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HUMAN HEALTH
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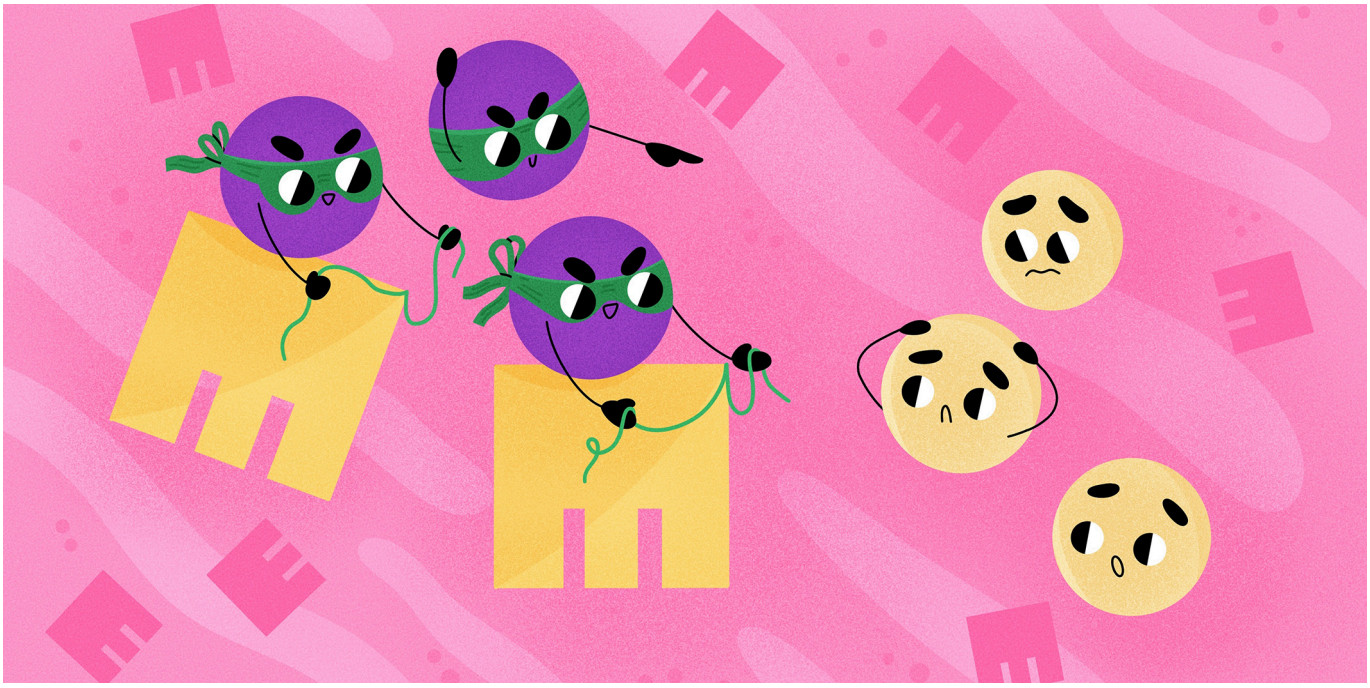

# HOW CANCER CELLS HIJACK PROTEIN PRODUCTION TO GROW QUICKLY

***Esteban A. Orellana*** [1,2*] ***and Richard I. Gregory*** [1,2,3,4]

[1] *Stem Cell Program, Division of Hematology/Oncology, Boston Children's Hospital, Boston, MA, United States*

[2] *Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, United States*

[3] *Harvard Stem Cell Institute, Cambridge, MA, United States*

[4] *Harvard Initiative for RNA Medicine, Boston, MA, United States*

**YOUNG REVIEWERS:**

**AYESHA**
**AGE: 9**

**CORINNE**
**AGE: 15**

**HENRY**
**AGE: 8**

**REVATI**
**AGE: 8**

The cells in your body contain genes made of DNA. Genes store the genetic information passed on to you by your parents. This information serves as the recipe to make proteins, and proteins build, maintain, and heal every tissue in your body. The cellular machinery that makes proteins reads this recipe with the help of small molecules called transfer RNAs (tRNAs), which supply the necessary building blocks in the correct order to construct specific proteins. To function properly, tRNAs must fold into the correct three-dimensional shape—a process that requires tRNA to be decorated with chemical modifications. Scientists have discovered that cancer hijacks and boosts this decorating process for its own benefit, favoring the production of proteins involved in cell division. This is an exciting finding because it could allow for the development of better ways to diagnose and treat cancers in the future.

