How cells 'read' artificial ingredients tossed into genetic recipe

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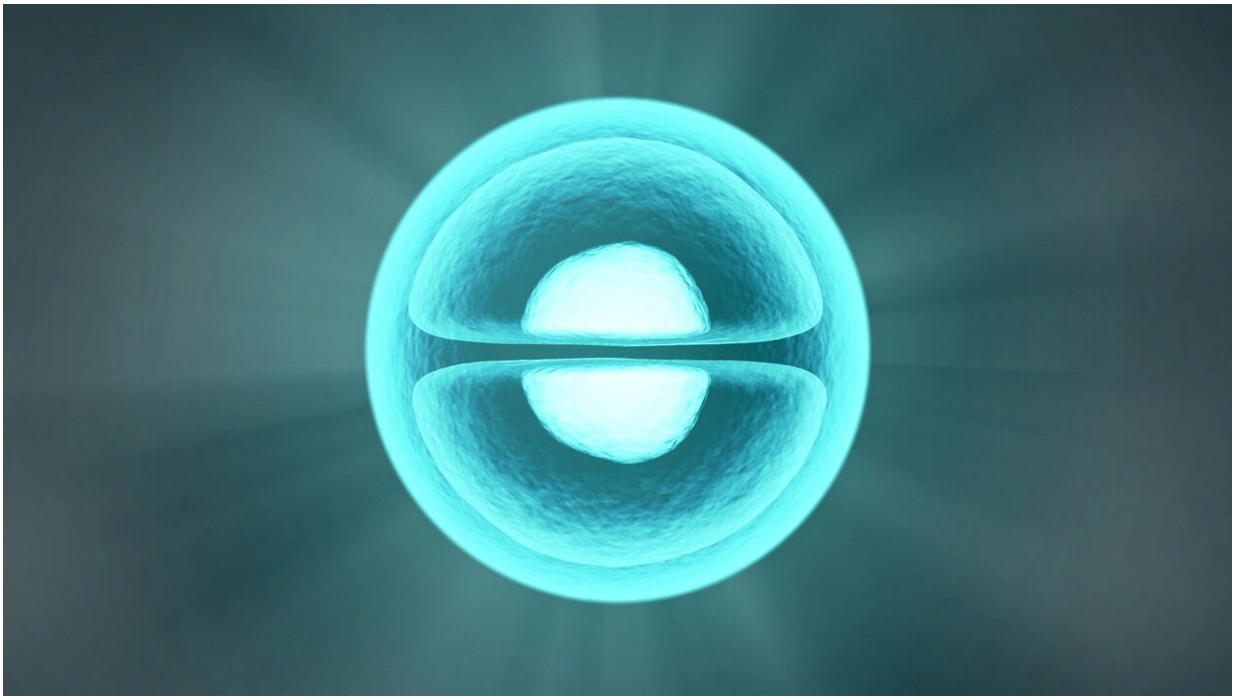

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If the genome is the recipe of life, base pairs are the individual ingredients listed. These chemical structures form DNA, and every living organism on Earth has just four. The specific arrangements of these four base pairs—A, T, C, G—make us who and what we are.

So it was a big surprise when Scripps Research scientists revealed in

2014 that they could introduce two new, unnatural base pairs (they called them X and Y for short) into the genetic code of living bacteria in the lab. It was like two never-seen-before ingredients tossed into the recipe, hypothetically expanding the variety of dishes a cell can whip up.

Researchers immediately saw the potential applications: With more control and selection, they might be able to use cells as tiny kitchens to cook up new medicines and vaccines. But just because there are more letters in a genetic recipe doesn't mean the cell can read them, or knows what to do with them—or that any of it works in the cells of organisms more complicated than bacteria.

In a study published June 17, 2021 in *Nature Chemical Biology*, a team led by researchers at Skaggs School of Pharmacy and Pharmaceutical Sciences at University of California San Diego helped address these hurdles.

The team revealed that yeast cell machinery seamlessly "reads" the unnatural X and Y ingredients, the way it would A, C, T and G, and translates them into RNA, which could eventually be translated into proteins, the basis for just about every part of the cell. Unlike bacteria, yeast are eukaryotes, part of the same multicellular class of life as animals, plants and fungi. (A note about safety: These synthetic cells can't survive without special liquid food provided in the lab.)

"Now we can see exactly how eukaryotic cell machinery interacts with unnatural base pairs, but it's not perfect, there's room to improve in terms of selectivity and efficiency," said senior author Dong Wang, Ph.D., professor in the Skaggs School of Pharmacy. "It's our hope that this finding will have a profound impact in the field by enabling the design of more effective, next-generation unnatural base pairs."

Wang's lab has long studied RNA polymerase II, an essential enzyme

found in every fungal, plant and animal cell. RNA Pol II reads the DNA recipe and helps convert the genetic code into messenger RNA. (That mRNA then carries that genetic recipe out of the nucleus and into the cytoplasm, where it's translated and used to assemble proteins as instructed.) In the past, the team has studied the structure of RNA Pol II and how it responds to normal genetic recipe hiccups such as DNA damage caused by radiation.

In their latest study, Wang's team revealed for the first time step-by-step what it looks like, structurally speaking, when eukaryotic RNA Pol II picks up and incorporates unnatural base pairs as it transcribes a piece of DNA. In doing so, they discovered, for example, that RNA Pol II is selective—it can bind X or Y on one strand of a double-stranded DNA genome, but not the other.

"What we have now is a unique view of what is and what is not well recognized by RNA Pol II," said Wang, who is also professor at UC San Diego School of Medicine and Department of Chemistry and Biochemistry. "This knowledge is important for us to design new unnatural base pairs that can be used by host RNA polymerases."

More information: Juntaek Oh et al, Transcriptional processing of an unnatural base pair by eukaryotic RNA polymerase II, *Nature Chemical Biology* (2021). DOI: 10.1038/s41589-021-00817-3

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