

The Primordial Genes Are Conserved as Stem Cell Genes and Proto-Oncogenes

The Ancient Earth

Amino acids and nucleotides coexisted before cells. Amino acids and nucleotides were formed readily from small organic molecules [2–4a, b]. Hypercyclic networks of polypeptides (L-enantiomers dominating), and nucleic acids (RNA, catalyzing ribozymes, and ribonucleoproteins (RNP) coexisted in the ancient Earth some four milliard (billion) years ago in a pre-cellular era [5–10]. Lipids and sugars could be synthesized without hypercycling. The primordial chemical reactions resulted in the formation of virus-like agents (viroids) different from extant cell-dependent viruses. Extant viroids are relics from the precellular era [11–14a, b]. Ribozyme-armed precellular ribosome-like units might have generated the ancestral viroids. Fused viroids might have formed ancestral large viruses. The first pre- or protocellular entities consisted of vesicles with double lipid membranes. These vesicles incorporated the interactive large molecules (Figures 11 and 12), including complex nucleic acids and “self-replicating and supercycling polypeptides” (Figure 13). The vesicles grew in size and complexity and were able to divide (chemotons of Gánti; coacervates/коацерват of Опарин/Опарин); and replicators of Szathmáry [15–17]. The primordial genomes and proto-ribosomes might have consisted of RNA complexes (mRNA, rRNA, tRNA, ribozymes, and RNP ribonucleoproteins), replicating with genetic variations due to copying errors. It is not known how and when DNA appeared first and if more than once, and by possible different mechanisms of origin: synthesis, like the original RNA, or conversion from RNA to DNA. The precellular origin of viruses (virus-like agents) is very likely, since ribozymes/RNPs and polypeptides existed and interacted before cells were formed. The double-walled vesicular entities were invaded by the pre-existing virus-like agents. The virus-like agents experienced losses of their independent genes, preserved their “virus hallmark genes” of Koonin (genes not shared with host cells), and acquisitioned new genes deriving from their host cells (*vide infra*). Their replication has become dependent on the metabolism of their host cells, which the

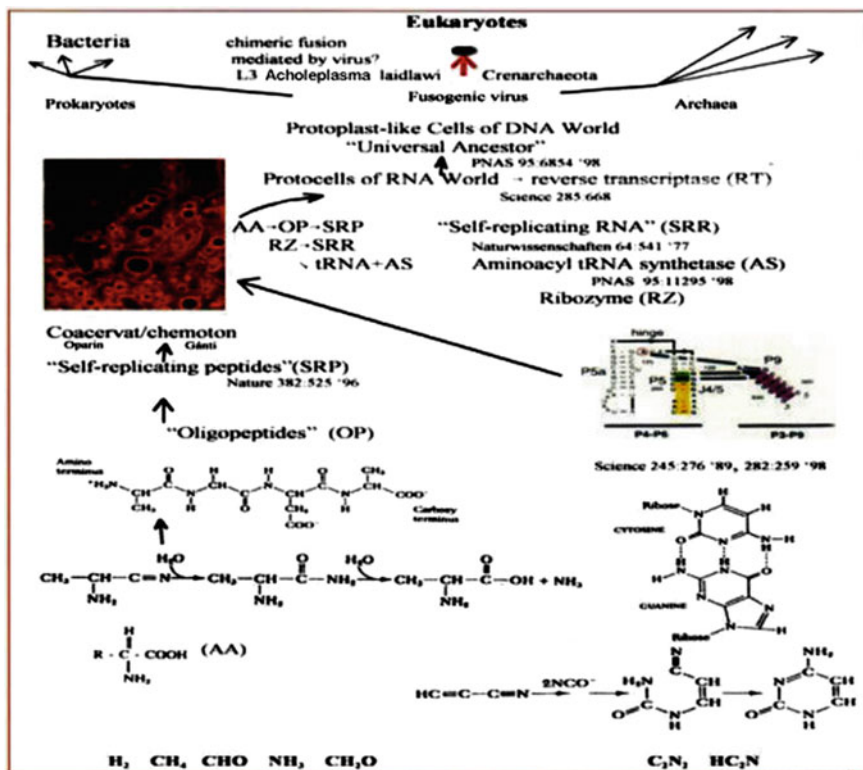


Figure 11 Biomolecules on the Ancient Earth. Reference Appendix 2, Explanations to the Figures

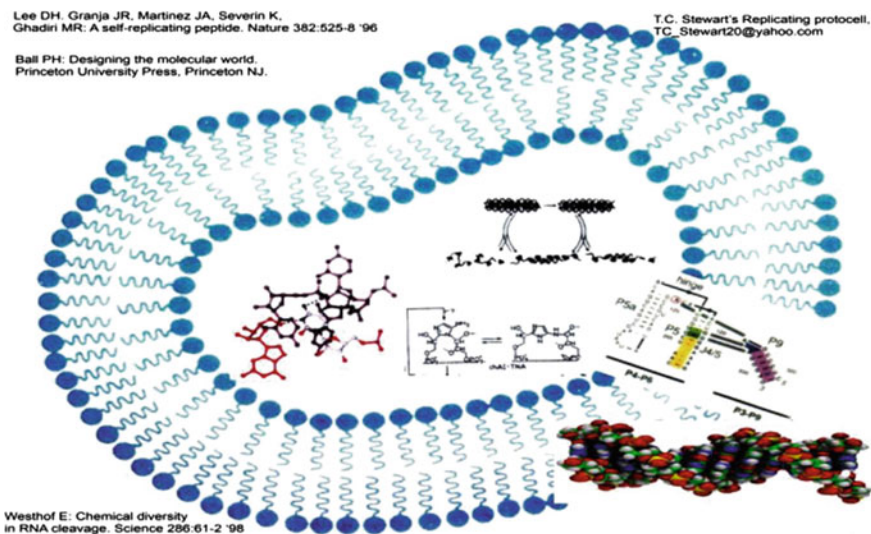


Figure 12 Chemotons, Koacervats, Protocells. Life in the Protocell. Reference Appendix 2, Explanations to the Figures

