Origin of the Universe – stars, planets, elements

Origin of biorelevant monomers – primordial soup

Complex chemical processes on the way to living systems

Protocells and LUCA

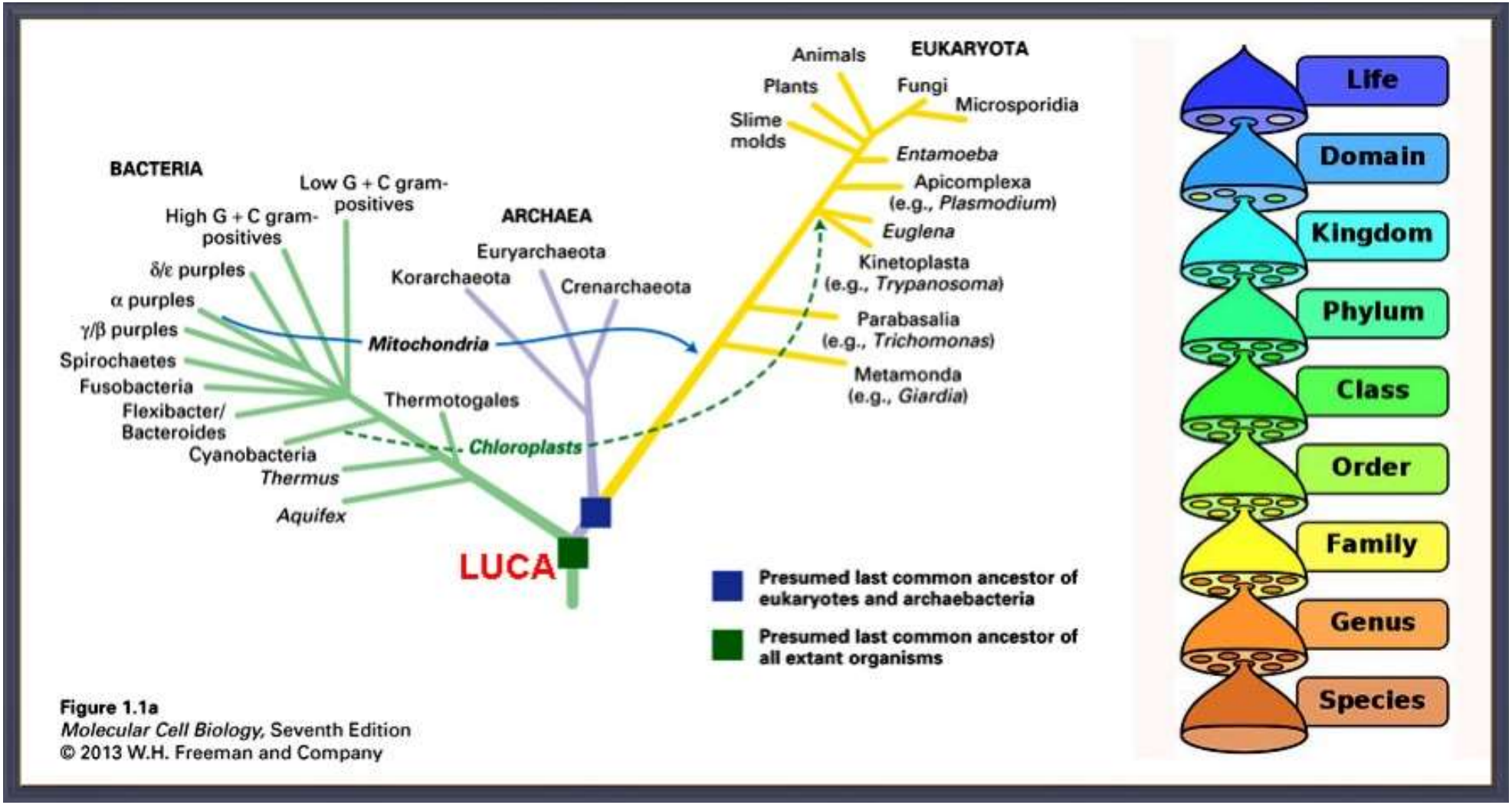
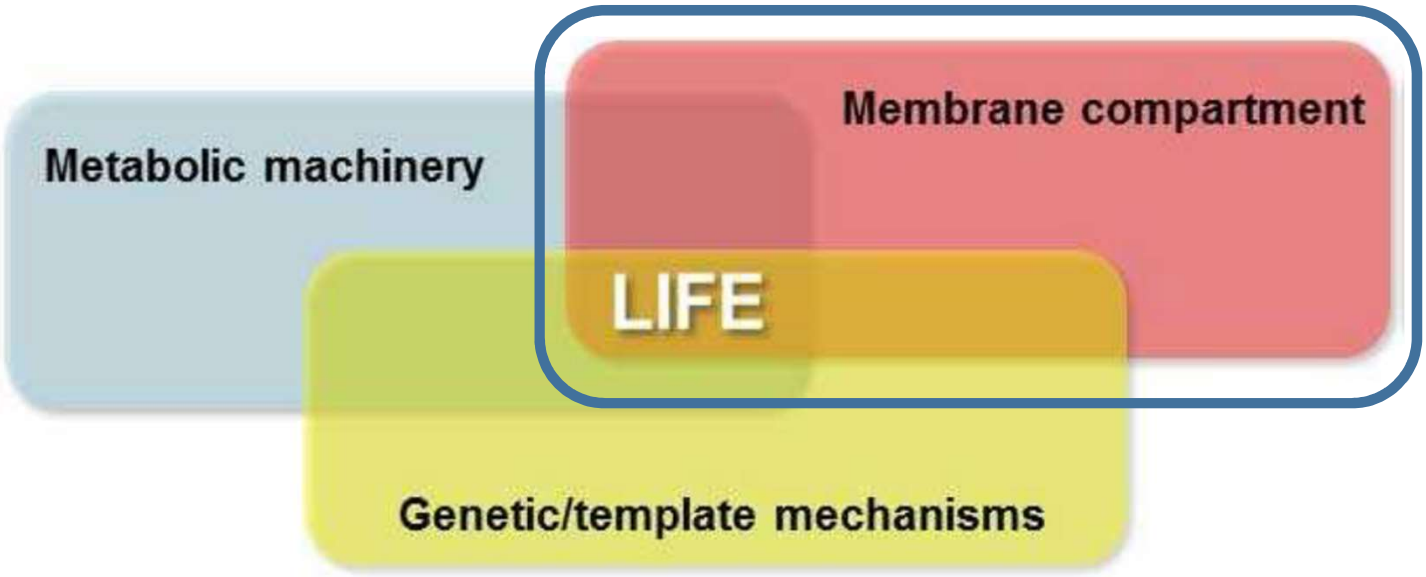
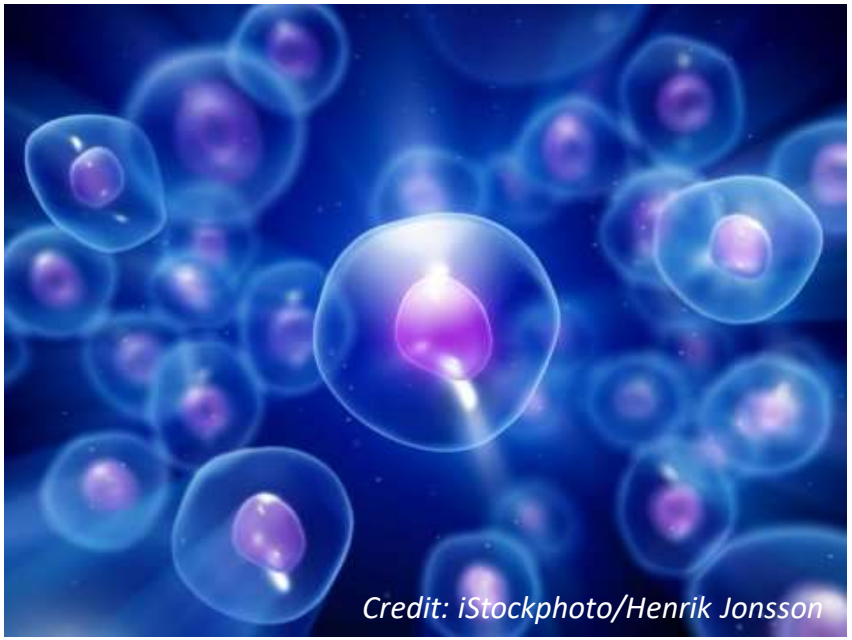


Figure 1.1a
Molecular Cell Biology, Seventh Edition
© 2013 W.H. Freeman and Company

