To the End of Dogmatism in Molecular Biology

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COMMENTARY

To the End of Dogmatism in Molecular Biology

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Abstract

Denis Nobel looks at four important misinterpretations of molecular biology concerning evolutionary processes and demonstrates that the new synthesis today looks rather outdated. The modern synthesis is nearly 80 years old. The proponents who worked out the modern synthesis had no access to the current knowledge on cell biology, genetics, epigenetics, RNA biology and virology. Therefore this contribution adds several aspects which Nobel's article does not explicitly mention, providing some examples for a better understanding of evolutionary novelty.

Keywords Dogmatism · RNA biology · Virosphere · Natural genome editing · Mechanistic error

Introduction

Denis Noble's Target Article is very attractive because it presents the list of mistakes in the neo-Darwinian concept of the new synthesis. In an outline of thoughtful arguments he presents the conceptual errors of the neo-Darwinian narrative of evolutionary processes that represent a belief status hidden in empirically masked arguments. Especially "natural selection," "the Weisman Barrier," "The Rejection of Darwin's Gemmules," and the "Central Dogma" represent the four illusions of the modern synthesis.

"Dogma" is a main assumption in religious beliefs designating that ultimate core principles cannot be questioned because they are beyond doubt; that they need no further rational justification or debate and serve as Archimedean point around which several lines of logical argumentations are built. Similar to this the "central dogma of molecular biology" describes the direction of information flow on the genetic level from DNA to RNA to protein which is irreversible (Mattick 2009).

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Noble's argumentation does not touch the falsification of the old explanatory model that error replications (mutations) are the driving force of genetic novelty. While he rejects "gene-centrism," he does not mention that all gene regulatory elements, which are part of the genome also, represent both the driving force in evolutionary novelty and an essential contradiction to the central dogma.

RNA World Agents

Single RNA stem loops react in a physical chemical way only. If multiple RNA stem loops interact, biological selection starts (Vaidya et al. 2012). Out of an abundance of RNA stem loop groups which constantly infected each other in competitive or cooperative interactions they built unlimited interconnections with larger groups stabilized by protein structures.

Direct decendents out of these RNA stem loop groups are viruses which can be seen in viroids consisting of RNA sequence structures only (Flores et al. 2014). Infectious RNA agents that escaped out of a highly competitive RNA world by reverse transcriptase (which is the original polymerase) into the stable DNA storage medium provided a strong immune function against RNA infections at that time (Belfort et al. 2011). Escape out of a highly competitive RNA world was reserved for such RNA nucleotide sequences that have been transcribed into single stranded DNA which was complemented by a second strand to form double stranded DNA. This we know as a stable genetic information storage medium and the prevalent genetic heredity material for cellular life (Gilbert 1986).

But the ancient RNA networks that predated cellular life are still present in an abundance of RNA mediated processes without which cellular life cannot function (Cech and Steitz 2014). We now know that cooperative consortia of RNA groups and viruses or its "defectives" such as retroviral *env, gag, pol* or well investigated transposons, retrotransposons, long terminal repeats, non-long terminal repeats, long interspersed nuclear elements, short interspersed nuclear elements, alu's, group I introns, group II introns, phages, and plasmids build highly dynamic networks that shape genome structure of cellular host (Villarreal 2015). There is clear evidence that evolution, conservation and plasticity of genetic identities of cellular host are the result of cooperative consortia of RNA stem loops being able to use natural code and edit this code. (Villarreal and Witzany 2015). Especially the ability to generate really new sequences (not simply derivatives of previous ones) allows such groups constantly to infect other nucleic sequence-based agents, whether virus-like or cellular genomes.

Virosphere

Viruses are the most abundant biological entities on this planet and outnumber cellular organisms ten times. In one drop of seawater we find one million bacteria but ten million viruses. If we think a lineup of all the viroids of this planet we reach a distance of more than 43 million light years spanned by 10^{31} phage virions placed side-by side (Rohwer et al. 2014). They represent a variety of genetic sequence structures not found in any cellular organisms, which indicates they are older than cellular life (Koonin

2009). Viruses infect every cellular organism since the beginning of life. Most viruses colonize host cells especially host genomes without harming the host. They remain in most cases as defective viral parts such as mobile genetic elements that are coopted for cellular needs and provide host organisms with all the known non-coding RNA elements essential for gene regulation such as replication, transcription, translation, repair and immunity in all detailed steps and substeps (Witzany 2011). If we look at eukaryotic genomes we typically find this intron/exon division in genome architecture. Whereas the introns have to be spliced out to reach an exon lineup for appropriate translation into proteins, the remaining introns serve as regulatory networks with an abundance of non-coding RNAs. This leads to a perspective of genomes as a certain ecosphere and as rare resource and habitat for a tremendous number of infectious genetic parasites (Villarreal and Witzany 2013).

Most importantly, several natural genome editing techniques have been found to change the protein-meaning of given DNA such as epigenetic markings, alternative splicing, RNA editing, pseudoknotting, alternative frameshifting, loop kissing, bypassing translation. All of this coordinated processes modify the final protein result out of the transcription and translation of a given genetic sequence syntax (Witzany 2020a). The DNA syntax remains the same, while the modifying processes may change the meaning of this syntax according pragmatic (context dependent) needs which derive from real-world circumstances, such as environmental changes, conflict and/or cooperation activities or health problems (pain stress and disease). Virus-derived elements we know as mobile genetic elements which insert and delete, copy and paste, cut and paste within host genomes. Observing repetitive nucleotide sequence structures always reminds us of RNA- world decendents, in contrast to non-repetitive sequences which code for proteins (Witzany 2017).