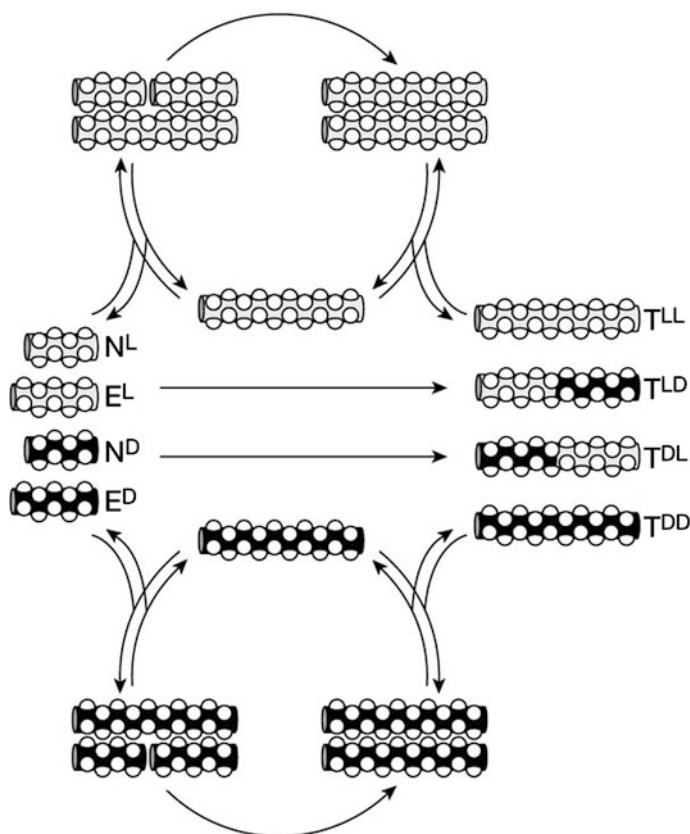


Figure 13 Autocatalytic Chiroselective Reactions of Hypercycling Peptides. [8] Reference Appendix 2, Explanations to the Figures

viral agents expropriated and ruled. The successful viral genomes could readily overtake and redirect the host cell genomes. Other viruses inserted their genomes into the chromosomes of their host cells, where these proviral units were retained and remained conserved (*vide infra*).

The primordial virus world and gene pool included the RNA/DNA complex. The precellular virus-like agents possessed either or both RNA and DNA strands forming the precellular “Virus World” and “Primordial Gene Pool” of Koonin, Senkevich and Dolja [18], dominated by ribozymes, and ribonucleoproteins (RNP). The fact that extant cells possess long non-coding RNA strands with RNA $\rightarrow$ cDNA structures being embedded in them, the human *sox2* gene at 3q26.3–27 with an overlapping intron (P.P. Amaral *et al*, *vide infra*), suggests that RNA and DNA might have already co-existed in similar constellations in the pre-cellular and proto-cellular environment. The DNA either evolved from RNA, or these two master molecules co-evolved side-by-side, but RNA predating DNA. In the precellular era,

RNA and DNA united and reacted with each other and with polypeptides. Indeed, nucleic acid hybrids (RNA:RNA; DNA:DNA; RNA:DNA; DNA:RNA) are formed spontaneously both *in vitro* and *in vivo*. In the yeast cell, RNase H removes RNA:DNA hybrids in order to prevent “genome instability”. In contrast, heterochromatic non-coding ncRNAs form physiologically complexes with DNA: the RNA:DNA hybrids [19, 20]. One can presume that such hybridization of the two co-existing master molecules might have taken place in the precellular, or in the immediate protocellular, worlds. The immense storage capacity of DNA for information and for encoding proteins (through mRNA and tRNA in the ribosome under the genetic code), and its inexhaustible mutability were acquired through a milliard (billion) years of evolution in the pre-cellular and protocellular era. These faculties became fully operational approximately 3 milliard years ago within the first living cells. Within the cell, it is reverse transcriptases that transcribe RNA into DNA [28]. Large polypeptides have become the first DNA-binding proteins. These interactions required the fitting molecular structures in the grooves of the DNA and in the proteins. First, DNA genes encoded the proteins in mRNA-tRNA interactions; then microRNAs guided the proteins to the chromosomes (within the cytoplasm in prokaryota and archaea; from the cytoplasm into the nucleus in eukaryota). Structurally receptive DNAs accepted the proteins and reacted to them (*vide infra*, DNA-binding proteins, in the Appendix 1).

RNA/DNA and Cancer

Sinkovics, J.G.

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