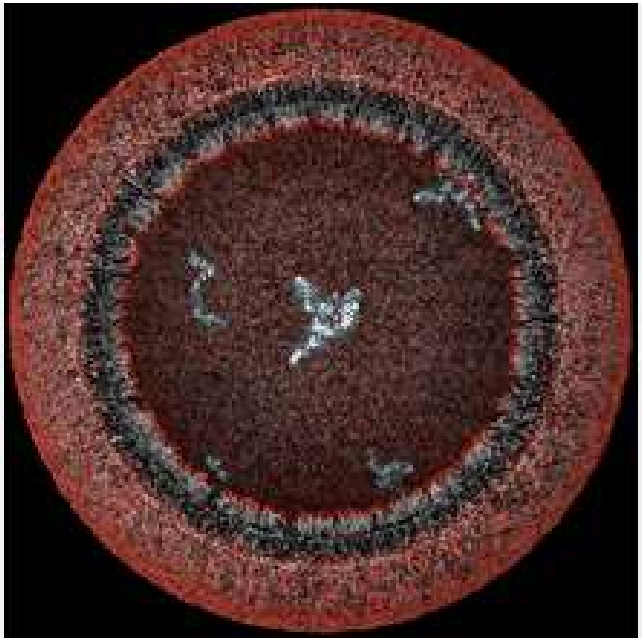

Membrane compartment
Metabolic machinery
LIFE
Genetic/template mechanisms

Encapsulation – essential for life



Membrane compartments

Assembly of amphiphilic monomers into protocellular compartments

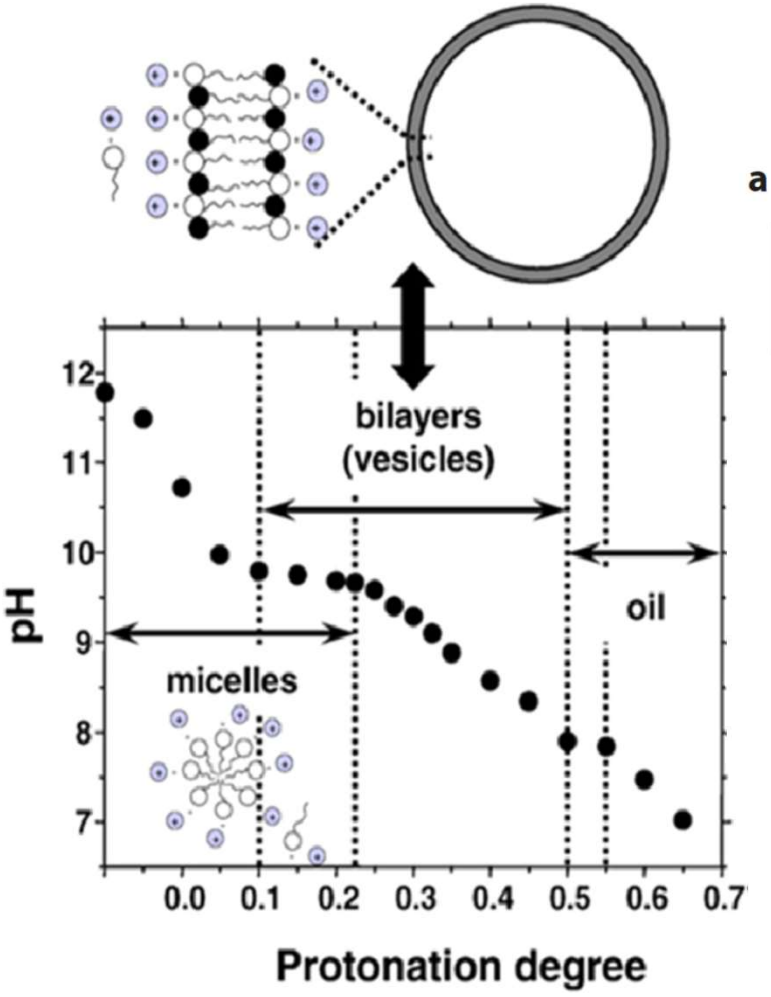


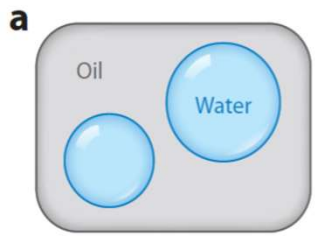
Credit: *Janet Iwasa*

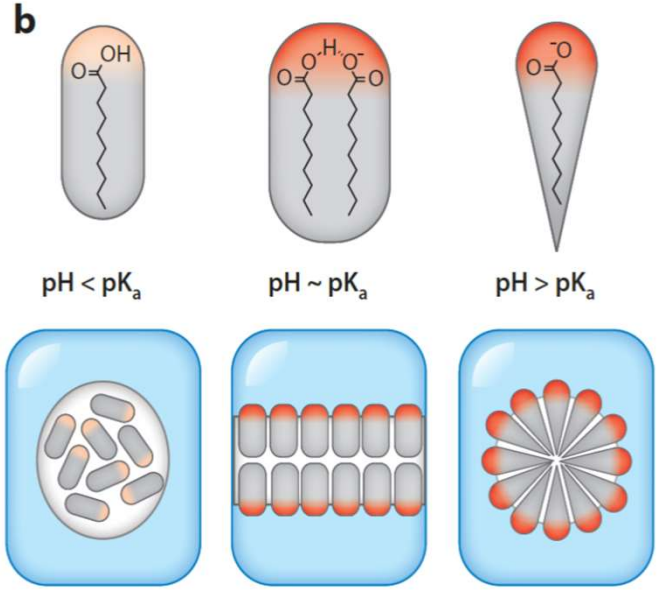
A three-dimensional view of a model protocell (a primitive cell) approximately 100 nanometers in diameter.

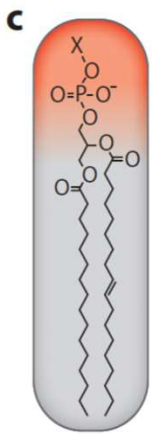
The protocell's fatty acid membrane allows nutrients and DNA building blocks to enter the cell and participate in non-enzymatic copying of the cell's DNA. The newly formed strands of DNA remain in the protocell

