Austin Journal of Genetics and Genomic Research

Open Access

Review Article

The Genetic Underpinnings of DNA Autopoiesis: A Review

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Received: March 26, 2015; **Accepted:** May 20, 2015; **Published:** May 22, 2015

Abstract

The primary goal of this review is to appraise the genetic underpinnings of DNA autopoiesis. An autopoietic system must meet six criteria: that system must have an identifiable boundary, that boundary is self -produced, the components of that boundary is self-produced, that system is subject to cause and effect, that system possesses constituent elements/components, and those constituents are self-produced. In this review the evaluation of relevant literature in genetics and genomic research were surveyed in order to determine if there is enough scientific proof that can be enumerated which supports that the DNA molecule meets the six criteria of autopoiesis. The results were that there is a significant amount of genetic underpinnings identified that affords the DNA molecule the ability to meet all six criteria of autopoiesis. By understanding the genetic underpinnings of DNA autopoiesis we can begin to objectify DNA as a conscious, autopoietic, and intentional system; rather than myopically viewing DNA as nothing more than a genetic storage unit. Finally, it is important to establish a gene-based framework of DNA autopoiesis as this will give researchers a starting point in proposing testable models.

Keywords: Autopoiesis; DNA consciousness; Interaction-complexity-consciousness paradigm; Neppe-Close triadic dimensional vortical paradigm

Introduction

A brief description of some new concepts

In order to approach an understanding of DNA as an autopoietic and conscious system a few concepts in theoretical biology and quantum physics need to be briefly highlighted. These concepts are: the interaction-complexity-consciousness paradigm, the triadic dimensional vortical paradigm, and the theory of DNA consciousness. Only a brief description will be given of these concepts as the goal of this review is to provide examples of the genetic underpinnings of DNA autopoiesis.

The Interaction-Complexity-Consciousness (ICC) paradigm (sometimes called the interaction-based model of consciousness) simply states that consciousness, at all scales, emerges from the interactions of things, which can be- fermions, atoms, molecules, cells, and neurons; with each other, forms of energy, and the four basic forces of physics- gravity, electromagnetism, strong nuclear forces, and weak nuclear forces [1]. As things interact they become entangled and more complex as a system. Here are two examples, fermions interact to form subatomic particles and atoms interact to form molecules. Hence, increases in this interaction-based complexity results in systems with higher degrees of consciousness. To clarify, let us look at this example- the interaction-based complexity of the cell yields a degree of cellular consciousness, whereas the interaction-based complexity of the human brain (which is much higher than any single cell) yields a higher degree of consciousness. Under this paradigm it may appear that consciousness is an emergent property founded on interaction-based complexity. However, this is not altogether true.

If we take a look at the Neppe-Close Triadic Dimensional Vortical Paradigm (TDVP) it is demonstrated that there is a unification of three substrates- time, space, and consciousness (or c-substrate); which are tethered from the origin point of the universe [2,3]. In terms of how substrates are to be classified in this paradigm, they are constituents that underlay the process by which the universe comes into existence. According to Neppe and Close, these three substrates (space, time, and consciousness) are separate entities but they are always tethered together. Consequently, they may appear separated as they can be perceived in various degrees that are dependent on different higher mathematical dimensions of distinction. Thus, according to this paradigm, consciousness would appear to be a fundamental property of the universe, but this is not completely true.

When the ICC and TDVP are connected by the c-substrate it is, in a simplified version, demonstrated that consciousness is both a fundamental substrate of the universe and an emergent property. The c-substrate is a fundamental element tethered to space and time, but as interactions yield more complex systems the degree(s) of consciousness can be increased an infinite number of times. These newly emergent degrees of consciousness, like their predecessors, are now tethered with space and time (at a higher mathematical dimension).

Understanding consciousness as both a fundamental and emergent property can be confusing, but it is analogous to the difficulty encountered when physicists were attempting to understand light as both a wave and a particle. Moreover, the unification of the two paradigms- TVDP and ICC provides a unique definition that allows the possibility for genomes to be considered consciousness systems that are autopoietic. The c-substrate is a fundamental substrate of the

Citation: Grandy JK. The Genetic Underpinnings of DNA Autopoiesis: A Review. Austin J Genet Genomic Res. 2015;2(1): 1012.

universe, and as charge and mass undergo change (by interactions), new degrees of consciousness can emerge and evolve. DNA affords the ability for the emergence from the micro-scales of consciousness onto the macro-scales of consciousness. More details can be found on the ICC-TDVP paradigm unification in a forthcoming publication [4].