**SAROJINI**

**AGE: 12**

**VIVIAN**

**AGE: 15**

**GENES**

Genetic information in the form of DNA that is inherited from your parents.

**PROTEINS**

Chain-like molecules that are made up by small individual units called amino acids.

**MESSENGER RNA (mRNA)**

Copies of genes that contain instructions to make a protein.

**RIBOSOME**

Cellular "factory" that makes proteins.

**AMINO ACIDS**

Building blocks that form a protein.

**TRANSFER RNA (tRNA)**

Molecule that "reads" the instructions on a messenger RNA and transports amino acids to ribosomes to make proteins.

## GENES: BLUEPRINTS TO CONSTRUCT PROTEINS

**Genes**, which are made of DNA, contain the instructions to make you who you are. Genes carry the information that determines which features or characteristics are passed on to you from your parents: height, eye color, or hair color, for example. Our bodies contain many different types of cells (skin, muscle, blood, fat, and others), each with a specialized job—yet every cell in your body has the same set of approximately 20,000 genes. However, not all genes are "turned on" in every cell because each gene has a special job to do, and those jobs determine the job a cell will do in your body. Genes spell out specific instructions (like a recipe) to make **proteins**. Everything in your body is made of proteins: your teeth, bones, hair and muscles, to name a few. Proteins help our bodies function properly, and changes in the normal functions or abundance of proteins can result in disease.

The information in genes is encoded using a specific sequence of molecules, called bases. There are four bases in DNA: A, C, T, and G. To produce a protein, the information contained in your genes must first be converted into **messenger RNA (mRNA)**, which is similar to DNA but contains one different base: U instead of T. mRNA can leave the nucleus, where the DNA is found, and be read by the cellular machinery in charge of creating proteins—the **ribosome**. Ribosomes work like tiny factories that build proteins according to the recipes provided by mRNA (Figure 1A). Proteins are made up of small building blocks called **amino acids**, and every protein in your body and in all known organisms, from bacteria to plants, is made of a specific combination of 21 unique amino acids.

## TRANSFER RNAS: DECODING THE INSTRUCTIONS IN A GENE

The ribosome reads the instructions from the mRNA with the help of another kind of RNA called **transfer RNA (tRNA)**. tRNAs supply the necessary amino acid building blocks in the correct order to construct a particular protein. How do tRNAs know which amino acid to add? Each tRNA has a three-base sequence that determines which amino acid it will carry. For example, the tRNA with the sequence CUU carries the amino acid lysine, and the tRNA with the sequence CGA carries serine. Within the ribosome, tRNAs scan the genetic code in the mRNA, reading the instructions three letters at a time. When the tRNA sequence is a "match" for the mRNA sequence, it deposits its amino acid on the growing protein chain.

## tRNA MODIFICATIONS ARE IMPORTANT FOR NORMAL FUNCTION

Scientists have found that tRNAs are decorated with many chemical modifications, and that these modifications have specific jobs in