pH-dependent phase behavior of fatty acids in water



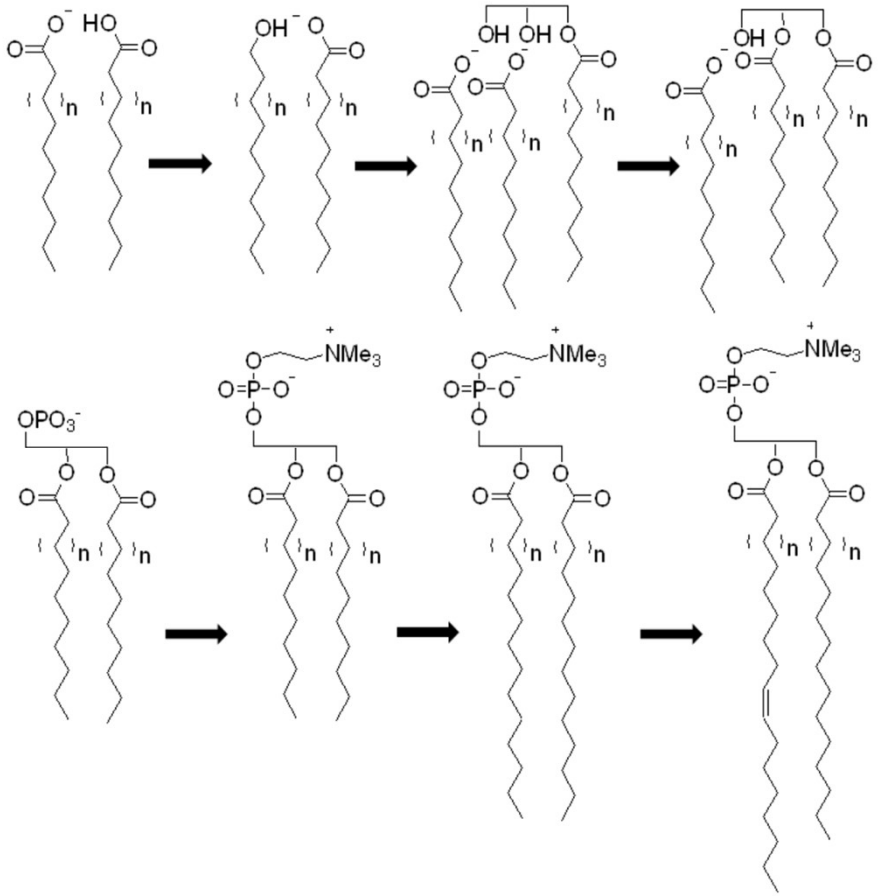




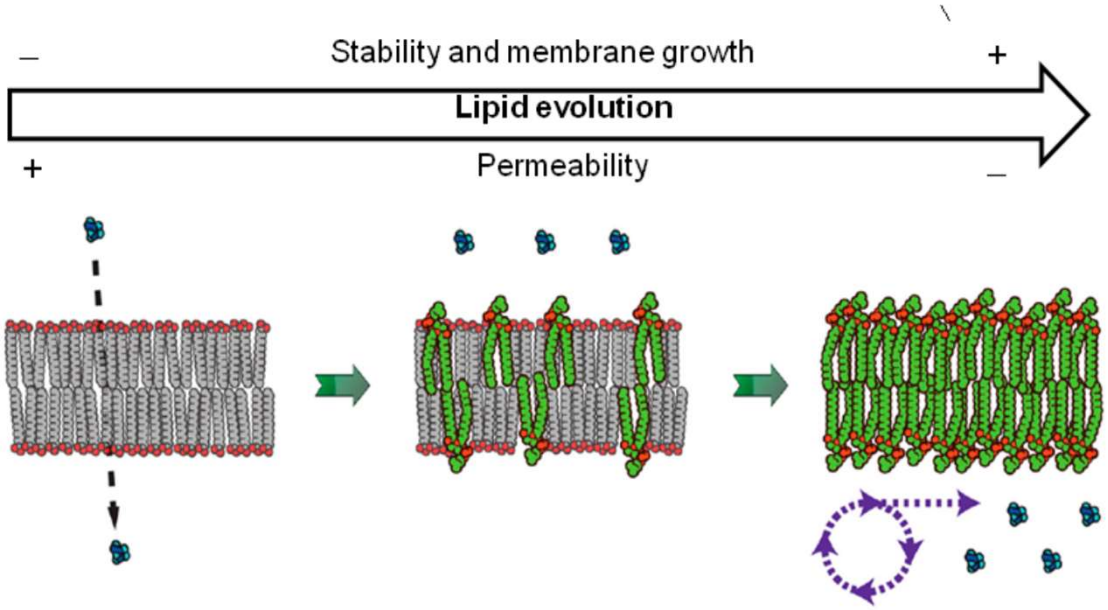


80 mM oleic acid/ sodium oleate in water

Scheme of the membrane evolution

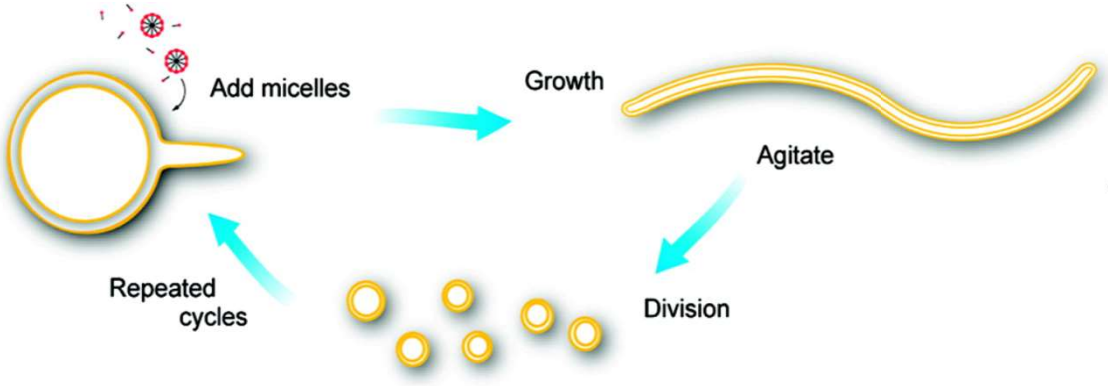


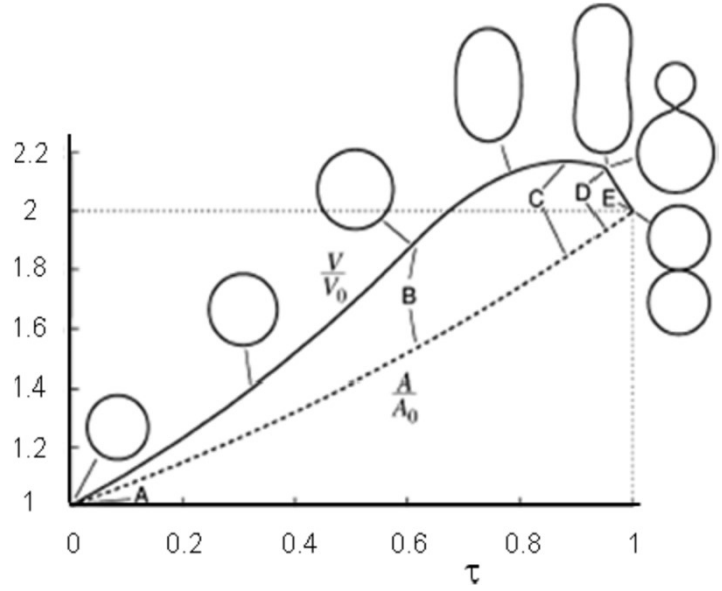
Chemical evolution of membrane components



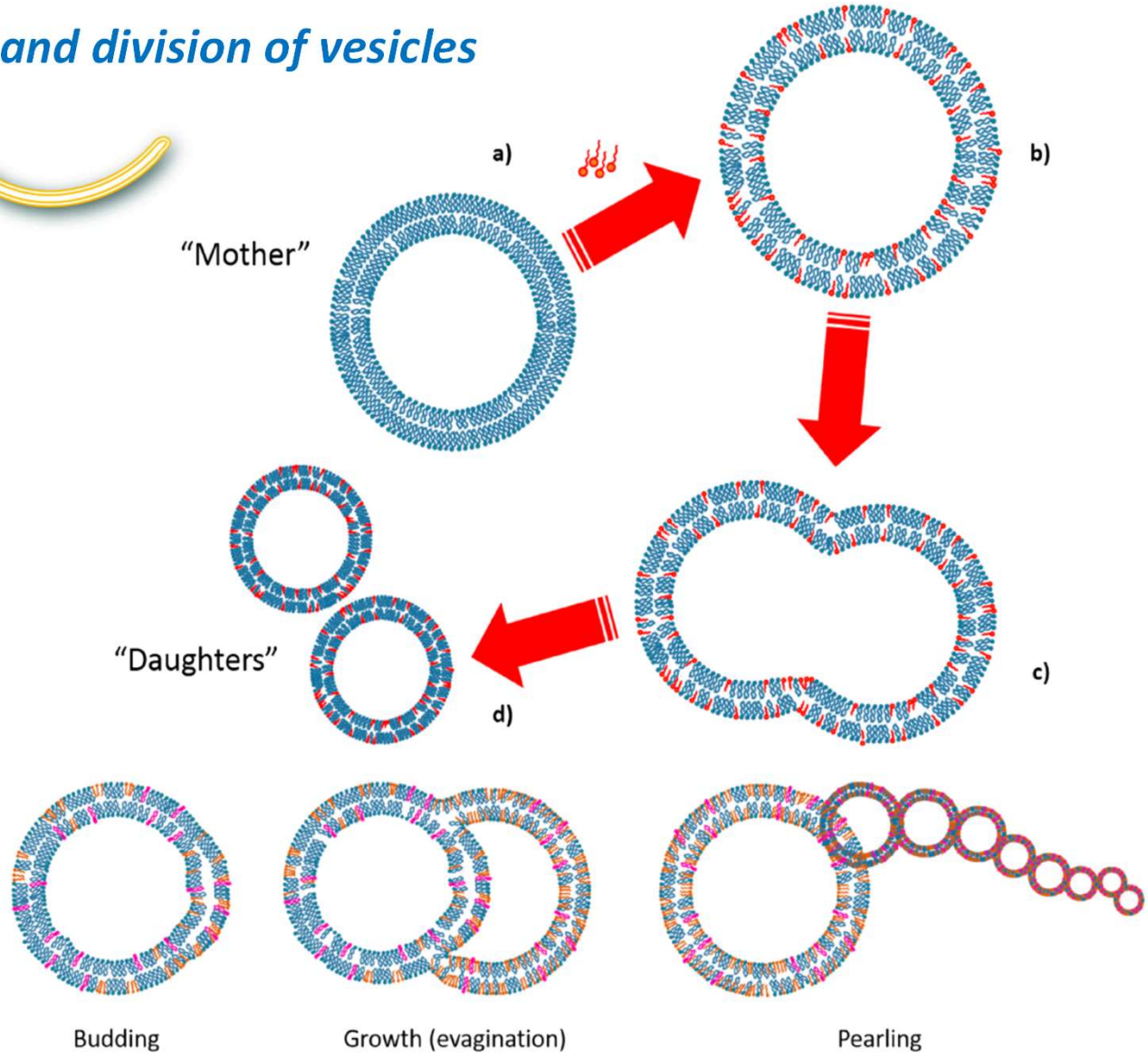
More complex components lead to slower amphiphile desorption and thus faster growth of the protocell. Decreasing permeability is a selective pressure for the emergence of internalized metabolic and transport machinery in the system

Growth and division of vesicles



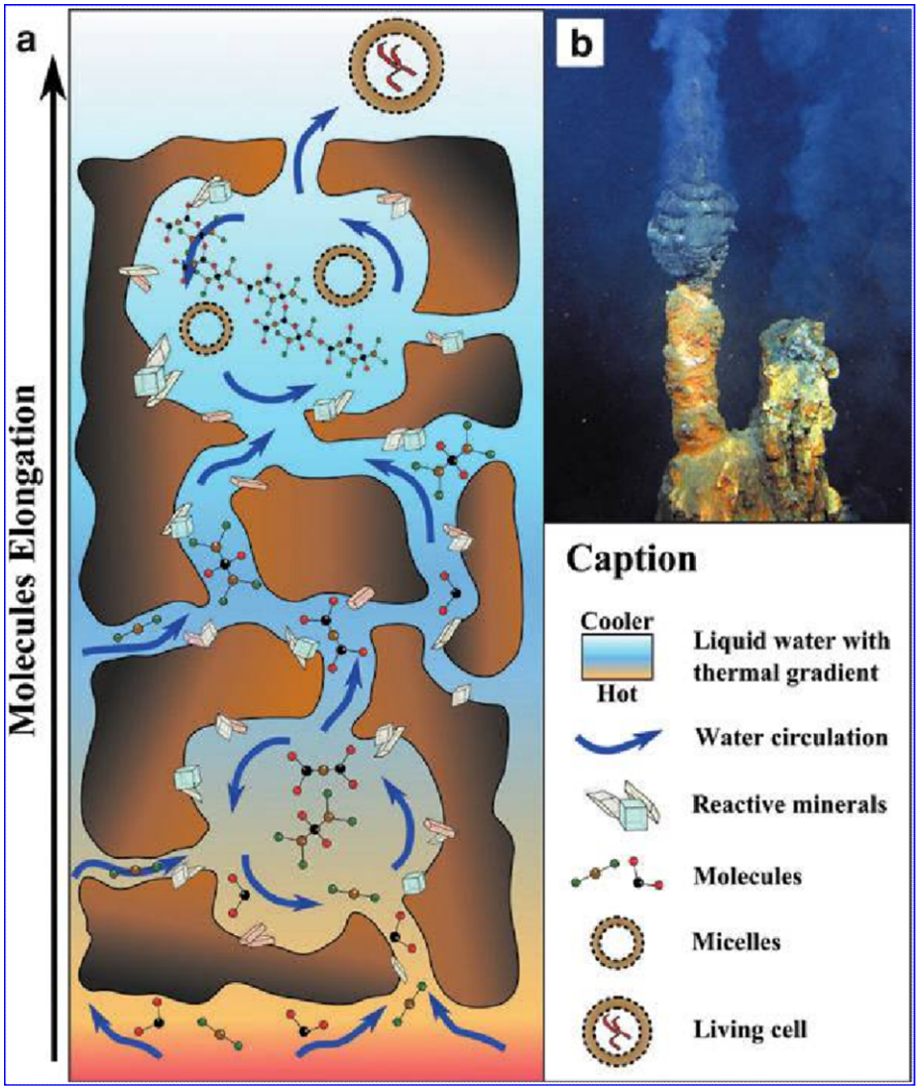


Ting F. Zhu, and Jack W. Szostak
J. Am. Chem. Soc., **2009**, 131 (15), 5705-5713



A. Lopez, M. Fiore *Life* **2019**, 9(49), doi:10.3390/life9020049

Deep sea vent origin of life



Possible origin of life in porous hydrothermal vents.