So what does the unification of the ICC and TDVP paradigms have to do with DNA autopoiesis? As the evolution of consciousness travels through the trajectory of the atomic and molecular world RNA emerges. RNA is able to transmit and store small amounts of genetic information. It can even give rise to higher degrees of consciousness, e.g., RNA viruses, which can be considered the simplest of nucleic life forms. However, RNA's ability to give rise to higher degrees of consciousness, as far as we know, ends here with the RNA virus. It is the emergence of the DNA molecule with immeasurable interactions that affords an unfathomable explosion in complexity and subsequent degrees of consciousness!

The concept of DNA consciousness has two main tenets: 1) DNA is a degree of molecular consciousness supported by the unifications of the ICC-TDVP paradigms 2) DNA possesses the ability to give rise to higher degrees of consciousness [5-10]. When DNA consciousness gives rise to human consciousness, this happens in three neurogenetic phases which has been outlined in previous publications [11-15]. The concept of DNA consciousness can be reified by identifying and organizing some of the genetic underpinnings of autopoiesis, which, in effect, provides a biological framework of intentionality (the advancement toward energy concentrations that are required by a biological system) and autonomy.

Autopoiesis: the six criteria and the identification of genetic underpinnings

Essentially, biology is a melee between order and entropy. The advantage is overwhelmingly in stark favor of entropy. It is very difficult to circumvent this advantage. Consequently, biological systems must efficiently process and transmit information in an attempt to produce order, perform self-replication, and engage in the evolution of complexity. One phenomenon that affords biological systems the ability to do this is autopoiesis.

Autopoiesis, or the dynamics of the autonomy proper to living systems, was first defined by Chilean biologists Humberto Maturana and Francisco Varela to define processes that are self-maintaining, i.e., they produce, maintain, and replace their components; which distinguishes the biological system from the environment [16]. There are six criteria that must be met for a biological system to be considered autopoietic: 1) the system must have identifiable boundaries that distinguish it from the environment, 2) those boundaries must be self-produced 3) the components of those boundaries are self-produced 4) the system is mechanistic and subject to cause and effect 5) the system possesses constituent elements and components, and 6) those constituent elements and components are self-produced. In this review, examples of the genetic underpinnings of DNA autopoiesis will be presented that will provide evidence that all six of these criteria are met. This will be done by reviewing relevant literature in genetics and genomic research.

First, the system must have identifiable boundaries that distinguish it from the environment, second, those boundaries must be self-produced, and thirdly, the components of those boundaries are self-produced

In eukaryotic cells, DNA resides in the nucleus, which consists of a lipid double membrane- the nuclear envelope that is populated by nuclear pores. Beneath the nuclear envelope is the nuclear lamina which is a net-like arrangement of protein filaments that maintain the integrity of the nucleus. The nuclear envelope and the nuclear lamina give the DNA an identifiable boundary from the cytoplasm of the cell. Therefore, the first criterion is met. Next, it will be demonstrated how this boundary is self-produced and how the components of this boundary are also self-produced, which will fulfill the second and third criteria of autopoiesis.

The components of the nuclear membrane are composed primarily out of phospholipids. The production of these lipids takes place during mitosis prior to cytokinesis and the production of two new daughter cells. This means that after the separation of the two daughter genomes that two separate boundaries must be produced status post cytokinesis. Thus, one manner in which the structure of the nuclear membrane is maintained and regulated is via phospholipid synthesis and membrane biogenesis. The pah1 gene, dgk1 gene, reb1 gene, and various other genes encode for a multitude of enzymes and transcription factors that are vital to phospholipid synthesis and biogenesis.

Pah1-encoded Phosphatidate Phosphatase (PAP) is involved in the critical step of catalyzing the dephosphorylation of Phosphatidate (PA) into Diacylglycerol (DAG). PA is an important phospholipid intermediate in the synthesis of membrane phospholipids.DAG is a glyceride covalently bond to two fatty acids and also forms various intermediates for the biosynthesis of membrane phospholipids. In yeast, PAP has been demonstrated to be a critical factor in nuclear membrane structure by regulating the synthesis of phospholipids [17-20]. Mutations in pah1 gene has demonstrated reduced levels of the enzymatic activity of PAP, abnormalities in PA and DAG levels, and abnormal nuclear membranes [21,22]. While pah1p converts PA into DAG, the dgk1 gene encodes diacylglycerol kinase enzyme (dgk1p) which catalyzes the CTP-dependent phosphorylation of DAG into PA [17,23-24].

