Italian scientist proposes new model of evolution based on epigenetics

EVOLUTION

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Corrado Spadafora | Provided by Corrado Spadafora

The modern synthesis view that random genetic mutations and natural selection drive evolution has predominated in science for almost a century. More recently, experimental evidence, made possible by advanced technological methods, is challenging this view.

Instead of a gene-centered theory, new evidence points to epigenetics as playing a major role as a basis for inheritance. Epigenetics are those changes that persist through generations but do not involve changes in DNA sequences.

In a comprehensive review of independent lines of evidence challenging the modern synthesis, Italian scientist Dr. Corrado Spadafora proposes a novel evolutionary model based on emerging new epigenetic data.

Specifically he reports on experimental evidence that RNA-based information produced in somatic cells in response to environmental stress is passed on via extracellular vesicles that deliver it to the bloodstream. The extracellular vesicles transmit this extrachromosomal "cargo" to sperm cells and from there to oocytes with the potential for "phenotypic novelties in the embryo" that can be passed on across generations.

His work appears in the journal **Progress in Biophysics and Molecular Biology**, March 2023.

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and the role of epigenetic mechanisms in adaptation, and sees developmental processes, non-gene-based inheritance, epigenetics, niche construction and environmental conditions as multifactorial driving forces in evolution."

The environmental factors seen in different species include nutrition, temperature, light, toxins and stress. Spadafora cites evidence showing that such environmental triggers can "be transmitted through gametes and be inherited with variable frequency across generations that have not been exposed to that trigger."

Ongoing research

Several years ago, Spadafora's laboratory at the National Research Council in Rome discovered the ability of sperm cells to take up external DNA molecules and deliver them to oocytes at fertilization. They called the process sperm-mediated gene transfer (SMGT) and his lab and others have been studying the phenomenon and working on possible applications for gene modification and cancer therapies.

Summing up his model, Spadafora said, "Evolution is not a collection of random traits increasing over time, nor are these traits dependent on contingent events. On the contrary, variations are finely tuned by organisms and are integrated by generating structures, forms and functions."

Corrado Spadafora. "The epigenetic basis of evolution." *Progress in Biophysics and Molecular Biology*. March 2023. https://doi.org/10.1016/j.pbiomolbio.2023.01.005

Interview with Corrado Spadafora

Epigenetics drives evolution

Dr. Corrado Spadafora is a researcher at the Institute of Translational Pharmacology of Italy's National Research Council. He discussed his views on epigenetics and evolution with Current Science Daily *via email.*

Discuss how your evolutionary hypothesis challenges the modern synthesis view of evolution.

According to neo-Darwinism (or the theory called “modern synthesis”), evolution is fueled by two independent, yet convergent, processes: randomly occurring genetic mutations and natural selection. In summary, mutations generate phenotypic variants that are then “sieved” through natural selection, which preserves and fixes those conferring an adaptive advantage (greater fitness) and counter-selects those with poor or no adaptive value.

ultimately generate unviable cells mainly acting as “disruptive agents” of pre-existing genetic information rather than generators of evolutionary novelty.

Moreover, no paleontological evidence supports the emergence of the many mutation-induced phenotypic variants that would be expected to originate from random mutations.

What is some of the evidence of epigenetic data?

In the last few years, growing epigenetic data are showing that organisms are sensitive to a variety of epigenetic stimuli that do not cause mutations of the genomic DNA but alter the spatial conformation of the genome architecture and reprogram the gene expression profile. Mounting data suggest that epigenetic alterations have strong evolutionary implications.

In the wake of these studies, I have proposed that gametes and early embryos have intrinsic evolutionarily relevant features.

First, spermatozoa, besides carrying the male genome, also accumulate and carry a load of extrachromosomal RNA-based information that can be delivered to the oocytes at fertilization.

Second, zygotes and very early embryos at the one- and two-cell stages--that is shortly after fertilization or just emerging from the first cell division that follows fertilization--offer a highly permissive context, capable of accepting and transmitting the information carried by the sperm RNA along with the genetic pool of the developing embryos.

In this crucially permissive environment, the sperm RNA can exert all its potential to reprogram development, inducing micro- and/or macro-evolutionary variations. Furthermore, the accumulation, across multiple generations, of RNA-based information delivered after each fertilization can increase the variation effects with significant evolutionary reach.

RNA is transmitting material that is not DNA?

RNA is not transmitting material, but extrachromosomal information that is not coded in the genomic DNA. Most of the RNA stored in spermatozoa has a somatic origin, most likely transcribed in the somatic cells of the sperm donor (the father) in response to stressors and environmental stimuli, then packed in extracellular vesicles (ECVs) that are released in the circulating blood.

Part of the ECVs reach the epididymis, where their RNA cargo is eventually taken up by mature spermatozoa, which are naturally permeable to molecules and vesicles. Thus, the sperm RNA-based information is not the remnant of some random transcription but reflects the impact exerted by the environmental conditions on the organism’s cells.

The stress-induced RNAs, in turn, can impact the modeling of developing organism. This proposed model integrates these lines of evidence and suggests that the emergence of developmental novelties is largely driven by the information-containing RNA inherited via sperm cells across generations. Evolutionary progression, therefore, is an

neo-Darwinian gene-centric view.

What about the actual differences in DNA that distinguish species?

There are various quantitative and qualitative differences that distinguish the genomes of different species: genome size varies among different species; gene content varies because different species have different numbers of genes; gene rearrangement varies because genes are differentially distributed in chromosomes.

However, none of these differences shows clear correlations with the evolution progression of the species. A different and more interesting landscape emerges instead when coding and non-coding DNA sequences are compared. Coding sequences, also known as exons, are the protein-coding sequences, while the non-coding is predominantly constituted by sequences exerting genomic regulatory functions.