(a) Sketch showing a porous beehive structure where hydrothermal fluids and seawater can circulate, leading to the accumulation of organic molecules. The reduced mineral surfaces within the vent pores could be favorable locations for the structural organization of macromolecules. We hypothesize the formation of lipid micelles in these environments and the incorporation of information-transferring molecules within the micelles, perhaps due to moderate agitation of the hydrothermal effluent.

(b) Image of a modern black smoker

(image credit: National Oceanographic and Atmospheric Administration). Color images available online at www.liebertonline.com/ast

F. Westall et al., *Astrobiology* **2013**, *13(9)*, 887-897

Transition from the RNA world to LUCA

Ribozymes – self-acting → metabolic

Evolution of ribosome

Incorporation of aminoacids and peptides

The genetic code and archival storage

Enzyme-driven metabolism and membranes

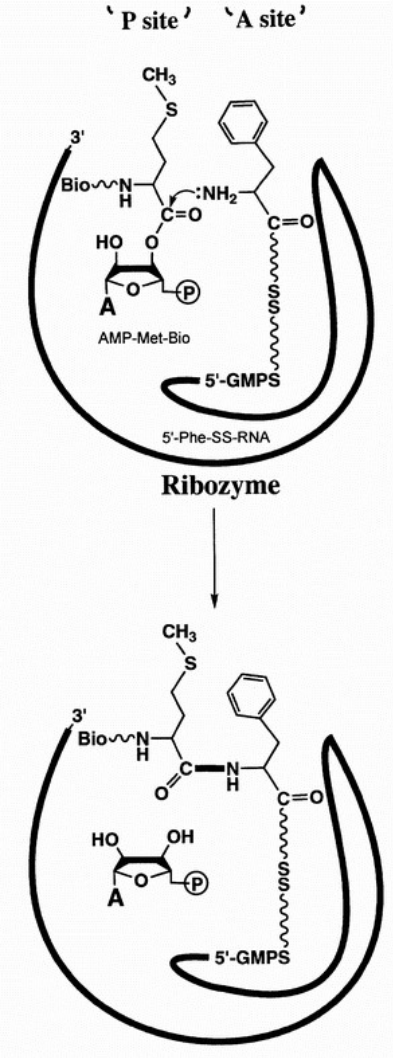
Ribozymes

Initially only self-processing ribozymes (introns, RNAses) discovered.

1992 – first ribozyme isolated capable to cleave the bond of methionine with its tRNA (also the reverse reaction – transacylation – is catalysed)

1995 (Yarus) – a random RNA sequence found capable of attaching an activated aminoacid to itself

1997 (Szostak) – an RNA sequence that transfers one aminoacid to another one, forming a dipeptide → analogue of the peptidetransferase center of the ribosome



Ribozymes

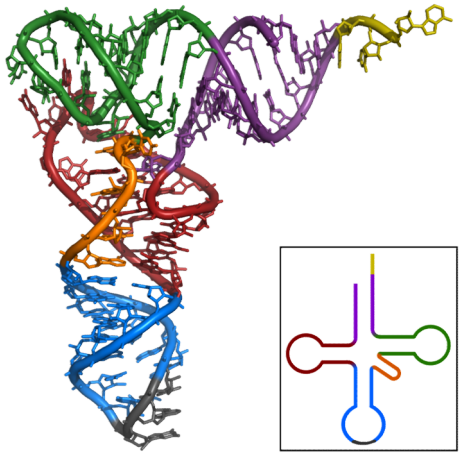
Ribozymes incorporate aminoacids to enhance their catalytic abilities

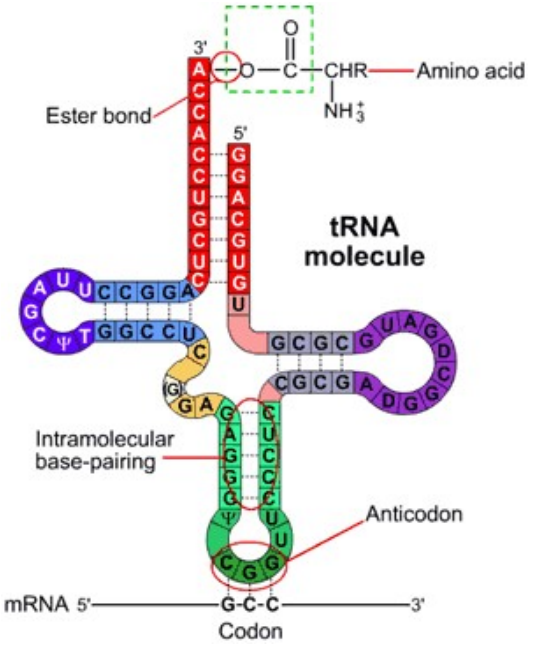
It opens ways to improved metabolism and provides evolutionary advantage in receiving energy from outside

Initially incorporation of aminoacids may have improved synthesis of nucleotides to produce more RNA

Primordial tRNAs were most likely self-charging, today special enzymes do it (tRNA synthethases)

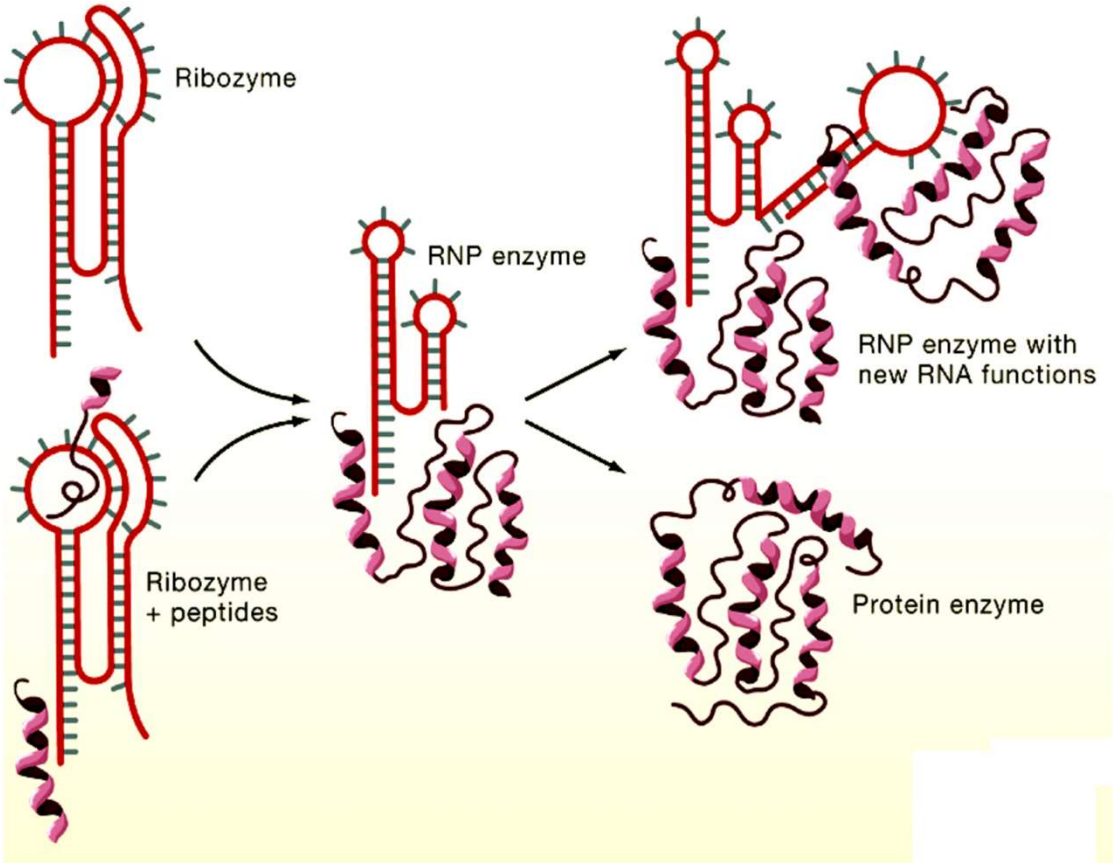
Peptide chains increase in size, the RNA part decrease → non-covalent binding of nucleoside cofactors to contemporary enzymes





