RNA folding at low temperatures sheds light on primordial biochemistry

September 10 2024

An artistic representation of the temperature dependence of the RNA freeenergy landscape (FEL) of folding. The authors showed that RNAs undergo a phase transition in the cold and misfold due to the FEL changing with temperature. Upon lowering the temperature, the smooth desertic landscape where the system readily finds the energy global minimum to fold into the native hairpin makes way to deep gorges separated by high barriers. The system gets trapped in these local minima that yield a diversity of misfolded conformations. Credit: Paolo Rissone

Ribonucleic acid (RNA) is a biological molecule with crucial functions in the genetics of organisms and plays a key role in the origin and evolution of life. With a composition quite similar to DNA, RNA is able to perform a variety of biological functions conditioned by its spatial conformation, i.e. the way the molecule folds in on itself. Now, a paper published in the journal *Proceedings of the National Academy of Sciences* describes for the first time how the process of RNA folding at low temperatures may open up a novel perspective on primordial biochemistry and the evolution of life on the planet.

The study was led by Professor Fèlix Ritort, from the Faculty of Physics and the Institute of Nanoscience and Nanotechnology (IN2UB) of the University of Barcelona, and also included UB experts Paolo Rissone, Aurélien Severino and Isabel Pastor.

New biochemistry for RNA at low temperatures

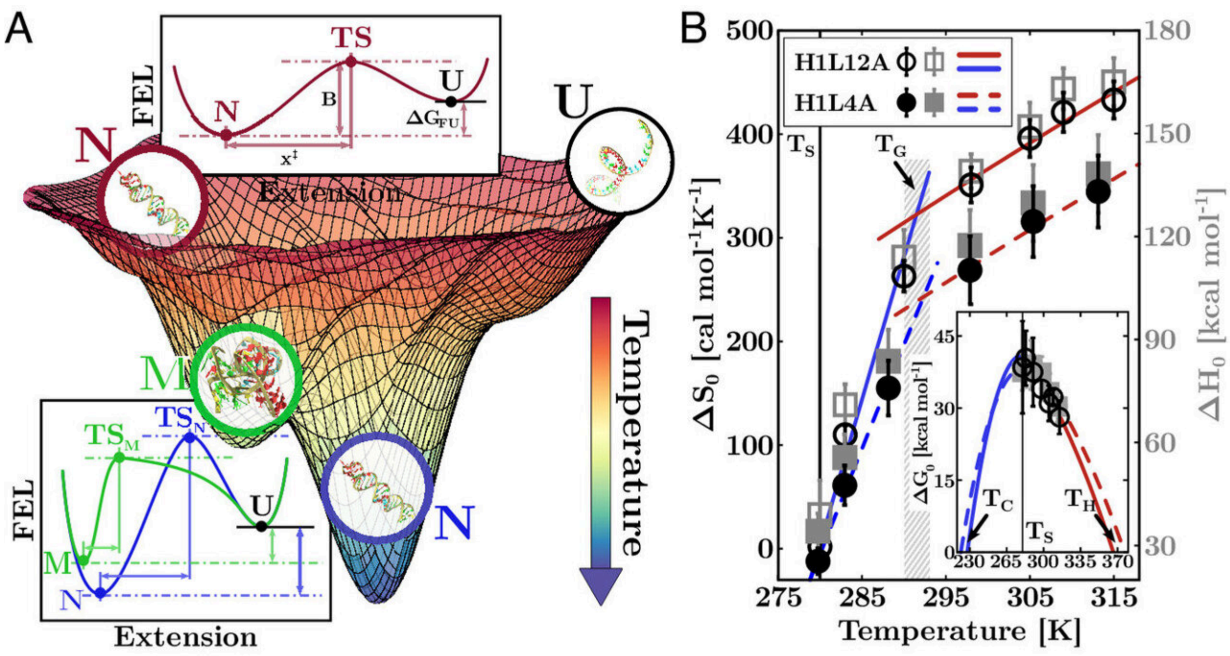
RNA is formed by linking molecules of ribose (a monosaccharide) with phosphate groups that bind to four types of nitrogenous bases: adenine (A), guanine (G), cytosine (C) and uracil (U). Both the sequence of bases and the three-dimensional structure of RNA are determining factors in the great versatility of functions that characterize the molecule.

The team used the mechanical unfolding of RNA to understand precisely the diverse forms that RNA takes when it folds in on itself.

Fèlix Ritort, head of the Small Biosystem Lab at the UB's Department of Condensed Matter Physics, says, "The folded structures of biological molecules, from DNA to RNA and proteins, determine their biological action. Without structure there is no function, and without function there is no life."

The study reveals that RNA sequences that create hairpin structures begin to adopt new, compact structures below 20°C.

"All the RNA molecules studied share unexpected novel structures at low temperatures," Ritort notes. "We identified a range of temperatures between +20°C and -50°C. Below +20°C, ribose-water interactions start to become important, and a maximum of RNA stability is reached at +5°C, where the density of water is maximal. Below 5ºC, the new RNA stability is determined by ribose-water interactions until -50ºC, when the RNA unfolds again, leading to the phenomenon of cold denaturation."



Cold RNA misfolding and phase transitions. Credit: *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2408313121

The paper hypothesizes that this temperature range is universal and common to all RNA molecules, although it is modulated by sequence and other environmental conditions such as salt and acidity of the medium.

These RNA ranks are simple structures stabilized by the formation of complementary base pairs, in which adenine binds to uracil (A-U) and guanine binds to cytosine (G-C). The researchers believe that these new structures "are created due to the formation of hydrogen bonds between ribose and water that weigh as much or more than the interactions between complementary bases in RNA (A-U and G-C)."

"In fact," adds Ritort, "this phenomenon is only observed in RNA, whereas it is not observed in DNA, where the proton at the 2' position of deoxyribose does not form hydrogen bonds with water."

To reach their conclusions, the team applied the technique of optical tweezer force spectroscopy, a fine and precise technique for measuring molecular thermodynamics. This technique has made it possible to measure entropy changes and heat capacity during the folding of different RNAs.

Therefore, it detects a decrease in the heat capacity of the folded state around 20°C, indicating a reduction in the number of degrees of freedom of the folded RNA (probably due to the effect induced by the ribose-water bonds).

Beyond the traditional view of RNA

But what implications might this phenomenon have for the biochemistry and biological functions of RNA? A first point to note is that the dominance of ribose-water interactions represents an alteration of the hitherto known rules that determine how RNA biochemistry is stabilized by A-U and G-C pairing and base-to-base stacking forces.

The UB professor adds, "This new altered biochemistry that we define in the article has implications for organisms that inhabit cold regions of the Earth (psychrophiles), from alpine regions to the deep waters of the oceans and arctic territories, at temperatures below 10ºC in the eutectic phase of saline water."

Beyond the specific A-U and G-C pairing rules, "The new RNA biochemistry determined by ribose-water interactions indicates the existence of a primitive, coarse biochemistry based on ribose and other sugars that predates that of RNA itself, which we have called the sweet-RNA world. This primitive biochemistry possibly began to evolve in cold environments in vast outer space, most likely on celestial bodies close to stars and subject to thermal cycles of heat and cold," concludes Ritort.

More information: Paolo Rissone et al, Universal cold RNA phase transitions, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2408313121

Provided by University of Barcelona

Citation: RNA folding at low temperatures sheds light on primordial biochemistry (2024, September 10) retrieved 10 September 2024 from https://phys.org/news/2024-09-rna-temperatures-primordial-biochemistry.html