Researchers identify non-coding RNA molecule in trypanosome parasites

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Researchers at Bar-Ilan University in Israel have identified a non-coding RNA molecule that regulates protein translation in Trypanosomatids, single-cell parasites that cause major diseases affecting millions of people. The discovery may lead to the development of novel medications, based on anti-sense RNA, to treat, and prevent the spread of, these diseases. Indeed, the recent success in RNA delivery in the vaccine for COVID-19, holds promise for this biotechnological approach. Credit: Bar-Ilan University

Trypanosomatids are single-cell parasites that cause major diseases, such as sleeping sickness and Rose of Jericho, which affect millions of people. Trypanosoma parasites are transmitted to mammals by the blood-sucking tsetse fly. The parasite's stopover in the insect-host consists of two stages. They live in the insect's gut for two to three weeks and then migrate to the saliva glands. When the fly eats its next meal, the parasites are transferred via saliva to the prey, infecting its bloodstream. In this way mammals become host to the parasite, and the disease is spread.

Prof. Shulamit Michaeli, vice president for research and a faculty member of the Mina and Everard Goodman Faculty of Life Sciences at Bar-Ilan University, has made significant strides in understanding the internal functions of trypanosomatids. Now, she and a team of scientists have identified a non-coding RNA (ncRNA) molecule that regulates protein translation in the parasite. The finding was recently published in the journal *iScience*.

All proteins, which determine hereditary traits, are encoded in DNA. DNA is "locked" in the nucleus of the cell, which is barely permeable, and thus, one of the important functions of RNA is to transport the information stored in DNA from the nucleus inside the cell to ribosomes outside the cell. This is accomplished through messenger RNA (mRNA), a copy of DNA that enters the ribosomes. The factory-like ribosomes subsequently translate this information and synthesizes proteins. This is the template according to which proteins are made.

The ribosome is composed of ribosomal RNA (rRNA), and proteins. Additional molecules also regulate its activity. One such molecule is non-coding RNA (ncRNA), which controls mRNA function and determines whether mRNA molecules survive or degrade, and whether or not they are translated into proteins.

The ncRNA molecule identified by Michaeli originates from the gene

that encodes for rRNA. When rRNA is processed in the cell, unnecessary domains in the RNA are spliced or processed out. These domains usually undergo degradation, and until now their purpose was unknown and considered insignificant. However, Michaeli and team showed that these domains are actually used to produce ncRNA regulating translation, a function never previously known to occur in trypanosome parasites. "These organisms found a special localization for ncRNA. This novel ncRNA interacts with rRNA when it is formed in the nucleus and moves with it to the cytoplasm, where translation and protein synthesis takes place," says Prof. Michaeli.

Prof. Michaeli developed a method that captures the interaction between ncRNA and mRNA which is based on cross-linking via UV radiation. "We can then sequence these hybrid molecules so that we know which molecules interact with each other. This is very elegant, because it enables us to discover which genes are regulated by these novel, non-coding RNA based on the idea 'tell me who you interact with or who your friends are, and I'll tell you who you are." We were able to elucidate ncRNA in such a way that we could learn about the molecules with which they interact and regulate."

This finding in one species leads Michaeli to believe that it may also be common to the entire family of trypanosomatids, and may even exist in other organisms. "Years ago people referred to introns (information that is spliced out of RNA during its maturation) of mRNA as "junk," though it was subsequently discovered that such introns carry information for non-coding RNAs. However, nobody ever suggested that ncRNA exist in rRNA introns," adds Michaeli.

Prof. Michaeli's discovery may lead to the development of novel medications to treat, and prevent the spread of, the diseases caused by trypanosomatids based on anti-sense RNA. RNA therapy will be useful in the future for many diseases, including infectious diseases, since these

can be used to interfere with their regulatory function. Indeed, the recent success in RNA delivery in the vaccine for COVID-19, holds promise for this biotechnological approach.

More information: K. Shanmugha Rajan et al, Developmentally Regulated Novel Non-coding Anti-sense Regulators of mRNA Translation in Trypanosoma brucei, *iScience* (2020). DOI: 10.1016/j.isci.2020.101780

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