The RNA Exosome: Gene Expression Terminator


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The Exosome and RNA Degradation

In addition to transcription, the steady state levels of RNA within a cell are also determined by RNA degradation. RNA degradation also serves to remove defective RNAs that might be toxic or lead to production of toxic proteins. The RNA exosome is a multicomponent molecular machine with many functions in trimming and degradation of mRNA. RNA degradation is a natural process in all branches of life and plays a prominent role in regulating protein abundance.

The minimal exosome is made up of eleven proteins that form three overall domains. The cap protein, Rrp4, contains an active site that unfolds RNA into single strands. The cap pulls in a single strand of RNA and feeds it into a six-protein core, which directs the strand into the Rrp44 protein (also called DIS3) at the bottom where the RNA is degraded by RNB RNase domain from the 3′-to-5′ direction. A host of ‘add-on’ proteins give unique activities to the exosome in the nucleus and cytoplasm. Structures from bacteria, archaia, and eukaryotes reveal evolutionary conservation of this important machine.

In humans, exosome variants may also predispose people to cancers like multiple myeloma, as exosome mutations are recurrent in these patients. Thus, the understanding of how these mutations influence exosome structure and function would be beneficial and may lead to treatments for these cancers.

Figure 1. An illustration of the structure of the RNA exosome. From Robinson et al., 2015

RNA Must Traverse the Entire Exosome to be Degraded

Since this protein machine is found in all living organisms on earth, it must be of great importance, which is reflected in similar structure and function. The machine has maintained a generally similar structure over time with minor modifications as organisms have become more complex. The prokaryotic exosomes have the barrel, which has RNase activity, and may have a cap-like structure (a,b). Archaeal exosomes resemble bacterial complexes (c). Eukaryotes display the basic exosome structure, including the cap and barrel, but the barrel proteins are inactive; additional proteins (e.g., Rrp44) act as the RNase. Therefore, the preservation of the basic exosome structure over time reveals the essential function of the exosome complex.

Figure 2. RNA Exosome based on 41FD.pdb.

Figure 3. At right, an illustration of the RNA path through the exosome and the protein–RNA interactions within the structure. Polar interactions are illustrated by dotted lines, and stacking interactions with thick black lines. From Makino et al., 2013

The Rrp4 cap (pink) contains an active site consisting of Arg 110, Arg 123, Phe 177, and Asp 179 that unwinds the RNA (yellow).

The core consists of six proteins (blue) that the RNA travels through.

Evolutionary Significance

The RNA exosome exists in all organisms with slight evolutionary differences. From Januszyk and Lima, 2014.

Conclusion

The RNA exosome degrades mRNA as a means of regulating protein production and preventing potentially fatal results. Further research may find a link between exosome mutational malfunctions and excessive production of proteins such as human growth hormones, which may cause uncontrolled cell division and consequent cancers.

Figure 4. The RNA exosome.

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References