Is it fair to say that your proposed model flows out of traditional evolutionary theory and makes use of new experimental data?

Yes, it is correct. Like any other branch of science, biology has evolved over time and it is now time to incorporate both new experimental findings and theoretical concepts in a novel evolutionary landscape. Studies have revealed that a wide spectrum of factors and mechanisms contributes to the evolutionary processes.

Among others, fundamental roles have emerged for evolutionary developmental biology (merging into the new field of research termed evo-devo), which aims at identifying developmental mechanisms that generate the vast diversity of morphologies in organisms within and between populations and species. These include:

• Epigenetic inheritance, or non-gene-based inheritance, which consists in the ability to reprogram gene expression, without altering the underlying DNA sequence, and to transmit stably the reprogrammed information across generations;

• Developmental plasticity, that is the ability of an organism to modify its own phenotype in order to adapt to the environment in response to external stimuli.

Again these variations-inducing processes are epigenetic in nature not requiring mutations nor natural selection

Your laboratory made some important discoveries in regard to epigenetics.

The work of my laboratory has mostly focused on reproductive and developmental biology. Our main finding was that spermatozoa of virtually all animal species, including human, have the spontaneous ability to take up foreign molecules, as DNA and RNA, and particles, as vesicles and viruses and to internalize them in their nuclei.

This extrachromosomal cargo is delivered to the oocyte at fertilization and has the potential to introduce novel traits in the developing embryo. Such spontaneous ability of sperm cells provided the functional basis for

Where did environmental factors come into play?

This was not our exclusive finding but we contributed to it together with the work of many other laboratories which discovered that the composition of the RNA cargo in ECVs is heavily influenced by the environmental conditions to which the originating cells/tissues were exposed. For that reason the composition of the information flowing from stressed cells is variable and expresses their adaptation to specific environmental changes.

In the model, ECVs play a crucial role as vectors of the extrachromosomal RNA-based information from the originating somatic [non-reproductive] cells to the epididymal spermatozoa. [The epididymis is where the sperm cells mature and are stored.] By doing so, they cross the “Weissman barrier,” a metaphorical barrier traditionally considered as the insurmountable boundary separating somatic cells from germ cells.

You proposed this sperm transfer as an RNA-based blueprint that can "rewire genetic circuits in the embryos."

The ECV RNA cargo originating from somatic cells, and taken up by epididymal spermatozoa, is essentially constituted by “regulatory” RNAs, often small RNA molecules that control the expression of target genes and modulate transcription profiles. At fertilization, the sperm RNA cargo is delivered to zygotes. Therein, it modulates the expression of embryonic genes and resets the transcription profile of the early developing preimplantation embryos. This can lead to the emergence of phenotypic novelties.

In other words, evolutionary changes are not caused by progressive mutations, but rather emerge from a functional meshwork.

Evolutionary variations are directly correlated with the sperm RNA delivered at fertilization, whose composition depends on the stimuli and response to the environmental conditions in the originating somatic cells. In this perspective, the sperm RNA can be considered as their “blueprint.” This mechanism has a specific adaptive value because it conveys relevant environmental information to the developing embryos.

How do you hope your model for an epigenetic evolution-promoting "assembly line" will change the study of evolution?

Evolution is an extremely slow process that unfolds over geological ages and is not observable within the human lifespan. Consistent with this, no experimental approaches can study evolution. The trajectory of evolution is usually reconstructed on the basis of retrospective “backwards” studies, using paleontological remnants left over the eons, while basic molecular mechanisms can be recapitulated from phenotypic, genomic, and epigenetic features of living organisms.

Moreover, evolution is tightly correlated to the problem of the origin of life, a major question whose answer remains shrouded in deep mystery. This lack of direct experimental data leaves wide gaps in our knowledge which, not surprisingly, were filled with a variety of philosophical speculation, ideological references, and religious implications. On these

vs. a teleologically driven process are harshly opposing.

All these reasons make evolution a complex and challenging area of study. The primary intent of the model I propose is to bring together solid experimental data, concepts, and hypotheses from various area of biology and integrate them into a multifaceted model of global evolution.

What is the "assembly line"?

The following key steps can be recognized.

1) Spermatozoa take up information-containing RNA of somatic origin and deliver it to oocytes at fertilization.

2) Zygotes, one- and two-cell embryos, are highly “permissive,” and thus provide contexts capable of assimilating the RNA-based extrachromosomal information.

3) Functional asymmetries are established in oocytes and early embryos, based on the distribution of miRNAs and morphogens, and represent a natural blueprint of “hot spots” that will drive the future development.

4) The sperm-delivered RNA acts as a symmetry-breaking agent, able to modify the natural blueprint and to redirect the evolution trajectory.

5) The re-deployment of pre-existing genetic networks and the re-adaptation of pre-existing structures prone to accept morphological innovation are thus key for the emergence of evolutionary phenotypic variants, independent on the occurrence of mutations.

Conclusion

This information/innovation-generating machinery is continuously triggered in organisms in response to environmental stimuli to which they are exposed. Overall, the process provides conditions that favor evolution and channel it along specific trajectories, constraining the myriad of possible variants that could potentially be generated by random mutations. In that sense, chance plays little role in evolution and, as such, it can be defined a “goal-directed process” and, why not, also repeatable.

Spadafora concluded, '"Nothing in biology makes sense except in the light of evolution' is the famous statement by biologist Theodosius Dobzhansky that could be paraphrased as 'Nothing in evolution makes sense except in the light of the human mind.'"

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