells unharmed.

The research, published today in *Molecular Cell*, provides strong evidence that developing drugs that block the RNA-modifying protein known as METTL1 could give people with aggressive brain, blood, skin, and kidney cancers new treatment options.

RNA-modifying proteins, in particular the METTL family, are involved heavily in cell replication. These proteins have been found in higher levels in certain cancer cells, including some brain, blood, pancreatic, and skin cancers, and are associated with poorer outcomes.

Previously, Dr. Tzelepis, along with his team at the University of Cambridge, and their collaborators at the Wellcome Sanger Institute, used CRISPR-Cas9 gene-editing technology to screen cancer cells for vulnerable points. The researchers identified the *METTL1* gene—a gene that produces the RNA-modifying METTL1 protein—as a target for drug development.

In a new study that builds on that research, researchers at the Wellcome

Sanger Institute, University of Cambridge, and Harvard University have now found that mutations in the *METTL1* gene which lead to higher levels of the METTL1 protein, cause the cells to replicate faster and transform into a cancerous state, producing highly aggressive tumors.

When the team inhibited the METTL1 protein by knocking out the gene, it stopped cancer cell growth while leaving the normal healthy cells unharmed, in both laboratory and mice models, suggesting it would be a good target for cancer treatments.

Recently, the team also developed a small-molecule inhibitor for a similar protein, METTL3, to help treat acute myeloid leukemia, which will be entering clinical trials in 2022. It is hoped that this new research provides the evidence needed to start to develop a similar drug that targets METTL1, which could be used to treat a wider range of aggressive cancers if they have a mutation in the *METTL1* gene or high levels of its protein.

As the METTL1 protein is elevated in cancer cells with poorer outcomes, it could also be used as a biomarker to inform treatment plans and identify those who would benefit if a drug was developed, to ensure clinical trials are as streamlined and personalized as possible.

Professor Richard Gregory, co-lead author and Principle Investigator at Boston Children's Hospital and Harvard Medical School, Boston, said: "Cancer cells benefit from an unregulated cell cycle, leading to increased replication, and while some of the reasons behind this are known, there is still a lot to discover. This research illuminates deeply the role of the METTL1 protein in cancer development and proves that mutations in this gene can cause a cell to become cancerous. The more we understand about the genetic basis of cancer and how we can combat this, the more life changing targeted treatments we can create."

Dr. Esteban Orellana, first author and Research Fellow at Boston Children's Hospital, said: "Our research gives incredibly strong evidence that targeting the RNA modifying protein, METTL1, is an effective treatment against certain cancers, helping to kill cancer cells while leaving the other cells in the body untouched. This is important as it could mean that there will be fewer unpleasant side effects of a potential new treatment. The next step for this research is to try and develop a small molecule inhibitor to block METTL1 to see if our encouraging results can be translated across to the clinic."

Dr. Konstantinos Tzelepis, co-lead author, group leader at the University of Cambridge and visiting scientist at the Wellcome Sanger Institute said: "This study provides another great example of what is possible with the use of CRISPR technologies and how we can take and prioritize precise genetic information and turn it into something of potential clinical benefit. Targeting RNA-modifying proteins can effectively destroy cancer cells and we hope that this research will provide the evidence necessary for drugs to be developed that target METTL1, potentially providing a new therapy against aggressive cancers with clear and unmet therapeutic need."

More information: METTL1-mediated m7G modification of Arg-TCT tRNAÂ drives oncogenic transformation, *Molecular Cell* (2021). DOI: 10.1016/j.molcel.2021.06.031

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