aminoacyl-tRNA

Evolution of biocatalysis



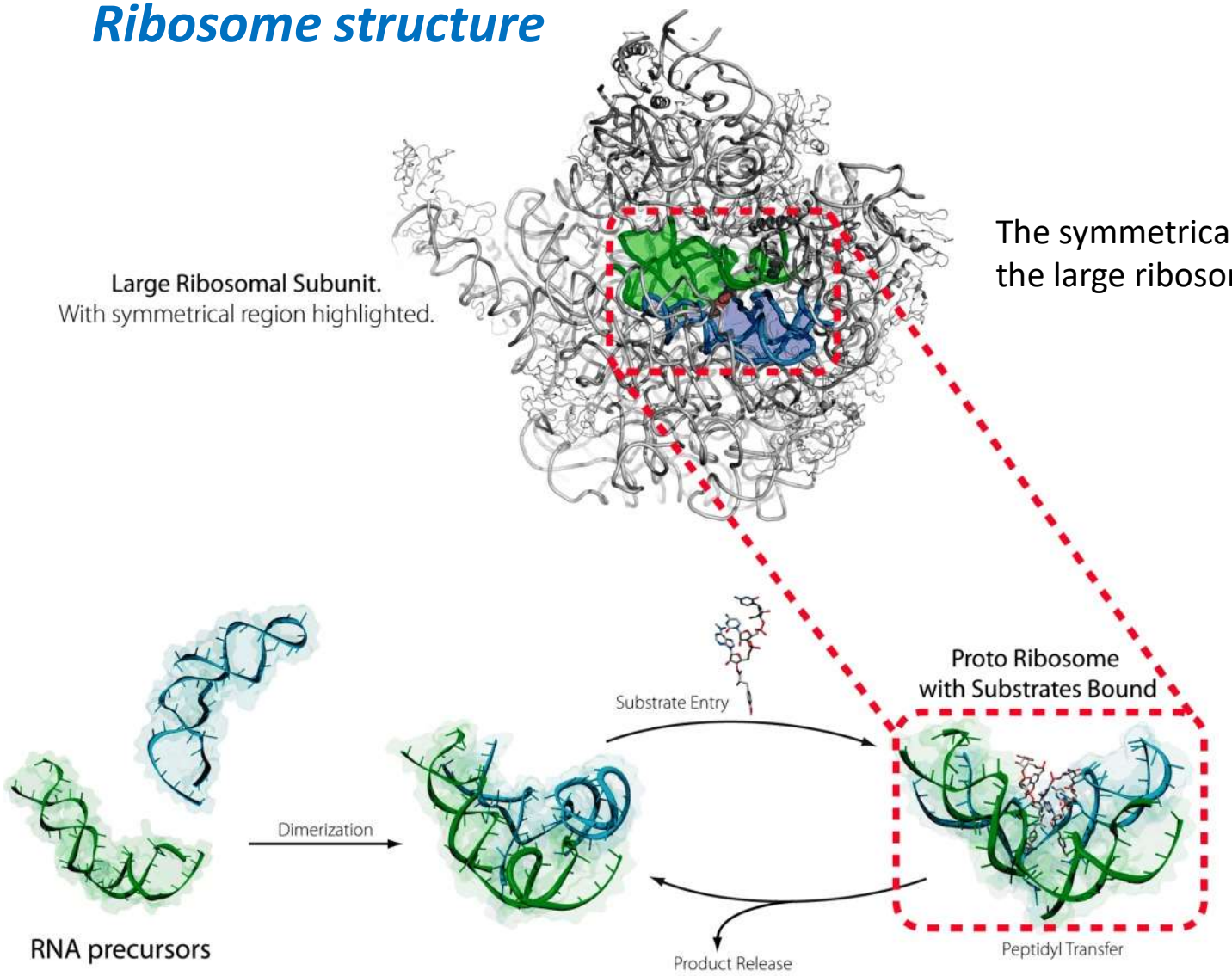
Primordial **RNA-only ribozymes** as well as **complexes of ribozymes and random peptides** could have acted as catalysts during the first steps of the RNA world.

In a more advanced stage, upon the advent of *peptidyltransferase ribozymes*, the availability of RNA-coded proteins allowed the assembly of **ribonucleoprotein (RNP) complexes**.

Some of the RNPs could have shown novel or improved catalytic activities, ultimately including the *translation of mRNA on protoribosomes*. Later, some **RNP enzymes** (upper right) evolved by adding or discarding some RNA subunits and fine-tuning their catalytic activity. In parallel, most RNP complexes (lower right) evolved to **protein-only enzymes**.

Cech, T. R. Cell **2009**, *136*, 599.

Ribosome structure

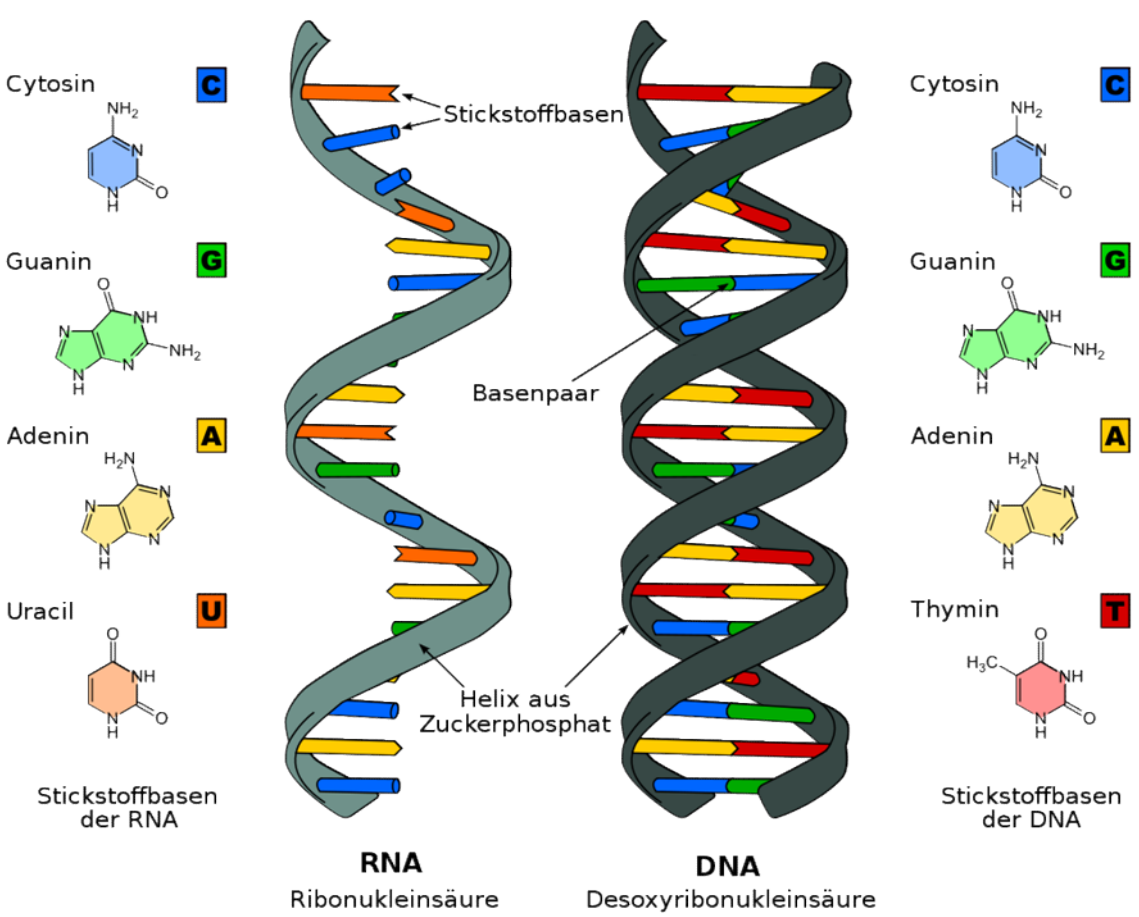


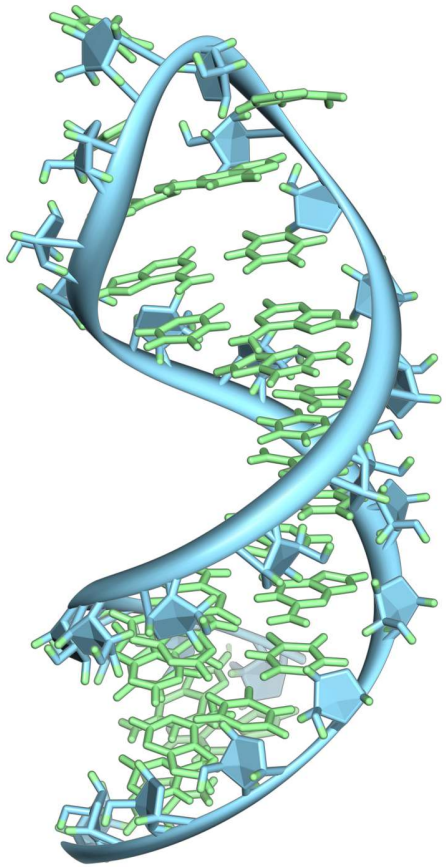
The symmetrical region within the large ribosomal subunit.

Schematic representation of "pocket-like" proto-ribosome formation from a RNA precursor, showing simple catalytic peptidyl transferase activity.

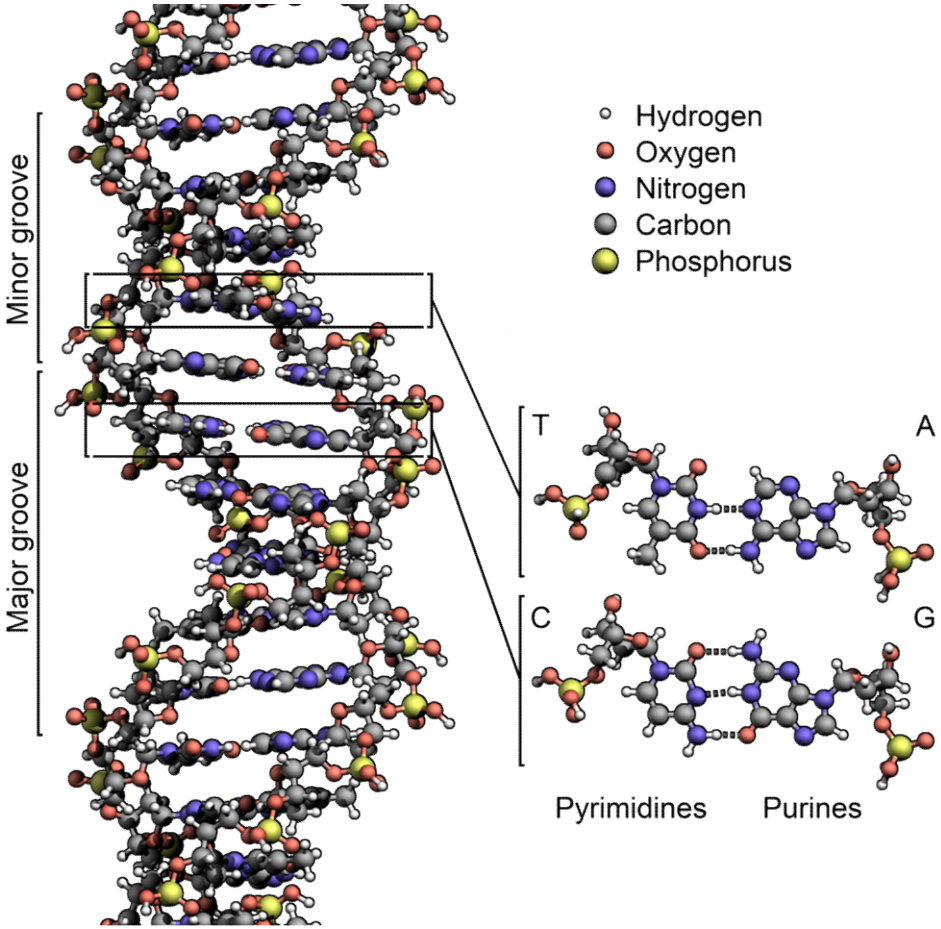
A. Yonath *et al. Israel Journal of Chemistry,* **2010***, 50,* 29-35

