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Life is translation

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Evolutionary origin of translation represents one of the key questions that Carl Woese addressed in his work. Here we give a personal account of his results in this area and the effect they have had on the field.

"A science which hesitates to forget its founders is lost," said Alfred North Whitehead, but I first encountered this quote in an article written by Carl Woese.[1] It is difficult for me to express the powerful mixture of admiration I feel for Carl Woese and inspiration I derive from his work, while still heeding this frightening, yet very true warning. In an attempt to bridge this divide, I will not dwell on the great evolutionary biologist himself, but will rather try to trace a celestial orb in biology's night sky that he kept pointing at throughout his life. That orb is translation. The gigantic stature of Woese in the context of modern biology is, of course, permanently defined by his development of physicochemical approaches to phylogenetic analysis, his discovery of the universal tree of life, and his explorations of horizontal gene transfer. However, it is the process of translation of the genetic message, and in particular, its evolutionary origins, where I think he found the ultimate enigma worth studying.[1-4] As not only the point where genotype and phenotype meet, but also the key nexus between the RNA world and the world of modern cells in which proteins and nucleic acids coexist and cooperate, one might even argue that trying to understand translation was the main driving force behind all of Woese's major discoveries. Or in the words of Woese himself: "You cannot understand the gene without understanding translation, and you cannot understand translation without understanding its evolution."[4] However, even in his later years, Woese saw the problem of the origins of translation, despite all the progress, as still being fundamentally open. What is more, he actually saw it as the pivot point around which modern biomedically driven molecular biology could swing back to its own more fundamental, philosophical self.[1-4]

The origin of translation is intimately and inextricably related to the origin of the universal genetic code. However, in the 50 years since its discovery, the focus has predominately been on the informational aspects of the relationship between codons and their cognate amino acids, seeing the code as a dictionary of sorts. A big personal epiphany for me, completely due to Woese, has been the realization that the celebrated discovery of the code, although practically of an utmost importance, was actually only the first step in understanding the essence of translation.[1-4] That UUU, for example, codes for phenylalanine and AGG for arginine defines biology as we know it, but an even larger question remains: why this pairing and not some other? Given how we understand, conceptualize, and explain translation in modern biology textbooks (i.e., by emphasizing the role of tRNAs as adaptors that link amino acids with appropriate codons), very little would fundamentally change if AGG suddenly coded for Phe and UUU for Arg, as long as the modified coding table was used consistently. Not in Woese's opinion. For him, the very mapping between specific codons and amino acids carries within itself important clues about the origins of the entire translation apparatus to begin with and is indelibly linked with the very essence of biological systems as we know them.[1-4] The principal result of Woese's efforts in this context was his experimental determination of preferences of amino acids to interact with nucleobase analogs such as substituted pyridines.[2,3,5-8] By using chromatographic techniques, Woese and co-workers discovered that different amino acids have markedly different propensities to interact with nucleobase-like compounds and that, remarkably, these propensities (which he termed "polar requirement") exhibit a surprising relation with the structure of the genetic code. Simply put, amino acids with similar polar requirement tend to be coded for by similar codons and vice versa. In what I personally consider to be a great example of inspired, extrapolative reasoning in science, Woese then used this to argue that the beginnings of translation were defined by direct, stereochemical interactions between bases and amino acids, and that before the development of tRNA-based ribosomal decoding, proteins were templated off of mRNAs directly.[2,3,5-8] After mid-1970s, Woese's research took him, to a large extent, away from the question of the origin of the genetic code itself, but his early work in this context stands a test of time and represents an important, inspiring foundation that I believe still harbors some major surprises.

