Sensei RNA: Iron fist in a velvet glove

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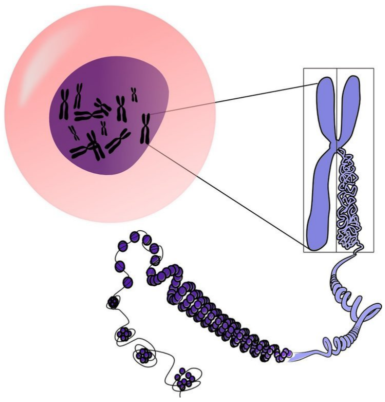

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"The real voyage of discovery consists not in seeking new landscapes, but in having new eyes."

Scientists would vouch for this statement because scientific pursuit has the habit of offering chance discoveries if we think about things differently.

In the lab of Arati Ramesh at the NCBS, the team loves to spy on the structure and sequence of Ribonucleic acids (RNAs; molecules that decrypt an organism's genetic code into protein messages). During one such instance, graduate students in Arati's lab were peering at a family of nickel and cobalt (NiCo RNAs) sensing bacterial RNAs that have a clover leaf-like structure. While sifting through this dataset, they noticed a set of RNAs that had retained this overall cloverleaf architecture but were subtly different. Upon chasing these 'variants', they realized that the 'NiCo-like RNAs' were in fact anchored in genomic turfs that were close enough to regulate iron -related enzymes and transporters. Could these NiCo look-alikes then be metalloregulators? Maybe of iron (Fe^{2+})?

To figure this out, the team kept NiCo-like RNA and Fe^{2+} in two separate cages separated by a membrane that only allows Fe^{2+} to bleed through. The experimental outcome revealed without a doubt that these RNAs enticed Fe^{2+} towards their chamber. Their guess was proven right and thus came the discovery of Sensei—short for Sense iron.

In their recent study, where the researchers describe the Sensei, they show that it acts like a riboswitch in the presence of iron. Upon binding iron, it undergoes a structural change to spur protein synthesis of the adjoining iron-related genes.

So, what is so fascinating about an iron sensing RNA?

Well, there are two parts to this answer. Firstly, iron is essential for many cellular processes and often acts as an accompaniment to chemical reactions in cells. If iron concentration is tipped off balance, it can reach toxic levels and perplex cells. Thus is it important for cells to be able to sense iron.

"Particularly, disease-causing pathogenic bacteria need to have the ability to sense iron so that they can be vigilant around heme-rich host tissues," explains Siladitya, the lead author.

Secondly, proteins have been the forerunners in iron sensing. Whereas the proverbial role of RNAs has been to act like embers in a pile of coal—waiting to translate into strings of amino acids. Even though the past few decades have seen a sea of change in this definition, the finding that biomolecules as delicate and transient as RNAs can detect iron comes as a revelation.

"This discovery puts RNAs in the limelight for sensing fundamentally important cellular metabolites like iron," says Arati. In fact, she further explains that it is the ability to adopt complex folds and structures that give RNAs their flexibility to interact with a plethora of molecules ranging from vitamins to metals.

Now, such a discovery commands high scrutiny. So, to check if Sensei is indeed a truthful sensor of iron, the team tested if the RNA was able to bind iron in the midst of a deluge of other molecules. True to its name, Sensei was a master. No matter what metal ions were present in the mix, Sensei was uncompromising and always chose to bind Fe^{2+} - making it one of the finest and strongest metalloregulatory RNAs discovered so far.

The question then was—what happens when Sensei binds iron? At the structural scale, the iron-bound RNA transforms itself and adopts a 'pose' that favors protein translation. In fact, it opens up its structure such that iron-related genes present in close genomic proximity can be rendered into proteins.

With this information in hand, the researchers then turned into crafty engineers. They tweaked the sequence of the RNA and identified the parts in the clover leaf-like structure that may bind iron. Then, they went one step further and made a small change in the RNA sequence which shifted the competence of RNA from sensing iron to now detect nickel and cobalt.

"This nanoscale engineering of iron sensing that we demonstrate, will hopefully set the stage for designing iron-biosensors which could be of use to both bacterial biology and biomedicine," explains Arati.

This story is as much about discovery by serendipity, as it is about what the discovery has taught us—the versatility of RNA, the unbending specificity behind an RNA's frail structure and its ability to sense something as fundamental as iron. What better way to honor it than by calling it Sensei, meaning teacher?

More information: Siladitya Bandyopadhyay et al, Discovery of iron-sensing bacterial riboswitches, *Nature Chemical Biology* (2020). DOI: 10.1038/s41589-020-00665-7

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