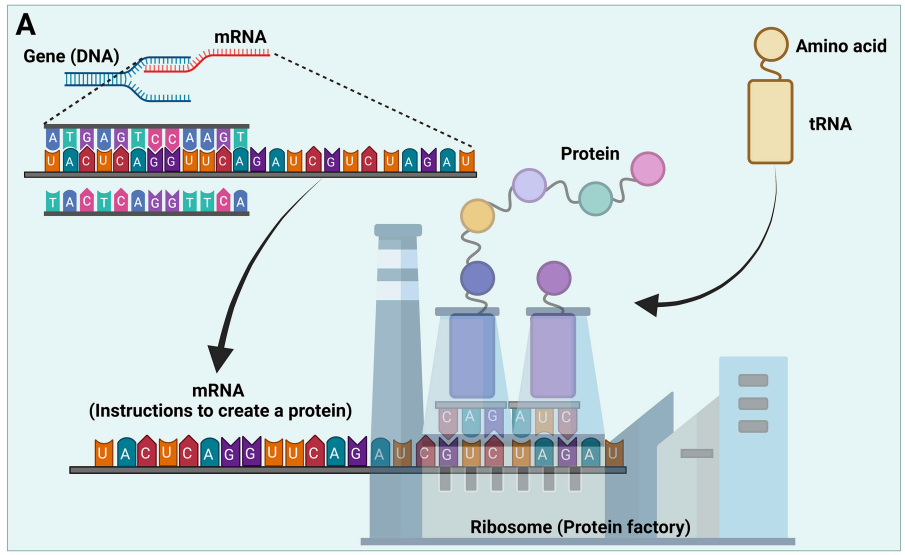


Figure 1

**(A)** Genetic information in a gene is converted into instructions, in the form of mRNA, that are read by ribosomes—the protein-making "factories" of the cell. tRNAs, which carry amino acids (the building blocks of proteins) deposit their specific amino acids onto a growing protein if their genetic sequence matches the instructions on the mRNA. **(B)** Like a Christmas tree, tRNAs are "decorated" with chemical modifications that allow them to work correctly, including modifications that help the tRNAs fold properly. These modifications are added by RNA modifying enzymes.

the production of proteins [1]. The chemical modifications are added to tRNA molecules by specialized proteins called **RNA modifying enzymes** (Figure 1B). For instance, there are tRNA modifications that restrict or expand the ability of a tRNA to recognize the mRNA instructions, and other modifications that provide resistance to environmental stresses, like high temperatures. Still other modifications are essential to keep the proper shape of a tRNA molecule. tRNAs must be folded in a particular way to do their jobs. This folding process resembles origami, in the sense that a linear tRNA molecule folds onto itself to form a three-dimensional structure that can be used by the ribosome. If the tRNA folding is not done correctly or if the folding is too loose, the tRNA cannot be used to construct a protein. RNA modifying enzymes add chemical modifications that work as molecular staples or screws, to fix the proper folding in place (Figure 2).

**RNA MODIFYING ENZYME**

Protein that changes the chemical structure of an RNA molecule by adding chemical modifications.

There is a growing field of research that studies tRNA modifications, the proteins responsible for those modifications, and the biological jobs of the modifications. To date, there have been over 150 tRNA modifications discovered, and scientists are working very hard to understand the functions of each of them.

**Figure 2**

tRNAs must be folded into the correct three-dimensional shape to participate in the protein-making process—loosely folded tRNA molecules are defective. Some RNA modifications, added by RNA modifying enzymes, help tRNAs to keep their shapes by working as molecular screw or staples to stabilize the tRNA in its tightly folded shape.