As a case in point, we have recently used the polar requirement (PR) scale to show that pyrimidine density along individual mRNAs matches the affinity profiles of cognate protein sequences for pyrimidine mimetics, as captured by the PR scale, with quantitative accuracy.[9,10] For example, one half of all annotated human proteins exhibit a correlation between the two with $|R| > 0.74$. Moreover, we have derived preferences of amino acids to interact with different RNA bases from the statistics of amino-acid/base contacts at interfaces in a large number of high-resolution structures of RNA/protein complexes.[10,11] Using this standard bioinformatics technique, we have not only confirmed

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the results obtained using the PR scale, but have also extended it to the case of purine bases. These results we believe provide strong evidence for the stereo-chemical foundation of the genetic code as promulgated by Woese i.e., the idea that the genetic code evolved as a consequence of direct interactions between amino acids and relevant bases.[9-11] Importantly, however, they simultaneously also move the focus away from the interactions between individual amino acids and individual codons, and suggest that strong signatures of binding can only be seen if one considers longer stretches of protein and mRNA sequences. Even more importantly, our results suggest that mRNAs and cognate proteins may be directly physico-chemically complementary to each other and bind, even in today's cells, and especially in unstructured regions, providing a novel, fundamental principle concerning protein/nucleic acid interactions in general.[9-11]

In his later writings, Woese argued that the question of the physico-chemical principles underlying the origins of translation may not even be the most important one, and opted rather to phrase the question in terms of the gradual evolution of the ribosomal structure.[1,3] Although he was one of the earliest champions of the stereochemical hypothesis concerning the origin of the genetic code, Woese was convinced that the simple templating idea, which was sufficient to satisfactorily explain the question of the replication of the genetic message, might not be powerful enough to capture the essence of translation, be it ancient or modern.[1,3] However, we believe that our recent results provide strong evidence for the claim that direct templating may indeed have been the defining characteristic of primitive translation apparatuses and draw the attention back to the basic physical chemistry of protein–nucleic acid interactions as the key ingredient.[9-11] Moreover, we believe that the idea of complementarity suggests a novel framework for studying primordial translation processes, but also potentially extends to different aspects of present-day nucleic acid and protein biology, including transcription/translation regulation, mRNA transport, processing, and decay, structure of ribonucleoproteins and others.[9-11] While only future work will show how much of this potential is actually real, it is impossible to overstate the importance of Woese's early results in this context and his influence on not only our work, but also that of many others in this field.[12-18] "Talent hits a target no one else can hit. Genius hits a target no one else can see." This quote by Arthur Schopenhauer epitomizes Woese's impact here better than anything else. In an era that was conceptually dominated by one of the biggest successes in the history of molecular biology, the discovery of the genetic code, Woese had vision, intellectual courage, and practical know-how to pursue an even grander question—that of its beginnings.

In the end, I also cannot escape to comment on my personal perception of Woese's research, and in particular, of his writing. Fiery, opinionated, eloquent, erudite, and above all, passionate for truth, and always only the biggest, most important, most far-reaching truth, Woese, whom I have gotten to known from the literature (without regrettably ever personally meeting him), has rekindled my own passion and belief in biology. One feature that characterizes modern molecular biology is a paralyzing specialization and fragmentation of interests and research themes. Do we really know, understand, or care about the research topic of a neighboring lab? Can we competently read all of the papers in the latest issue of even a journal as specialized as *RNA Biology*? Is this even possible any more? Woese's writings awaken my belief in the underlying unity of biology and the fundamental simplicity of principles, those known and those yet to be discovered, that define it. Indeed there exist questions that unite all of our interests, there exist questions that could touch us all, there exist questions, which we all should ask. The question of the origin of translation, with its central role in all of biology, is undeniably one of those. What is more, while certainly important, biomedical applicability of modern biological research is threatening to become the principal arbiter of quality in biological research. Woese's research opus and his piercing, inspiring writing serve as a clarion call reminding us of the importance of basic research and the beauty of simply knowing for the sake of knowing and understanding for the sake of understanding. A nonlinear, more complete, holistic biology awaits us: it encompasses mechanistic, reductionist, application-driven view of biological forms and patterns, but also fully accounts for their evolutionary histories and complex, dynamic relationships with each other and with the environment. In his mind, Carl Woese has already been there. Let us follow.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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