Too cold? - just change your genetic code. A literature review on how cephalopods edit their RNA to cope with external temperatures.

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Almost every species, including humans and fruit flies, can modify their RNA (Birk et al., 2023). However, cephalopods (the molluscan class that includes animals such as octopuses, squids, cuttlefish and nautiluses) engage in RNA editing on a relatively larger scale than most other species (Birk et al., 2023; Garrett & Rosenthal, 2012; Rangan & Reck-Peterson, 2023; Rosenthal & Eisenberg, 2023). It is even suggested that external temperature plays a role in RNA editing in cephalopods.

RNA editing

First of all, what is RNA editing? To understand this concept, some processes have to be explained first. DNA is the genetic code of organisms. DNA consists of two strings in the form of a double helix. On each string, nucleobases are attached, which form specific pairs. On DNA, the *A* and *T* nucleobases are paired up and the *C* and *G* nucleobases are paired up. In RNA, the *T* gets translated into an *U* nucleobase. To translate DNA code into proteins, the genetic information has to be transcripted onto a singular RNA string, which in turn can be translated into proteins (Clancy & Brown, 2008). Thereupon, a RNA string attaches itself to one of the DNA strings and produces the opposite nucleobase pair. Usually, the next step is the translation of the RNA into proteins, but sometimes the RNA can be edited prior to protein translation, on so-called recoding sites. The editing of RNA is a process where the nucleotide sequence (a phosphate group in combination with a nucleoside, which is a nucleobase attached to a five-carbon sugar) of an RNA string is changed compared to the originally encoded DNA string (Covello & Gray, 1993). This can happen in two ways: the adding or deleting of nucleotides to change the length of the RNA string, or the changing or replacing of nucleotide bases itself to modify the nucleotide, while keeping the RNA string at the same length (Covello & Gray, 1993; Rosenthal & Eisenberg, 2023).

A-to-*I* RNA editing, also called adenosine deamination, is one of the most common forms of RNA editing. Here, the *A* nucleoside gets translated into an *I* nucleoside, which gets read as a *G* nucleoside, and therefore modifies the RNA string (Garrett & Rosenthal, 2012). This RNA editing then modifies protein function through amino acid alterations (Rosenthal & Eisenberg, 2023).

RNA editing in cephalopods

A-to-*I* RNA editing is also the most common form of RNA editing in cephalopods. The main reason for RNA editing is to adapt to external environmental variations (Rangan & Reck-Peterson, 2023). Moreover, their physiological needs can therefore be supported better (Rangan & Reck-Peterson, 2023). Rosenthal and Eisenberg (2023) found that cephalopods are unique in this view, as in any other species, extensive recoding is not the norm, but for cephalopods, it is fairly common, and it has an important function. However, this extensive recoding is only seen in certain cephalopods, e.g., in octopuses, squids and cuttlefish, but not in nautiluses (Rosenthal & Eisenberg, 2023). Moreover, the RNA editing does not alter proteins in the body, but mostly in the nervous system (Birk et al., 2023;, Garret & Rosenthal, 2021; Rosenthal & Eisenberg, 2023). The exact reason why cephalopods edit the RNA instead of the DNA is an ongoing question, but some researchers suspect that the extensive recoding might be due to addictive aspects of recoding (Jiang & Zhang, 2019).

RNA and temperature

Garrett and Rosenthal (2012) suggested that RNA editing might be responsive to external temperature. They compared potassium channels from a tropical octopus (*Octopus vulgaris*) and a polar octopus (*Pareledone sp.*) and found, despite the different environments of the octopuses, that they displayed the same behaviour genomically wise, but found that the polar octopus engaged more in RNA editing of the potassium channels than the tropical octopus. Following, some researchers investigated the role of external temperature in RNA editing (Birk et al., 2023; Rangan & Reck-Peterson, 2023). Some octopuses and squids live close to the west coast of America, and are therefore exposed to harsh temperature changes in the water (Birk et al., 2023). Birk and his colleagues attempted to measure the effect of water temperature on RNA editing capacities in octopuses (Birk et al., 2023). For this, they captured adult wild octopuses (*Octopus bimaculoides)* and had them reside in temperature-controlled aquaria for three weeks to get used to the laboratory environment. After that, the researchers started to experiment with the temperature ranging from 13 to 22 degree Celsius, maintaining the temperatures for 24 days in each aquarium. They found that the octopuses who lived in the colder induced aquaria had higher RNA editing levels than the octopuses who lived in the warmer induced aquaria. They tested whether ADARs (enzymes that activate *A*-to-*I* RNA editing), double-stranded RNA or trans-acting proteins regulating ADAR activity could be contributors to the temperature sensitivity of RNA editing, but they could not make definitive statements about it. They do suggest that these three interactors can play a role in a larger complex temperature regulatory network. Moreover, they found that temperature affects about one third of all the recoding sites, the editing takes place within mere hours

and generally the colder it gets, the higher the frequency of editing (Birk et al., 2023). Another study, by Rangan and Reck-Peterson (2023), investigated RNA editing of motor proteins in longfin inshore squids (*Doryteuthis pealeii*). They measured RNA editing through gene analysis and found that RNA editing in motor proteins increases with colder temperatures, and enables specific motor proteins to get RNA recoded.

References

Birk, M. A., Liscovitch-Brauer, N., Dominguez, M. J., McNeme, S., Yue, Y., Hoff, J. D., ... & Rosenthal, J. J. (2023). Temperature-dependent RNA editing in octopus extensively recodes the neural proteome. *Cell*, *186*(12), 2544-2555. https://doi.org/10.1016/j.cell.2023.05.004

Clancy, S., & Brown, W. (2008). Translation: DNA up mRNA to Protein. *Nature Education*, *1*(1), 101.

Covello, P., & Gray, M. (1993). On the evolution of RNA editing. *Trends in Genetics*, *9*(8), 265-268. https://doi.org/10.1016/0168-9525(93)90011-6

Garrett, S., & Rosenthal, J. J. (2012). RNA editing underlies temperature adaptation in K+ channels from polar octopuses. *Science*, *335*(6070), 848-851. https://doi.org/10.1126/science.1212795

Jiang, D., & Zhang, J. (2019). The preponderance of nonsynonymous A-to-I RNA editing in coleoids is nonadaptive. *Nature Communications*, *10*(1), 5411. https://doi.org/10.1038/s41467-019-13275-2

Rangan, K. J., & Reck-Peterson, S. L. (2023). RNA recoding in cephalopods tailors microtubule motor protein function. *Cell*, *186*(12), 2531-2543. https://doi.org/10.1016/j.cell.2023.04.032

Rosenthal, J. J., & Eisenberg, E. (2023). Extensive recoding of the neural proteome in cephalopods by RNA editing. *Annual Review of Animal Biosciences*, *11*, 57-75. https://doi.org/10.1146/annurev-animal-060322-114534