The origin of DNA





The origin of DNA



Maximal size of RNA-based genome: 3000-5000 bases
(HIV, West Nile virus)

Reason: above that, statistically certain to generate at least one self-cleaving RNA sequence (ribozyme)

Maximal DNA size – unlimited

- no self-cleaving DNAzymes,
- tight storage as dsDNA,
- methylated uracil (thymine) → no accidental C-to-U mutations

The genetic code

1st base	2nd base: U	2nd base: C	2nd base: A	2nd base: G
U	UUU (Phe/F) Phenylalanine	UCU (Ser/S) Serine	UAU (Tyr/Y) Tyrosine	UGU (Cys/C) Cysteine
	UUC (Phe/F) Phenylalanine	UCC (Ser/S) Serine	UAC (Tyr/Y) Tyrosine	UGC (Cys/C) Cysteine
	UUA (Leu/L) Leucine	UCA (Ser/S) Serine	UAA Ochre (Stop)	UGA Opal (Stop)
	UUG (Leu/L) Leucine	UCG (Ser/S) Serine	UAG Amber (Stop)	UGG (Trp/W) Tryptophan
C	CUU (Leu/L) Leucine	CCU (Pro/P) Proline	CAU (His/H) Histidine	CGU (Arg/R) Arginine
	CUC (Leu/L) Leucine	CCC (Pro/P) Proline	CAC (His/H) Histidine	CGC (Arg/R) Arginine
	CUA (Leu/L) Leucine	CCA (Pro/P) Proline	CAA (Gln/Q) Glutamine	CGA (Arg/R) Arginine
	CUG (Leu/L) Leucine	CCG (Pro/P) Proline	CAG (Gln/Q) Glutamine	CGG (Arg/R) Arginine
A	AUU (Ile/I) Isoleucine	ACU (Thr/T) Threonine	AAU (Asn/N) Asparagine	AGU (Ser/S) Serine
	AUC (Ile/I) Isoleucine	ACC (Thr/T) Threonine	AAC (Asn/N) Asparagine	AGC (Ser/S) Serine
	AUA (Ile/I) Isoleucine	ACA (Thr/T) Threonine	AAA (Lys/K) Lysine	AGA (Arg/R) Arginine
	AUG (Met/M) Methionine	ACG (Thr/T) Threonine	AAG (Lys/K) Lysine	AGG (Arg/R) Arginine
G	GUU (Val/V) Valine	GCU (Ala/A) Alanine	GAU (Asp/D) Aspartic acid	GGU (Gly/G) Glycine
	GUC (Val/V) Valine	GCC (Ala/A) Alanine	GAC (Asp/D) Aspartic acid	GGC (Gly/G) Glycine
	GUA (Val/V) Valine	GCA (Ala/A) Alanine	GAA (Glu/E) Glutamic acid	GGA (Gly/G) Glycine
	GUG (Val/V) Valine	GCG (Ala/A) Alanine	GAG (Glu/E) Glutamic acid	GGG (Gly/G) Glycine