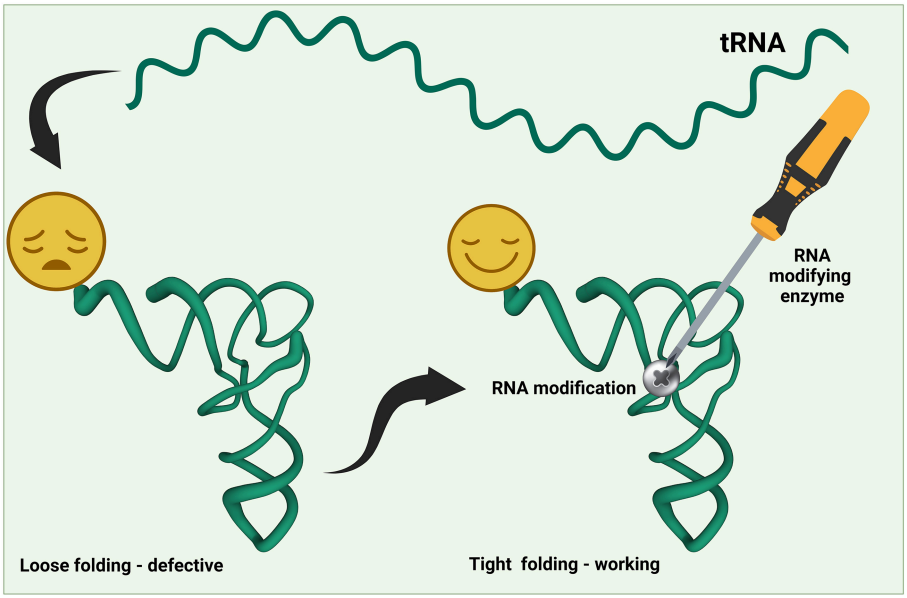


Figure 2

## DEFECTS IN tRNAs CAN CAUSE DISEASES

tRNAs are essential to construct proteins and small changes in their availability or the way they function within cells can have a profound impact on how fast or in what amount a particular protein is produced. Scientists have found links between defective tRNAs and human neurological (nerves and brain), metabolic, and developmental diseases, as well as cancer [2]. These defects could include defective tRNA modifications, incorrectly matched amino acid-tRNA pairs, or even mutations (changes) in the sequences of tRNAs. Studying how tRNAs work in normal and diseased cells might help scientists to find potential treatments for such diseases. Below, we discuss our findings on how cancers exploit tRNAs to support their fast-paced growth and the potential implications these discoveries could have in the way doctors manage cancers.

## CANCER GAINS CONTROL OF PROTEIN PRODUCTION BY HIJACKING tRNAs

In this moment, tens of millions of cells are dividing and dying in your body. This normal process allows you to grow and repair injuries. However, sometimes this highly controlled process can go awry and cause disease. For instance, cancer is a group of diseases that have one thing in common: uncontrolled cell growth. This means that cancer cells divide at higher rates than normal cells do. To divide so quickly, cancer cells must ramp up the production of proteins, particularly proteins involved in cell division. One way cancers do this is by taking over the machinery that makes proteins, including tRNAs.

**METTL1**

Methyltransferase like I–RNA modifying enzyme that adds internal m7G modification on tRNAs.

Scientists, including those in our research group, have identified a tRNA modification that is used by a variety of cancers. This modification is performed by an RNA modifying enzyme called **METTL1**, which is elevated in some cancers. This modification is one of those that acts like a molecular staple or screw, as we described earlier, to stabilize the folded structures of tRNAs [3]. We found that increased levels of METTL1 in cells causes increased levels of tightly folded, functional tRNAs. These changes in the abundance of tRNAs within cancer cells favor the production of proteins involved in cell division, and thus may contribute to the uncontrolled cell growth observed in many cancers (Figure 3).

**Figure 3**

Cancer cells divide more quickly than normal cells do. To do so, they must be able to produce proteins—particularly those involved in cell division—more rapidly. Some cancer cells have elevated levels of an RNA modifying enzyme that promotes the accumulation of tRNAs. Since tRNAs are necessary to supply the amino acid building blocks necessary to create proteins, cells with more tRNAs can divide faster, allowing cancers to grow.