Natural Genome Editing: Competent Modification of Genetic Texts

Non-coding RNAs and viruses shape the genome structure of cellular host organisms. It is not the gene number which defines genetic identity of cellular organisms; e.g., *C. elegans* and humans share approximately 20,000 genes. The genes of our closest relatives, chimpanzees, differ only by 1,5%. Interestingly the genetic sequences that code for proteins in humans compose only 1,5%, whereas the non-protein coding regions comprise 98,5% of the genome. Such findings clarify that the crucial biotic information at issue are not the genes that code for proteins but the various steps and substeps of their regulation by RNA- networks (Mattick 2003), as well as the regulatory elements of genes derived from former infection events that are coopted for the regulatory purposes of the host organism (Witzany 2009). This is not a mechanistic process, as suggested by the mechanistic description "natural genetic engineering," but it is natural genome editing, like editing of a written text, this requires competent agents that act as networks and groups to modify genetic sequences and avoid errors and damage (Witzany 2006a).

Mechanistic Error in the Twentieth Century

With the rise of molecular biology in the 20th century, understanding biology as a subdiscipline of physics and chemistry was mainstream thinking. Main influencers at

that time were physicists such as Erwin Schrödinger (e.g., life is physics and chemistry) or even chemists like Manfred Eigen (e.g., the self-organization of matter). The assumption that all living processes depend on mechanistic molecular and atomic forces and features still dominates. Evolutionary novelty depends on variations in the genetic heredity program and these variations in molecular structures could only under this model be errors in replication processes.

But as we learned from RNA biology and the comeback of virology, another perspective on RNA stem loop group behavior is more coherent with our observations (Higgs and Lehman 2015). RNA stem loops have an inherent tendency to build new sequences, new single stranded loops out of double stranded RNA stem sequence. Such single stranded loops are prone to bind to foreign (non-self) single stranded RNA loops to combine, to increase a group to form genetic group identities which then can be inserted into host genomes by infection events (Hayden and Lehman 2006). RNA groups with a certain genetic identity may cooperate with other RNA groups in building networks. We may identify such RNA groups that are conserved and transfered into DNA storage medium of cellular host organisms. They must be transcribed again back to RNA to become active agents in competent groups such as e.g., the subunits of the ribosome, the editosome and the spliceosome.

Not to forget a very important feature, RNA groups retain memory of past events via outliers, that are rejected or even degraded as "non-self" in former interactions but in more recent events and depending on the real context of interaction they may be integrated again into a group. Their survival does not depend on selection of a "fittest type" but rather on an ongoing process of selection for heterogeneity (Villarreal and Witzany 2019). As we know from current virology, even highly fragmented parasitic genetic elements can create new RNA networks that are directly involved in gene regulation found in organisms in all domains of life. This is not error, but pure productivity. This is a creative process, not copying previous elements, but generating genuinely new ones (Witzany 2020b). There is a crucial difference between interpreting RNA structures as results of error replication events, or as events of creative productivity. The one designates the mechanistic paradigm of the 20th century – the other, a paradigm that integrates more recent empirical knowledge on the capabilities of viruses, their relatives, and subviral RNA networks, therefore representing an increase in explanatory power than the previous one.

This Is Not an Error: Eukaryotes, Eukaryotic Nucleus, Placenta and Memory Proteins

What formerly was explained by a series of rare beneficial error replication events that lead to more complex evolutionary innovations can now be better understood avoiding this 20th century narrative. Lynn Margulis demonstrated convincingly that an evolutionary key event – the emergence of eukaryotic cells – was not the result of chance mutations of prokaryotic cells, but the merging of former free living prokaryotes into a social group that could be genetically conserved and heritable (Witzany 2006b). Also the evolution of the leading proponent of this process, the eukaryotic nucleus must seemingly have descended from a large double-stranded DNA virus which was able to build membrane structures and coordinate genetic integration of the various participants

of the eukaryotic cell (Takemura 2020). Also the placenta organ of mammals is not the result of a series of mutation processes, but dates back to a massive persistent viral infection of egg laying mammals, as it transferred retroviral syncytin genes that could protect the foreign embryo from the immune system of the mother by forming a certain layer of fused cells (trophectoderm) until the immune system of the growing embryo is strong enough to protect itself (Villarreal 2016). Also, the synaptic arc protein, which is a crucial player in storing neuronal based memory, stems from persistent retroviral infection (Pastuzyn et al. 2018). These few examples show that genetic novelty that leads to evolutionary innovation is not the result of error replication events but of creative productivity outlined by an abundance of RNA networks transferred by genetic parasites via persistent infections into host organisms.

Conclusion

Noble's review uncovers weakness of the scientific concept of the "new synthesis" that represents the mainstream narrative in the 20th century to explain evolutionary processes. This review could be usefully extended to integrate some crucial features of RNA networks and viruses. Viruses and their defective parts play essential roles in genetic content composition, and arrangements that help organisms rearrange genetic content for adaptational purposes in a non-mechanistic way, such as in immune systems or in the evolution of new organs, e.g., the placenta. Because nearly all the remnants of former infectious genetic parasites share a repeating nucleotide syntax, in contrast to the protein- coding non-repeating nucleotide syntax, we now know that, in most cases, they remain as non- coding RNAs playing essential roles in gene regulation in all organisms of all domains of life.

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