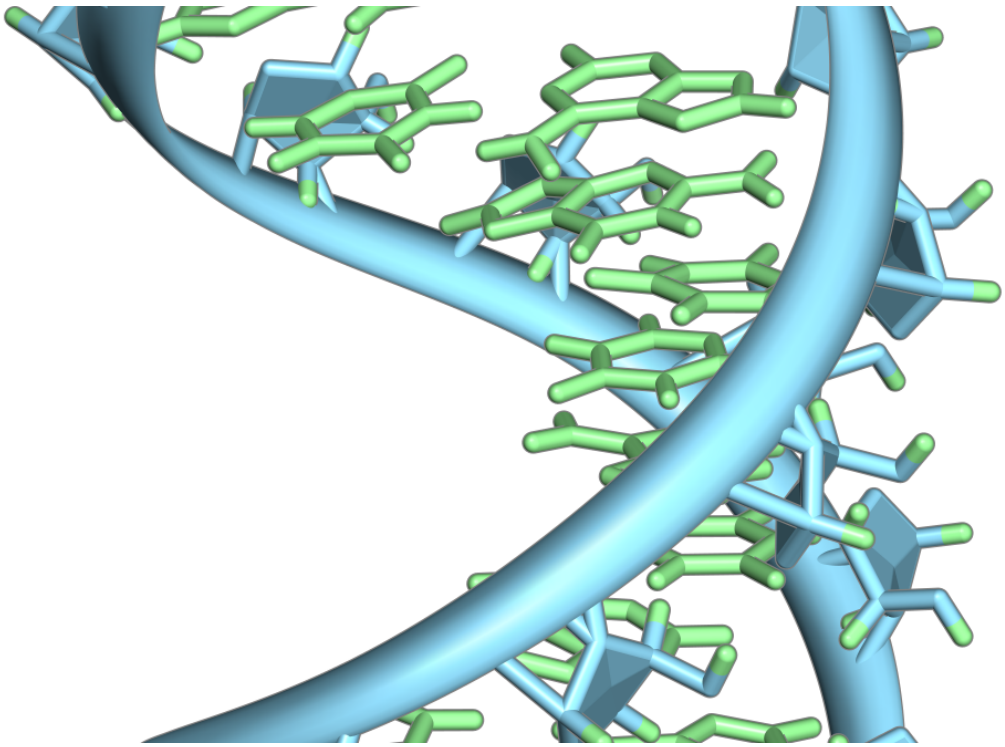
Researchers discover mechanism that allows non-coding RNA to amplify protein production

November 2 2020



A hairpin loop from a pre-mRNA. Highlighted are the nucleobases (green) and the ribose-phosphate backbone (blue). Note that this is a single strand of RNA that folds back upon itself. Credit: Vossman/ Wikipedia

Scientists from an international group led by the RIKEN Center for Integrative Medical Sciences and Yokohama City University have

discovered that a pair of proteins play a key role in allowing an important type of functional non-coding RNA, known as SINEUPs, to act to promote their target messenger RNA. SINEUPs are a recently discovered type of RNA that work specifically to amplify the production of proteins by messenger RNAs, and hence could be important for developing therapeutics for diseases where a certain protein is insufficiently synthesized.

While it was once believed that DNA was simply transcribed into RNA, which was then translated into proteins, it is now known that RNA plays a more complex role. While nearly all DNA is transcribed into RNA, it turns out that only 30% of RNA is translated into proteins. The remaining 70% play roles such as enhancing gene expression, epigenetic regulation and—in the case of SINEUPs—up-regulating the production of proteins by target RNA.

The current research, published in *Nucleic Acids Research*, looks at a certain type of non-coding RNA known as SINEUPs. These are essentially "genetic parasites" that have incorporated themselves as repeating elements within the genome. Though it is understood that they function to amplify the activity of the messenger RNAs that they are associated with, the mechanism behind this activity remained a mystery.

Hazuki Takahashi of the RIKEN Center for Integrative Medical Sciences, one of the corresponding authors of the paper, says, "We wanted to figure out the mechanism for the action of SINEUPs. Understanding how these RNAs work would be a tremendous breakthrough, because there are a number of diseases caused by a failure of genes to create sufficient quantities of a certain protein, and knowing how SINEUPs function could provide us with a way to remedy this."

The group did have clues from their previous research. They had noted that the SINEUPs only affected the action of their target messenger

RNA when they had been transported, together with the messenger RNA, out of the cell nucleus and into the cytosol where the protein production takes place.

Through a series of experiments involving both natural SINEUPs and artificial SINEUPs fitted with a fluorescent protein to allow the team to examine their movements, they discovered that a pair of RNA binding proteins, called PTBP1 and HNRNPK, interact with the SINEUPs both to allow their transport and to make it possible for them to act upon the messenger RNA. These two proteins are quite interesting as they have been found to work together in a variety of biological functions such as maintaining the pluripotency of cells. They are also biologically very important, as it has been shown that knocking out the HNRNPK gene in mice is lethal embryonically.

Piero Carninci of the RIKEN Center for Integrative Medical Sciences, the leader of the research group, says, "We are very pleased to have discovered the role of these binding proteins in the activities of SINEUPs. Because of the ability of SINEUPs specifically to modulate the translation of targeted mRNAs as needed, they are ideal for future therapies in humans where increasing the level of a specific protein could have a therapeutic effect. There are hundreds of diseases that would benefit from SINEUPs treatments, caused by deficiency of one functional copy of a gene: these diseases are known with the general terms of haplo insufficiencies. In addition, SINEUPs have potential to enhance currently limited antibody drug production. Understanding the mechanism of SINEUPs and other functional long non-coding RNAs mechanism is a very important first step for future applications of these RNAs for improving human health."

More information: Naoko Toki et al, SINEUP long non-coding RNA acts via PTBP1 and HNRNPK to promote translational initiation assemblies, *Nucleic Acids Research* (2020). DOI: 10.1093/nar/gkaa814

Provided by RIKEN