The pah1 and dgk1 genes are genetic underpinnings that allow the establishment of an identifiable boundary from the external environment. However, a member of the general regulatory factors, reb1 gene-encoded RNA polymerase I enhancer-binding protein (reb1p) also plays an important role in lipid metabolism. On a functional level, transcription factor reb1p regulates the expression of dgk1p by binding to the dgk1 promoter region [25]. Additionally, reb1p, when bound to the promoter region, acts as a road block for RNA polymerase II [26]. This allows efficient and timely transcription termination which is necessary for control over pervasive transcription and also prevents transcription via gene regulatory regions.

Lipids are the main constituents of the membrane matrix which determines the physical properties of this boundary. Some of these properties are membrane surface charge, membrane thickness, membrane fluidity, and the membrane intrinsic curvature. PA and DAG interact with many enzymes encoded by many other genes (see

figure one in reference 23 and figure one in reference 24), e.g., cds1, ino1, cho1, ekl1, ept1, psd1, cho2, opi3, ckl1, and cpt1. Collectively, these gene products interact to produce various glycerophospholipids- phosphatidic acid, phosphatidylserine, phosphatidylinositol, phosphatidylethanolamine, and phosphatidylcholine (and in mitochondria cardiolipin); all of which compose the nuclear membrane [27].Consequently, pah1, dgk1, reb1, and many other accessory genes produce self-made constituents that play a pivotal role in establishing the boundary of the nuclear membrane.

Hence, we have demonstrated that DNA, as a system, has an identifiable boundary, which is the nuclear membrane that distinguishes it from the environment. Additionally, it has been demonstrated that boundary and the components of that boundary are self-produced; primarily by various glycerophospholipids that are manufactured by enzymes encoded from genes within the DNA molecule. At this juncture the first three criteria of autopoiesis have been satisfied. More proof could have been amassed by evaluating genes that code for the nuclear pore proteins, the core scaffolding lamin proteins, and the Mur genes that produce the peptidoglycan cell wall of prokaryotic cells (as this is basically the nuclear membrane and the boundary distinguishing prokaryotic DNA from the external environment). However, these things do not need to be done; and for the sake of brevity will not be done.

Fourth, the system is mechanistic and subject to cause and effect

Collectively, the DNA in the nucleus is composed of a dynamic conglomeration of nucleotides, histones, chromatin, and methylation. This system provides stability and the ability to amass a small or large amount of genetic information- depending on the organism. However, there is some fragility to this system, in where internal and external agents can inflict an observable cause and effect to this system. Next, three examples of mechanistic cause and effect will be discussed.

The first example can be seen at the level of gene transcription. RNA polymerase can bind to the promoter region of a gene and can cause DNA to transcribe mRNA. However, if there is an uninhibited repressor it will bind to the operator region of the gene and prevent RNA polymerase from initiating transcription. On the other hand, enhancers can bind to the gene and incite gene expression. In a very simplified sense we have a two-way system of cause and effect. From one way there are molecular causes, e.g., RNA polymerase, inhibited repressors, and enhancers that result in gene transcription. From the opposing direction there are molecular causes, e.g., uninhibited repressors and RNA polymerase inhibition that result in no gene transcription.

The second example can be seen at the level of cell cycle control. The protein encoded by Tumor Suppressor p53 gene (TP53) is involved in G1-phase (duplication of the cellular content-excluding the chromosomes) and promotes a delay in the progression to G0-phase (cell arrest). This delay allows time for the detection and repair of defects in the DNA that may have occurred during mitosis. Damage to the TP53 gene can be caused by external sources, e.g., carcinogens, mutagens, and certain viruses, in addition to internal sources, e.g., cell cycle abnormalities, free radicals, and hypoxia. When the TP53 gene is damaged or mutated the delay between G1 and G0 is lost, which can cause cellular and genetic instability resulting in undifferentiated cancer cells. This was demonstrated by experiments in the early 1990's [28-31]. Therefore several intra-cellular and extra-cellular agents or events can cause damage to the TP53 gene and in effect result in cancerous cells.

The third example can be seen with external agents that can enter the body and damage DNA, e.g., radiation or drugs. For example, the drug Fluorouracil (5-FU), an antimetabolite pyrimidine analog, irreversibly binds to thymidylate synthase [32-34]. Thymidylate synthase is vital to the production of thymidine monophosphate, which is phosphorylated into one of the four basic building blocks of the DNA molecule, i.e., Thymidine Triphosphate (TTP). Consequently, 5-FU can cause a depletion of TTP and in effect prevent DNA replication.