3rd base in each row

ΔF508 deletion in cystic fibrosis

- Myotonic dystrophy
- SCA 8

β-Thalassemia

McArdle's disease

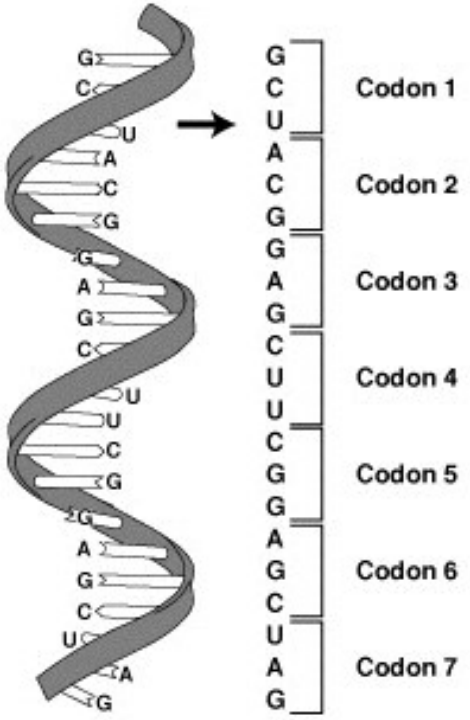
β-Thalassem

Prostate cancer

Colorectal cancer

Sickle-cell disease

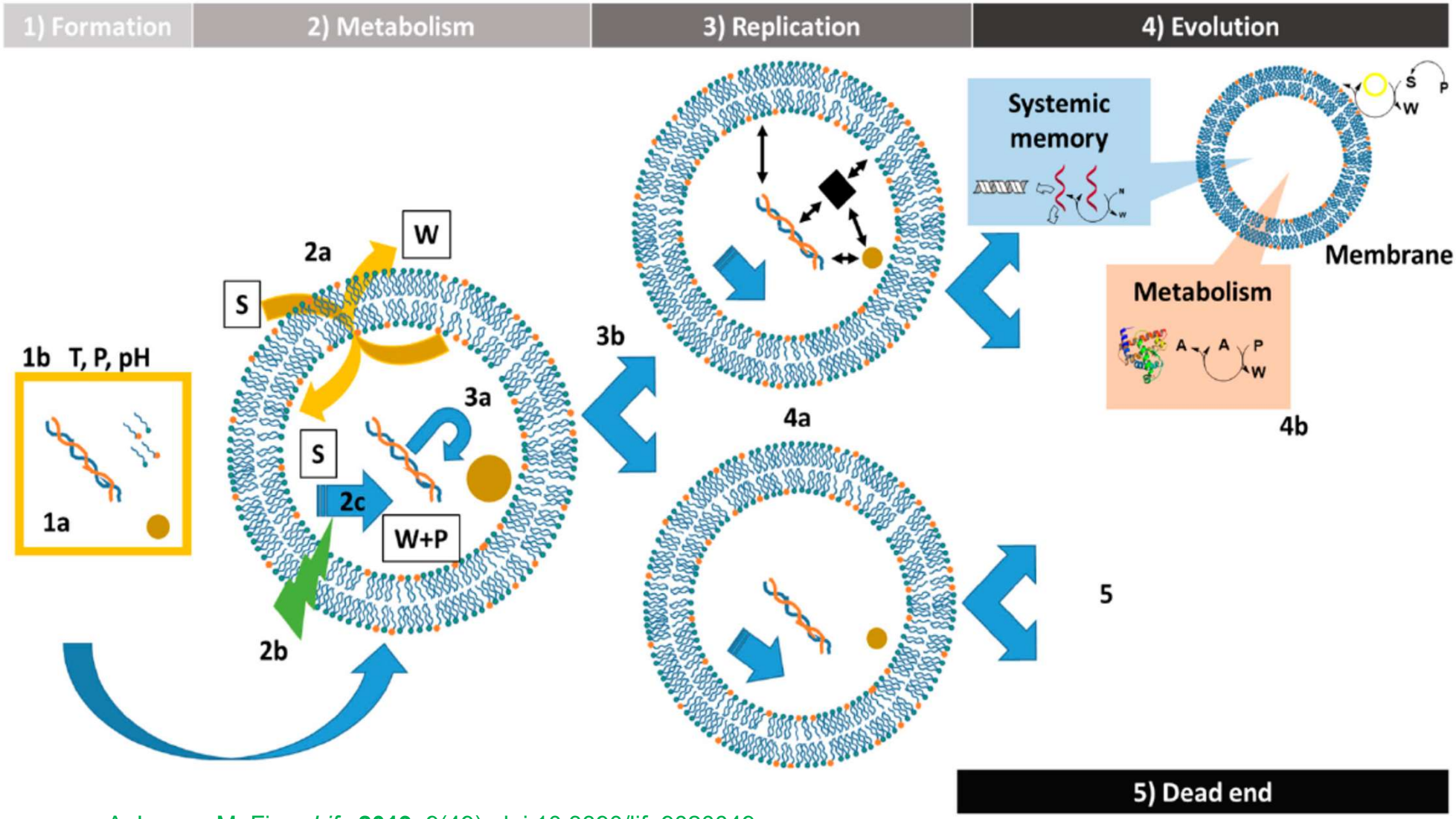
Friedreich's ataxia



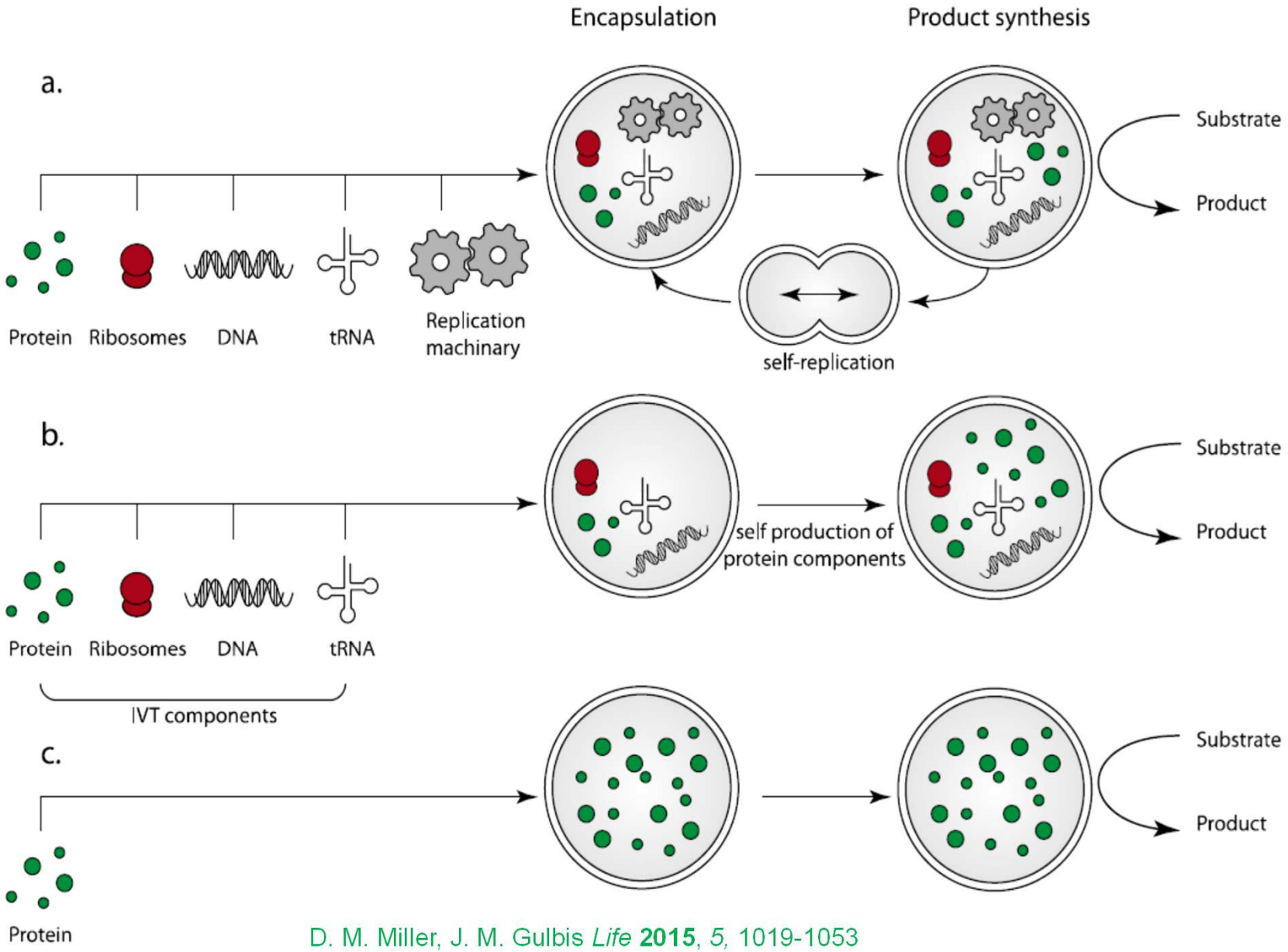
RNA

Ribonucleic acid

Increasing complexity of the protocells

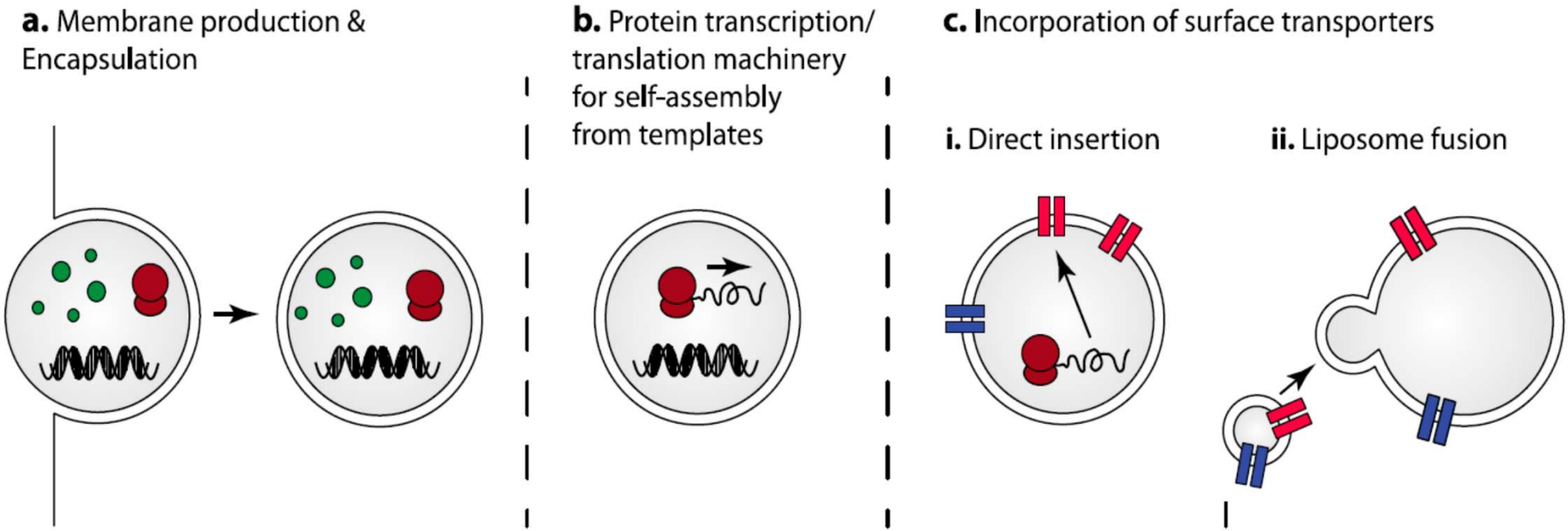


A. Lopez, M. Fiore *Life* **2019**, 9(49), doi:10.3390/life9020049

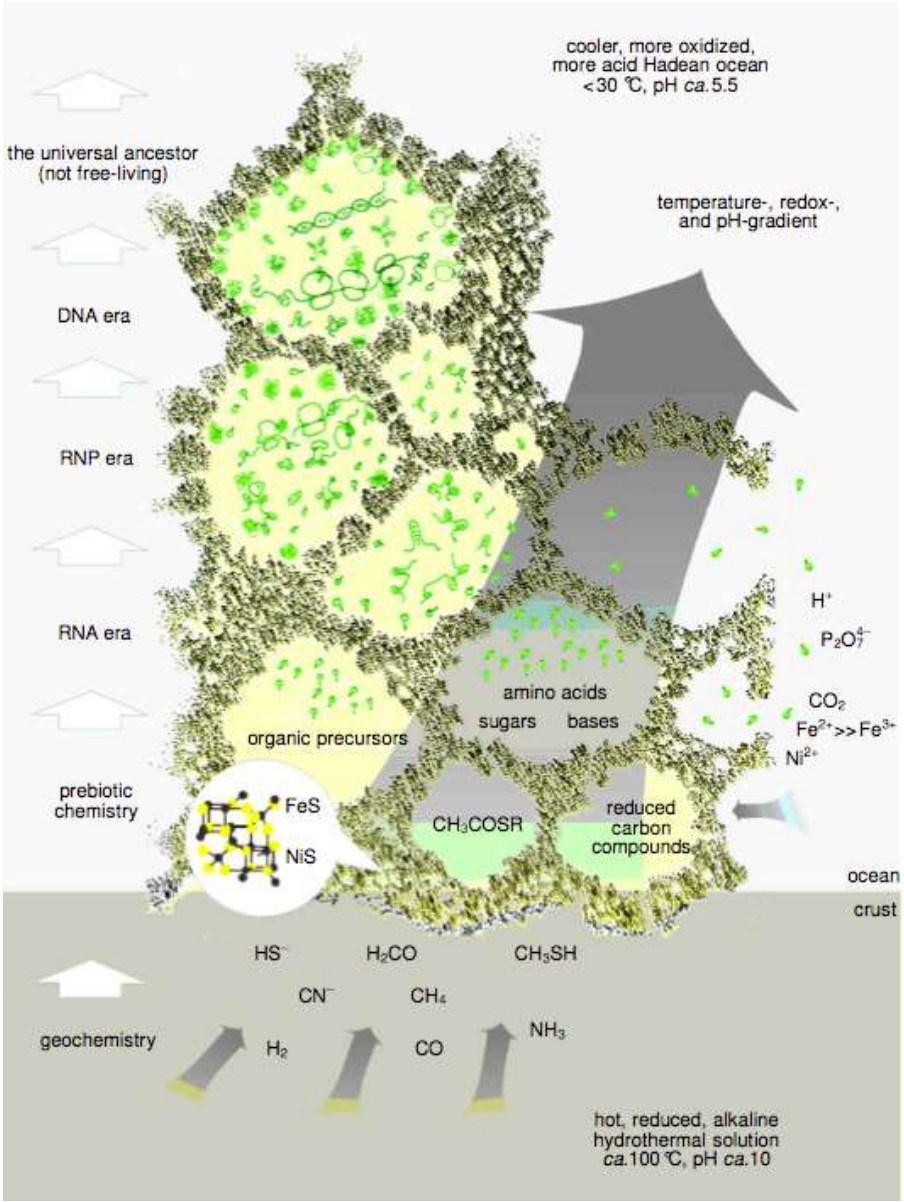


D. M. Miller, J. M. Gulbis *Life* **2015**, *5,* 1019-1053

Increasing complexity of the protocells

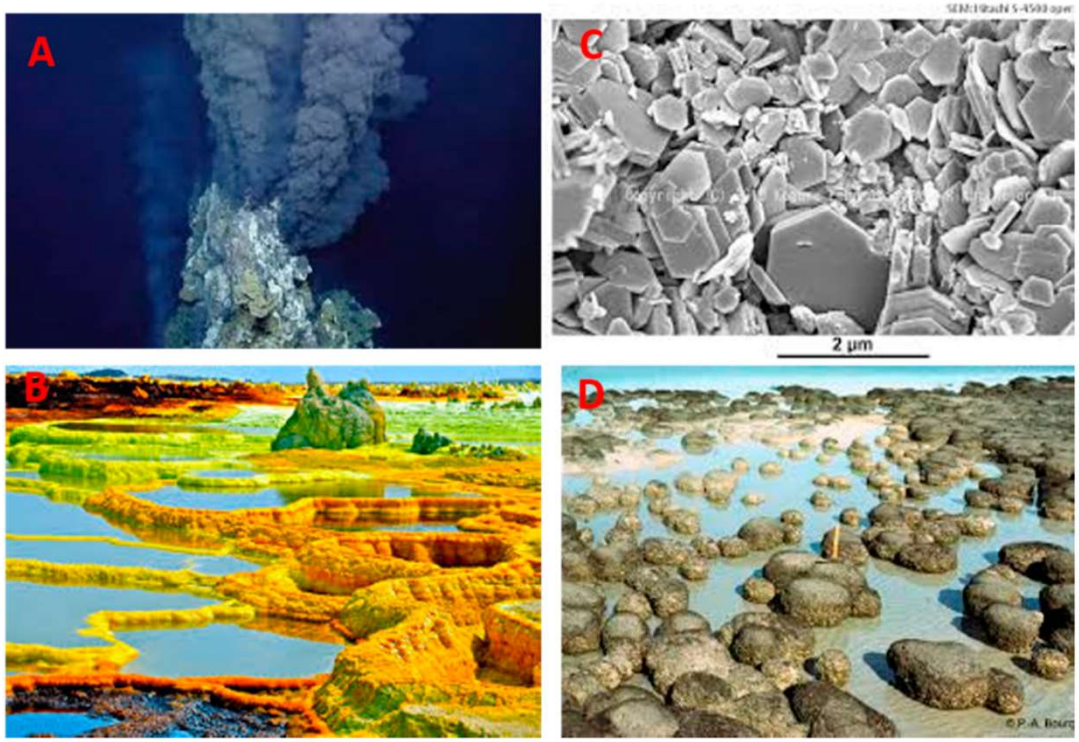


D. M. Miller, J. M. Gulbis *Life* **2015**, *5,* 1019-1053



Compartments in hydrothermal vents?

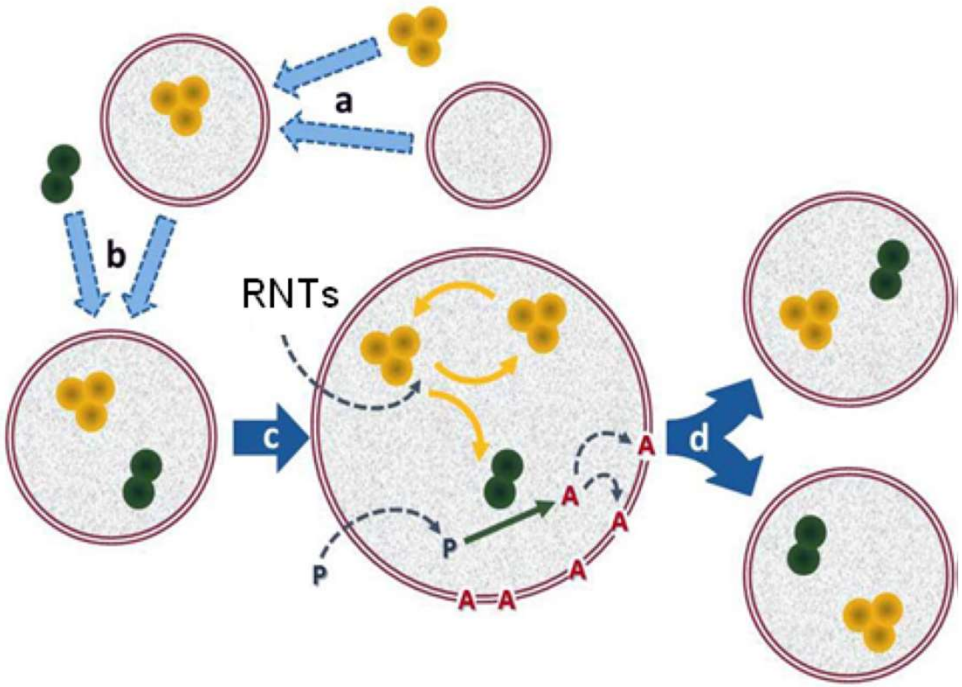
Complex metabolic machinery closed in the same compartment that genetic polymers (RNA) which generated it.



A. Lopez, M. Fiore *Life* **2019**, 9(49), doi:10.3390/life9020049

We don't see ribozyme-based metabolism today anymore, because protein catalysts (enzymes) for the same reactions are orders of magnitude faster than the ribozymes

Primordial synthesis of an RNA-based protocell



(a) A self-reproducing vesicle is combined with an RNA replicase (yellow).

(b) This system is further combined with a second ribozyme (green) that is able to synthesize amphiphilic molecules (A) from precursor substrates (P), thus leading to an RNA protocell containing two ribozymes.

