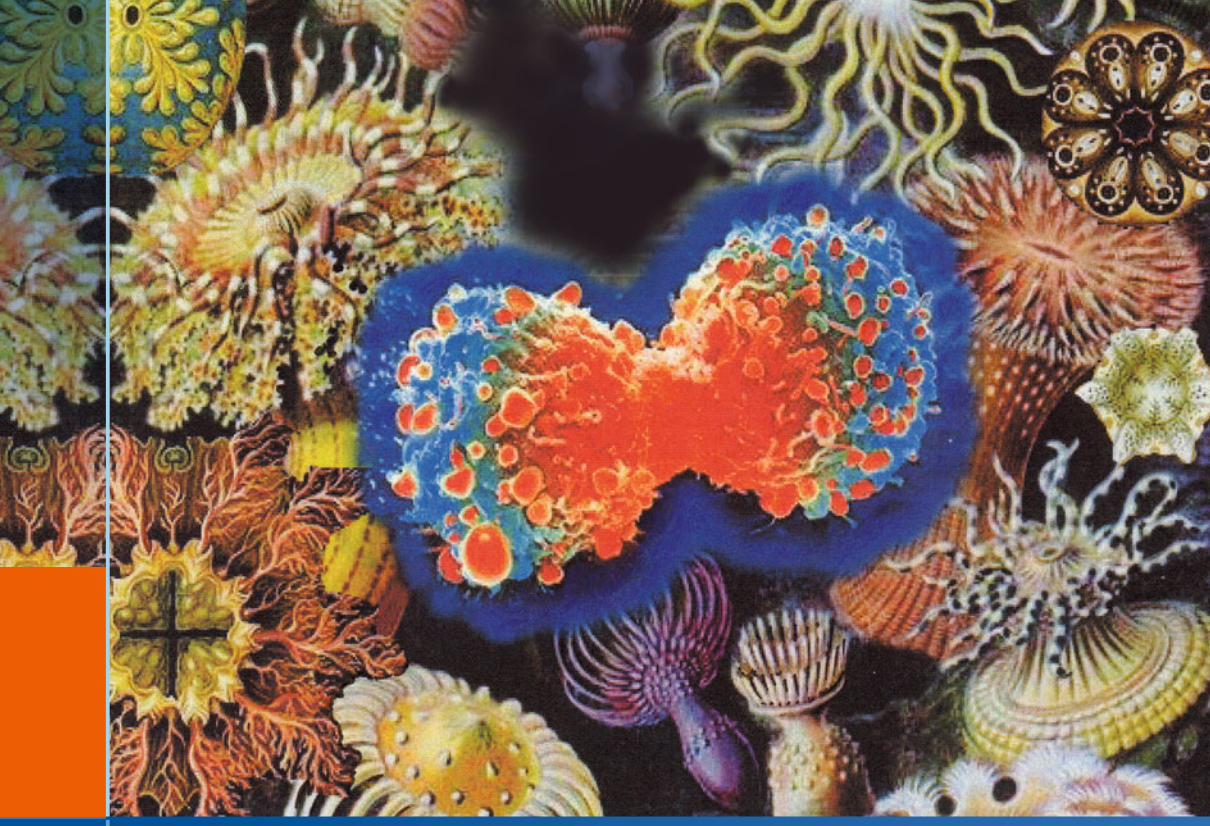

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The author dedicates his discussions in the text on, and references to, oncolytic viruses, in this article, to the memory of his medical school friend László K. Csatáry, who devoted the last decades of his professional life for the treatment of patients with "incurable" cancers ("unconventionally", as the need dictated) with inoculations of a British isolate of an attenuated Newcastle Disease Virus, imported to Hungary, which he renamed MTH ("More than Hope", without revealing its real origin). This virus was professionally purified and concentrated for him in preparation for clinical use in Budapest, Hungary (it was not licensed in the USA) (Ref. [71]).

The author expresses his gratitude to the long list of his colleagues and friends, who worked with him and supported him both in laboratory research and in clinical practice of infectious diseases and medical oncology/hematology, as listed in the postscript of the volume "Cytotoxic Immune Lymphocytes…" (Ref. [147]). The author is very much thankful to publisher János Schenk (Schenk Buchverlag), for his special attention to the editing and illustration of that volume, and for releasing some of those illustrations for this volume. All illustrations published by the author in the International Journal of Oncology were released free by the Editor-in-Chief Prof. Demetrios Spandidos.

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publisher, and for the digital transfer of the entire material to the publisher, the author expresses his ever-lasting deep gratitude. The author is especially grateful to Dr. Orsolya Nagy and Dr. Mária Takács for their expert management of the figures and tables, and for their extensive negotiations with copyright owners in order to obtain their permission for the publication of the figures (and for the replacement of those figures, the first choice of which was not possible to publish). The author is sincerely apologetic to those authors and copyright owners whose e-mail-donated figures he could not publish consequentially to the complexity of the copyright law and Springer's interpretation of it. He and his helpers exerted an honest attempt at credentialing and financially satisfying the copyright owners; the author accepts the responsibility with sincere regrets for any inadvertent errors.