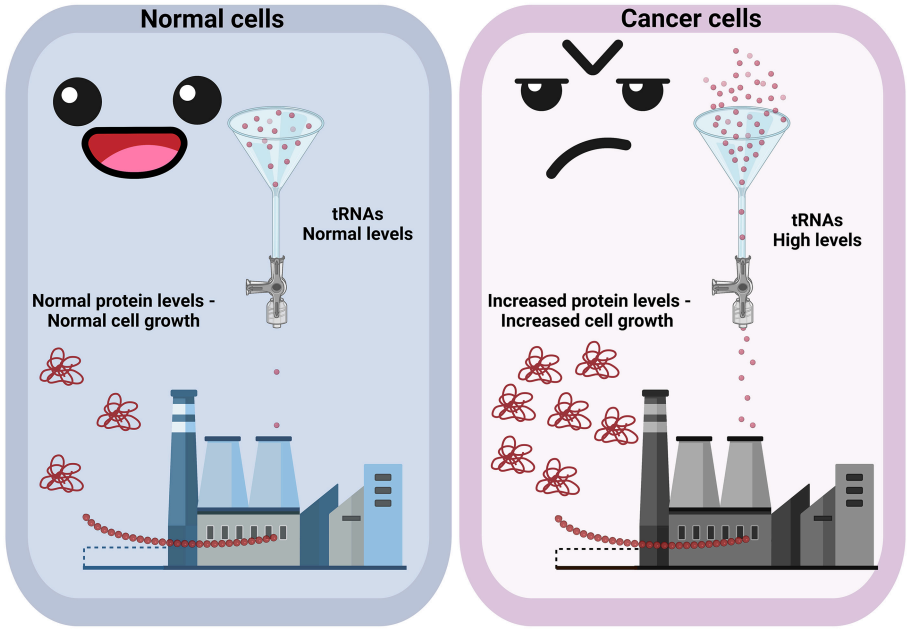


Figure 3

## WHY IS IT IMPORTANT TO STUDY tRNAs?

Cancer is a devastating disease and is one of the leading causes of death globally. Cancer can have many causes, and this complexity makes it very difficult to treat. To find effective ways to treat cancers, scientists around the world have been focusing their efforts on understanding how cancer works at the cellular level. tRNAs are essential cellular molecules that help both normal and diseased cells to make proteins. The study of tRNA biology in both normal and cancer cells could provide insights into the ways this disease hijacks protein production. This knowledge could help scientists identify novel targets for the treatment and diagnosis of cancers.

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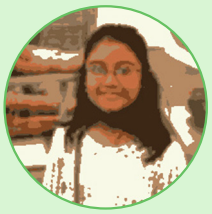
## YOUNG REVIEWERS



**AYESHA, AGE: 9**

Ayesha is a student of 5th grade at Massachusetts. She moved to USA from Vancouver, Canada in 2021 with her parents. She is keen to science and computer programming. In her free time, she watches scientific documentaries and practices computer programming to make different scratch-based projects. She is also very enthusiastic for traveling and visited many countries in the Western Europe, South Asia and North America with her parents.

**CORINNE, AGE: 15**

Hello! My name is Corinne and I am a 15 years old girl who loves reading, playing sports, and hanging out with my dog. I am very excited to be apart of this program, and cannot wait to read some of the articles other kids like me have been apart of!

**HENRY, AGE: 8**

I am in 3rd grade and I like mathematics and science. I have a younger brother, nand I like reading. Some of my favorite books are the Lord of the Rings. When I grow up, I would like to be a physicist. I like school and playing.

**REVATI, AGE: 8**

My name is Revati, I am 8 years. old and excited about starting travel soccer this year. I enjoy spending time doing art, piano and gymnastics. I have dog named Tootsie and a Zebrafish who is more than 2 years old. One of my favorite things in summer is to make ice cream with mommy. I also like to travel with my family.

**SAROJINI, AGE: 12**

My name is Sarojini, I am in 7th grade and my favorite thing in school is orchestra and band. I play the violin and oboe. My favorite sport is gymnastics, but I am also excited about starting track this year. In my spare time I like to play with my little sister and my dog. This summer, I enjoyed going hiking and going to the beach with my family.

**VIVIAN, AGE: 15**

Hi, my name is Vivian and I am in 10th grade. I like biology and hope to study medicine in the future. In my free time I like to draw and practice kickboxing.

## AUTHORS

**ESTEBAN A. ORELLANA**

Esteban is a research fellow at Boston Children's Hospital/Harvard Medical School, where he investigates RNA regulation in cancer. He was born in Quito, Ecuador, where he studied general biology and first became interested in gene regulation. During his undergraduate studies in Ecuador, he worked with beetles and later with plants and fungi. Esteban obtained his Ph.D. in cancer biology at Purdue University in Indiana, USA. His research focused on a small class of RNAs involved in gene regulation, called micro RNAs—and how they could be used to treat cancer.
*esteban.orellana@childrens.harvard.edu

**RICHARD I. GREGORY**

Dr. Gregory is a professor in the Departments of Pediatrics and Biological Chemistry and Molecular Pharmacology at Harvard Medical School, and principal investigator at Boston Children's Hospital. He received a Ph.D. from Cambridge University, UK in 2001, studying how genes are turned on or off at the Babraham Institute. Dr. Gregory performed his postdoctoral work at the Fox Chase Cancer Center and the Wistar Institute, in Philadelphia, USA. His postdoctoral research focused on studying microRNAs, a small class of RNAs involved in gene regulation. He is committed to exploiting the basic knowledge of RNA regulatory pathways for the discovery and development of new and effective therapies.