(c) In such a “ribocyte”, the RNA replicase is capable of replicating itself and also making copies of the membrane-forming ribozyme, provided that ribonucleotides (RNTs) are available in the surrounding medium and can permeate the vesicle membrane.

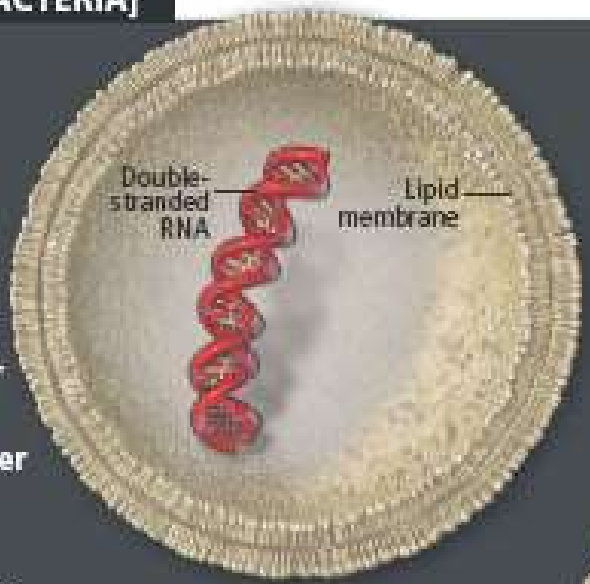
(d) Activity of the second ribozyme converts the previously internalized precursors into amphiphiles, which are further incorporated into the membrane; this leads to a progressive increase of the vesicle size and its subsequent division into two daughter vesicles, thus triggering Darwinian evolution of the whole (membrane−genome coupled) system

From RNA world to bacteria

[FROM RNA WORLD TO BACTERIA]

Journey to the Modern Cell

After life got started, competition among life-forms fueled the drive toward ever more complex organisms. We may never know the exact details of early evolution, but here is a plausible sequence of some of the major events that led from the first protocell to DNA-based cells such as bacteria.

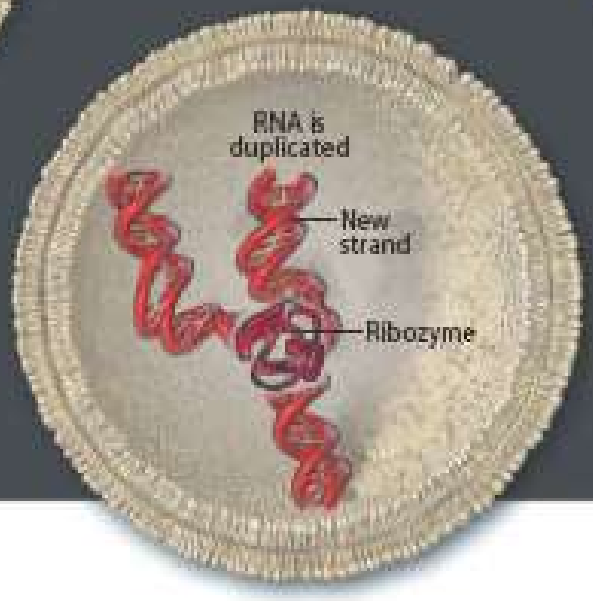


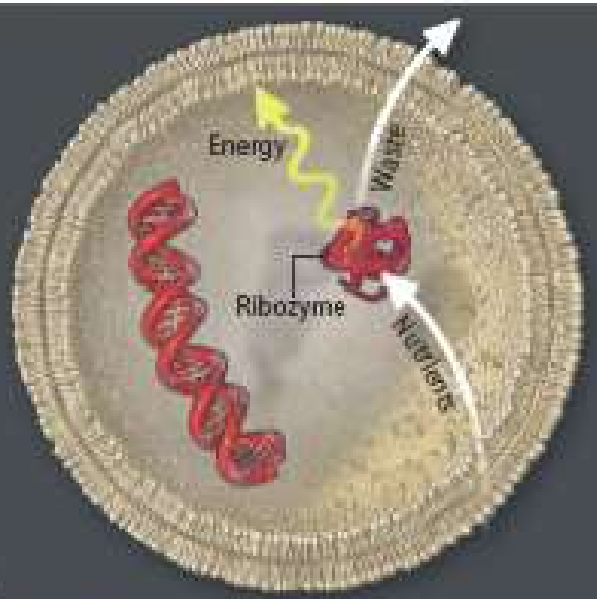
1 EVOLUTION STARTS ▲

The first protocell is just a sac of water and RNA and requires an external stimulus (such as cycles of heat and cold) to reproduce. But it will soon acquire new traits.

2 RNA CATALYSTS ▼

Ribozymes—folded RNA molecules analogous to protein-based enzymes—arise and take on such jobs as speeding up reproduction and strengthening the protocell's membrane. Consequently, protocells begin to reproduce on their own.





3 METABOLISM BEGINS ▲

Other ribozymes catalyze metabolism—chains of chemical reactions that enable protocells to tap into nutrients from the environment.

From RNA world to bacteria