Cotranslational folding of most proteins

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Abstract

Are the majority of proteins, in particular small and average sized global proteins folded spontaneously in vivo after their linear structures are translated on ribosome (Anfisen's dogma)? Here, I propose a theory that all or most proteins are folded cotranslationally based on three main theoretical foundations, which is supported with some critical experimental data. Protein synthesis is subject to quality and quantity control even though protein folding can spontaneously occur in certain degree in vitro. The well accepted knowledge of aminoacyl-tRNA synthesis could be used to modify and build a similar but novel mechanism: rRNAs and their protein etc. cofactors (or simply ribosome) as mRNA interpreter can not only translate primary amino acid sequence but also determine and guide a stepwise native conformation, the three dimensional folding of a nascent protein, which can occur cotranslationally. Transfer RNA (tRNA) can specifically recognize and bind amino acid to form aminoacyl-tRNA, which in turn can decode triplet-codon on mRNA through its anticodon and deliver residue for peptide synthesis. Ribosome may be able to decode both coded and non-coded mRNA regions for translation and regulation, including initiation, elongation and termination. Ribosome may decode coding region of mRNA to derive both linear sequences (proof reading or double checking) and folding pathways for higher structures, and guide the arrival of its native conformation within ribosome exit tunnel and associated endoplasmic reticulum. Therefore, with the similar working principle of a tRNA, ribosome can develop more complicated structure and function, for example, to recognize peptide sequence even conformation of proteins. Thermodynamics and informatics based information energy efficiency (IEE) also support such a cotranslational folding mechanism of nascent protein. Here, I use insulin, which is derived from its precursor, preproinsulin, as a model to illustrate. Therefore, the belief of protein self-folding without assistance or guidance after or during translation, which was based on some results of in vitro and in vivo experiments, may be an oversimplification and may be an example of exceeding reductionism.

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Genetic information transfer from RNA to DNA: dsRNA binds dsDNA

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Abstract:

The recent proposal of the complement of central dogma of molecular biology,

Protein→ RNA → DNA → RNA → Protein,

including RNA to DNA genetic information transfer

(Yang C. Complement of central dogma of molecular biology.2010. Available at www.energinity.com/2010proceedings1.pdf.
Also available at *Nature Precedings* http://precedings.nature.com/documents/5471/version/1)

has generated a legitimate issue: how an RNA transfers genetic information to a DNA? Here, I report my further studies on the mechanism of a possible principle, double stranded RNA (dsRNA) binds (or recognizes) double stranded DNA (dsDNA). I introduce three new concepts: 1. Genetic information can be read as two bits of a unit information on dsDNA or dsRNA, namely AT/TA or CG/GC in dsDNA and AU/UA, or CG/GC in dsRNA.
2. The principle of information energy efficiency (IEE), or information efficiency (IE), or energy efficiency (EE) is defined. Comparisons of different process pathways of information or information energy can derive higher IEE or EE. Therefore, one can derive the minimal free energy (ΔG) and favorable entropy to predict the feasibility of a pathway of information process. 3. Genetic information transfers from RNA to DNA through dsRNA pairing with dsDNA with their cofactors such as proteins and etc. DNA binding proteins such as transcription factors etc. may use dsRNA to help them specifically target genome. RNAs large or small, for example microRNAs, including RNAa and etc. can access specific genes through specific dsRNAs.

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Casting and Decoding Model of Protein RNA Signal Transduction in the Affinity Maturation of Antibody

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Abstract:

I recently proposed a general principle of signal transduction, protein to RNA, (Yang C. A new category of signal transduction: Protein to RNA. Available from *Nature Precedings* <http://precedings.nature.com/documents/5469/version/1>. 2010. Also available at <http://www.energinity.com/2010proceedings1.pdf>), which superimposed an important issue: how a protein transduces signal to RNA? Here I report the theoretic development of a novel mechanism of affinity maturation of antibody - the casting and decoding model. In this proposal, the "induced fit" mechanism is further developed as casting process: a mechanism is thought that the body has developed over millions of years, to measure the best binding conditions of an antibody to an antigen or ligand. The induced fit is considered a process of seeking favorable entropy and reach minimal free energy of the binding between the antibody (or protein receptor) and the antigen (or ligand). The unbound antibody, including the antibody which exists without prior specific antigen stimulation, is particular flexible and broad in specificity (multi-specificity). The bound antibody becomes relative rigid and specific to the bound antigen (lock and key), which we call casting, and which represents the protein sequence information of an arrangement of the contacting surface towards the antigen / ligand. Then, here comes the decoding process. A mechanism thought through RNA sensor, to identify the conformational changes at the protein sequence level. The decoding process like a reverse ribosome function (Yang C. Cotranslational folding of most proteins. 2011. <http://www.energinity.com/proteinfolding2011.pdf>. Also available from *Nature Precedings* <http://precedings.nature.com/documents/6742/version/1>) but only it seems at simpler scale for epitope and paratope with framework recognition. The tRNA or rRNA like RNAs recognize the casted protein structure and decode the protein conformation of the bound antibody, its framework as well as biding site. The decoded sequence information may be used to guide the modification of the recombinant VDJ genes, which in turn to generate antibody with increased affinity.

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Science and New Sciences

Consciousness research: where to revive

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Abstract

Ask this big question, why mainstream scientists have not engaged the studies of consciousness for so many decades? Although I have only attended a few seminars and symposia on consciousness research, my extensive reading and in depth searching in this field may have positioned me to identify critical pathways that may provide insight toward solving the mystery of consciousness. In this essay I report my personal experience of learning: 1, the opinions from mainstream scientists who are not engaging the research but envisioning negative future of consciousness study, e.g. genetics and experimentalism; 2, scientists or philosophers who are engaging consciousness research with very diverse and positive opinions; and 3, some recent work at DNA level that related to my research. My proposed definition of biological consciousness, or in short, bioconsci, and described innovative method to study it, may help to evolve consciousness studies - come to mainstream. To revive consciousness research, I believe we should take these two steps, namely to refine the concept of consciousness and to apply new ways of observation, hence to adapt, even to advance mainstream research. Bioconsci has also explained mental consciousness critically through evolutionary biology, e.g, from virus (DNA or RNA) through all ranks to human. I also propose that it is about time to recognize some fundamental truth, such as consciousness, including spirit and belief is a physical existence, a reality with purpose. The hard problem of consciousness may be explained based on this new view. It is also about time to prepare ourselves for fundamental advances in science, philosophy and other related fields.