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Opinion

Does the High Binding Affinity of Analogue Caps to the elF4E Obey the Laws of Thermodynamics for Cellular Health?

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Living organisms can be defined, as far as thermodynamics is concerned, as open systems at a state of non-equilibrium with many internal variables unlike the Prigonine's system [1] of non living matter, such as a chemical reagent's solution, where equilibrium can be achieved. The entropy of living organisms is also defined by the sets of internal variables which are finely categorized and described by Zotin AA, Prokovskii (2018) [2] and Prokovskii (2013) [3].

The artificially synthesized messenger RNAs are devised to be used against cancer, heart failure, storage diseases, and infectious diseases by entering into the human's cellular genetic machinery of protein translation [4]. These are equipped by chemically defined analogue caps to improve binding with Eukaryotic Translation Initiation Factor E4 (elFE4) and thus favor the efficiency of translation of their encoded proteins [5].

In the case of the cells receiving the analogue caps of synthetic mRNAs used for vaccination which should be for short-term production of an antigen, they acquire additional internal fluxes of energy from a novel internal variable or else called complexity variable [2] causing a system's deviation from a previous non equilibrium state to a new non-equilibrium state. In this case, considering that there are no external fluxes coming out from temperature or heat change, the change of internal variables is determined by the internal laws of thermodynamics and these are expressed as a movement of particles within the non equilibrium system, which in our consideration is the cellular living system and consequently the human organism [2 (equations 15 and 16)]. Taking into account that entropy and enthalpy from reactions between analogue caps and elF4E raise according to the increase in complexity of the synthetic analogue cap structure and in comparison to the entropy released from the binding of natural caps to the elF4E [6], this comes in argument to the measurement of the specific entropy S/M = 1/*k*T of the living system which is governed by the first law of thermodynamics as exemplified in the above equation where S: Entropy; M: Mass; T: Temperature; *k*, g/mW.day) [2]. The same rule also defines the rate of growth of a living organism and further destinations of ontogenesis, morphogenesis and differentiation [2]. In the normal case of evolutionary changes in living organisms, the entropy can be considered as constant during a significant time period, and as evolution advances there is a decrease of specific entropy from yeasts to insects to reptiles and birds [2]. However, this seems not to be the case with analogue cap reactions where a) the enthalpy gained by the reaction of binding to the elF4E, and as complexity of synthetic cap structures increase, is always greater than the entropy loss, and b) the elevation in structural complexity of analogue caps corresponds to an increase in affinity of binding to elF4E [6]. In other words the reaction between cap analogues of synthetic mRNAs and elF4E is both enthalpic and entropic [6,7] and the increase in synthetic (analogue) cap structural complexity associated with unusual heat capacity changes (considered as internal fluxes to the system of a living organism) needs further elucidation [6]. In this study [6], the unnatural ("exceptional" according to authors), "non trivial statistically important entropy - enthalpy compensation" recorded in the experimental results profoundly needs a thorough "theoretical" explanation. On the other hand, the same group of scientists in a later study [7], have recorded a similar "enthalpy driven and entropy opposed" reaction between synthetic cap analogues and elF4E where the enthalpy raises in respect to the raised structural complexity of

the synthesized analogue cap. Remarkably, in this study [7] authors have recorded a difference (increase) in enthalpy release of the same cap analogues between the yeast and mammalian elF4Es [6] suggesting an evolutionary optimization of elF4E, coming in accordance with other studies [2,3]. In other words, evolution has conferred an improved binding affinity of mammalian elF4E to natural mRNA caps and this corresponds to a more efficient protein translation. In the case of synthesized analogue caps that are literary designed only to offer an increase in binding efficiency [3,4] in order to forward increased synthesis of proteins that will subsequently be delivered to the immune system to gain immunity against a certain pathogen, the artificially-driven entropic and enthalpic reactions will presumably be accelerated in the more evolutionary optimized system of human. In the case of analogue caps, a greater complexity is added to the living system and this involves greater entropy (S) values than normal (i.e. by those offered by the naturally existing caps). As the living organism cannot be compared with a system at equilibrium state, e.g. a corpse, the behavior of a living cell will attempt to maintain unchangeable energy flux deviations due to the increase in complexity [2], a condition called homeostasis. Following the law of conservation of mass that determines the rate of growth [[2] (equation 4)], which is applicable in a living system, and bearing in mind that the specific entropy can only decrease [2,3] in a non equilibrium system but cannot deviate hugely from its characteristic value of existence, the added performance of protein translation machinery as it is hijacked by synthetic mRNAs in vaccines and the increase in efficiency of analogue cap binding to the elF4E can only be added to the list of internal variables for consideration based on the uncertainties of cellular uptake, tissue mosaicism, and duration of existence in the human body [2]. The cell receiving the weight to perform the high enthalpic reactions of analogue cap - elF4E binding can then only obey to the law of conservation of energy and perform additional molecular reactions to equilibrate (excited molecules will follow their own relaxation times) the expected, due to increase in enthalpy, fast relaxation times of high enthalpy reactions that were not meant by evolution to perform at the given state of cellular complexity. The living systems (Humans) must then have to obey to the second principle of thermodynamics describing that internal variables cannot add any positive work to the system, since the reversal of evolution in time is impossible [2]. Meaning, mRNA technologies may change the balance of cellular homeostasis with respect to gene expression, protein synthesis, and catabolism of DNA, RNA, and proteins. The implications of massive synthetic mRNA translation events eventually throughout the human body must be considered to be a disruptive force in normal human cell biology which could be inadvertently disturbing the cell cycle, autophagy, auto-immunity, oncogenesis, mutagenesis, and teratogenesis [8]. This is important for disease onset as the relevant molecular events may directly influence the behavior of a powerful gene expression as synthetic mRNA is introduced into the RNA regulon motivator [9], the elF4E. The disturbance of cellular homeostasis by synthetic mRNA analogue caps as used for SARS-CoV-2 vaccines is warranted to be analyzed by further superior physical chemistry and biochemistry research to avoid dangers for human health.

Conflict of Interest

The authors state no conflict of interest.

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