Hence, here are three simple, but very effective, examples that demonstrate on many different levels that the DNA molecule is subject to cause and effect. Consequently, the fourth criterion of autopoiesis is satisfied. In addition, in a mechanistic system, if the network of production of the components which define the organization is disrupted, the unity disintegrates [35]. Therefore, any autopoietic system must have a process that can counterbalance any discomposure inflicted upon that system. In the case of DNA, there are two systems that counterbalance damage and abnormalities: the DNA repair system and transposable elements. In general, the transposable elements function by adding new splice sites, adenylation signals, promoters, or transcription factor binding sites.

Fifth, the system possesses constituent elements and components, and sixth, those constituent elements and components are self-produced

Essentially, the constituent elements and components of DNA are the nucleotides: two purines- adenine and guanine, and two pyrimidines- cytosine and thymine. One way that purine synthesis takes place, de novo, is in the liver and begins with Phosphoribosyl Pyrophosphate (PRPP). The pentose-phosphate, PRPP, is produced from ribose-5-phosphate phosphorylation by PRPP synthetase. After several enzymatic actions PRPP is converted into hypoxanthine which is transformed by Hypoxanthine-Guanine Phosphoribosyl Transferase (HGPRT) into Inosine 5′-Monophosphate (IMP). IMP has two pathways- one produces adenine and the other produces guanine, two of the four constituent elements of the DNA molecule. This same pathway manufactures uric acid (which becomes uracil) which is used for the structure of RNA; consequently there is no need to include uracil in this discussion.

For simplicity's sake, one key biochemical location in the production pathway of adenine and guanine will be objectified. PRPP synthetase is encoded by the PRPP synthetase gene. PRPP synthetase is coded by PRS gene in Bacillus subtilis, Escherichia coli, and Salmonella typhimurium [36-38]. In humans PRPP synthetase subunits are produced by PRPS1 and PRPS2 genes, and over-activity of PRPS1 (involving pre-translational dysregulation) expression results in the over-production of purine nucleotides and uric acid [39-41]. So here we have evidence, from several different species, that the genome has a gene(s) that self-produces a protein product that in turn is pivotal to producing purines, which make up a portion of the genome itself.

The two purines are produced from a similar pathway up to the production IMP and then the pathway splits; unlike the two pyrimidines, which are engendered by two different biochemical pathways. In the case of cytosine, carbamoyl phosphate undergoes several chemical reactions (one step involves PRPP) to produce UMP which is phosphorylated into UTP. One of the final key steps in the production of cytosine is the conversion of UTP into CTP by CTP synthetase (which adds an amine group) [42,43].CTP synthetase is encoded by the pyrG gene in Escherichia coli [44] and CTPS1/CTPS2 genes (forming isozymes CTPS1 and CTPS2) in humans [45]. Thus, we have evidence that a gene(s) in the genome produces a protein that in turn produces self -made components of the DNA molecule itself.

As mentioned earlier thymidylate synthase is involved in the production of thymidine monophosphate, which is phosphorylated into Thymidine Triphosphate (TTP). The TYMS gene encodes for thymidylate synthase which provides the sole source of de novothymidylate production, i.e., thymidylate synthase is a catalytic enzyme that methylates deoxyuridine monophosphate to deoxythymidine monophosphate [46]. Thymidylate synthase inhibitors have been shown to decrease thymidylate synthase which results in abnormalities in DNA synthesis and repair [47,48]. Consequently, we have direct evidence of a gene that is involved in the production of one of the four self-produced elements of the DNA molecule and inhibitors to that genome-derived catalytic enzyme results in abnormalities in the DNA molecule.

Based on these brief examples, this review provides approbation that the DNA molecule meets and fulfills the fifth and sixth criteria of autopoiesis. Many more examples could have been enumerated as many other genes make protein products that are involved in the creation of purines and pyrimidines. One should not undervalue the significance of this phenomenon, i.e., genes encoding for proteins that produce constituent elements of their very own makeup.

Conclusion

The DNA molecule possesses genetic derivatives that produce proteins, enzymes, nucleotides, and lipids that make autopoiesis possible, i.e., there are in fact genetic underpinnings to DNA autopoiesis as demonstrated throughout this review. But how does the DNA molecule know how to do this? Are we to assume that this is a merely random act or is there an underlying intentionality, a degree of consciousness?

In 1974, the concept of autopoiesis was relatively new. However, Varela, Maturana, and Uribe, had established that living organizations can be characterized unambiguously by stipulating the network of interactions of the components that constitute that living system as a whole, i.e., unity [35]. Furthermore, a complex system can be defined as a unity by the relationship amongst its constituent elements. DNA, as a system, does exactly this. In this review, it was demonstrated, very lucidly, that there are genetic derivatives and their relationship to those constituent elements make DNA autopoiesis possible.

In terms of consciousness, which is both a fundamental and an emergent property, it must be kept in mind that the phenomenon of autonomy is a consequence of an autopoietic organization. Another way of expressing this is that the recognition of any autopoietic system is, in fact, by the intentional product of its operation. In the case of DNA, that production is life beginning at the level of the cell and engaging in a trajectory of interaction-based complexity which gives rise to higher degrees of consciousness. In addition, an initial framework of DNA consciousness has been objectified into three dynamic levels in a previous publication 1) the interactions between DNA and itself (epistasis- gene-gene interactions), 2) the interactions between DNA and other nucleic entities (RNA species, viruses, mitochondria, and other cells, and 3) the interactions between DNA and the external environment [10].

In this review all six criteria of DNA autopoiesis have been validated using objective proof in genetic and genomic research literature. However, outside the confines of these six criteria, it has been discovered that single genes (and gene families) can drastically influence; and to an extent, control, the behavior and expression of the entire genome. In a recent review article, major signaling networks were outlined that demonstrate that the Myc gene family collectively modulates the dynamics of global gene expression (regulating approximately 10-15% of the global transcriptome) [49]. This affords Myc the ability to regulate vital cellular functions, e.g., cell proliferation, cell adhesion, metabolism, and protein biosynthesis. Another example is seen in the Hells gene that encodes for Lymphoid-Specific Helicase (LSH), which is vital to DNA methylation (gene-silencing) during the differentiation and determination of gene expression in embryonic lineage [50,51]. LSH controls genome-wide cytosine methylation that is essential for normal growth and mutations in the Hells gene have demonstrated substantial loss of methylation through the genome [52,53]. Consequently, it can be visualized how particular individual genes are responsible for emerging characteristics and behaviors of the infinite variety of cells seen in nature. Again, this cannot be a random auspicious event. There must be autonomy and intentionality, i.e., a degree of consciousness driving this phenomenon.

To further compound this mystery, DNA appears to have a semantic language of its own, i.e., the genetic code. This code contains a set of rules in which triplets of DNA sequences specify the amino acid sequences that produce proteins. There are 64 possible triplet codons that code for twenty amino acids. That means that there are overlapping triplets (and there are three different stop codons). Hence, there is degeneracy, in that different triplet combinations yield the same protein product. Mathematicians and physicists have used mathematical structures to represent this semantic genetic code that include a 64-part vector quaternion algebra, which is isomorphic to the algebra of the quantum mechanical Dirac equation, and a combination of the faces and vertices of a regular icosidodecahedron [54-56]. The codon structures have also been represented algebraically and geometrically, in a manner that relates their function in coding for amino acids suggesting that this is a biologically significant way to represent the genetic code [57].

The semantics of the DNA molecule also appears to have languages within its language. For example, the molecular recognition theory demonstrates that a purine nucleotide in the second codon position of the triplet always encodes for hydrophilic amino acids and that a pyrimidine in the second codon position of the triplet always encodes for a hydrophobic amino acid [58]. This has given rise to the foundation of a binary code-based interpretation of the genetic code. In a recent review, it was demonstrated that by reading this hidden binary code in the DNA database that protein-protein contacts can be

predicted [59]. By further understanding the language(s) of the DNA molecule it may be possible to further comprehend and define it as a conscious system.

In many ways this review has merely scratched the surface. There are likely hundreds of additional genes that underlay the various aspects of DNA autopoiesis, but here we have a starting point, an initial framework at where to begin. It has also been pointed out that there is a semantic language that can be represented algebraically and a hidden binary code within the DNA molecule. Compiling a larger, more detailed framework; and an understanding of the hidden language(s) of the DNA molecule will be required in future works prior to proposing testable models. This review may serve as a call for more research in this area. However, with the current information available, this review supports DNA as an autopoietic system, with its own language; and reifies it as a degree of consciousness, autonomy, and intentionality.

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Citation: Grandy JK. The Genetic Underpinnings of DNA Autopoiesis: A Review. Austin J Genet Genomic Res. 2015;2(1): 1012.