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The author has benefitted from the comments of and discussions on this topic with his audience at the special session arranged and held at the Hungarian Scientific Academy on July 27 2011. His lecture and discussion was entitled "Oncogenic Inflammatory Processes and the Awakening of the Primordial DNA". The session was chaired by Prof. Dr. György Berencsi; invited discussant was Prof. Dr. István Ember, who, and whose successor, Prof. Dr. István Kiss, published the author's presentation in the periodical Hungarian Epidemiology (Ref. [2224] last issue in 2014;11:55–69). The author was invited to pre-publish a brief article on the subject matter of this volume by Profs. Dr. Dóra Szabó and Dr. Ildikó R. Dunay in the European Journal of Microbiology and Immunology 2015;5:25–43.

Contents

Author's Credentials

In the late 1940s, the author served as a research fellow at the Institute of Pathophysiology, and as an assistant and adjunct professor at the Institute of Bacteriology/Immunology, Pázmány Péter Medical University (now Institute of Medical Microbiology and Immunology, Semmelweis Medical University, Budapest); and in the mid-1950s, as a senior staff virologist at the National Institute of Public Health, and as a board-certified clinical pathologist (the successor institute now is the National Epidemiological Center, Budapest, Hungary). In 1957, in the USA, he was a Rockefeller fellow at the Waksman Institute of Rutgers The State University, New Brunswick, NJ. Thereafter, he served as an intern and resident physician at Cook County Hospital and as a research fellow at the Hektoen Institute of Cook County School of Medicine in Chicago, IL (1958; 1960-1); and at the University of Texas M.D. Anderson Hospital, Houston TX (1959; 1962–1979). The author is USA specialty board-certified in medical laboratory virology, public health, internal medicine, infectious and tropical diseases, and in medical oncology (including malignant diseases of the bone marrow and lymphatic organs); he is board-eligible in hematology. He obtained licensure by examinations to practice medicine in the States of Florida, Indiana, Texas and Washington. After fulfilling services and the practice of academic and clinical medicine for six decades, he is now retired professor from the staff of the services of medical oncology-hematology at the Department of Medicine, The University of Texas M.D. Anderson Hospital, Houston, TX (1962–1980, on staff); and on the external professorial staff of the Departments of Medicine and Microbiology and Immunology (now Molecular Medicine), of the University of South Florida Morsani College of Medicine, Tampa, FL (1983–current). He is Honorary Member of the H.L. Moffitt Comprehensive Cancer Center, Tampa FL. He is retired Medical Director of the Community Cancer Center/Cancer Institute of St. Joseph's Hospital, Tampa FL, where he serves now in the position of Senior Scientific Medical Advisor.

The author designed the work, performed the research, and wrote the entire manuscript. The author reports no dependence on any financial rewards or payments; and there are no conflicts of interest.

Introduction

Background

The Mother Empress (RNA) and the Son Emperor (DNA) of all molecules. It is probably correct to envision the vast preponderance of ancient unicellular life forms as spheroplast-like entities forming communities and replicating by cell divisions in their mature age. Thus, the ancient cells were exempted of senescence and natural death. While their essential genes were propagated by vertical transmissions, horizontal transfers of useful genes were sought after, competed for, and avidly accepted. The precellular appearance of RNA, the ribozymes of the RNA World, predated the generation of DNA molecules. Inasmuch as single and organized nucleotides coexisted with polypeptides before the formation of cells, they remained in unison within the first cell membranes. Their story continues here in a narrative.

The deoxyribonucleic acid DNA consists of two polynucleotide chains wound around each other in the form of a double helix. It is the Watson-Crick left-handed Z-DNA double helix formed by dinucleotide repeats in sequences of alternating purine-pyrimidine CG/AT repeats. Its two helices are held together by hydrogen bonds formed between the alternating desoxyribose purine and pyrimidine bases. Each separate helix serves as a template for enzymes to resynthesize and re-unite the entire molecule. The master molecule revealed itself for the first time in the X ray diffraction photographs of Rosalind Franklin (Figure 1). The deep and narrow major groove, and the wide and shallow minor groove of the A-form DNA is accessible to various DNA-binding proteins. DNA-binding proteins provide the highest level of communication between cytoplasm and nucleus. Its versatile structure, organization in chromosomes, templated replication, unlimited mutability, repairs of its breaks, and its immense digitalized memory are described in volumes filling up entire libraries. The DNA molecule could condense all this enormous amount of information in a small capsule containing a roll of its strands.

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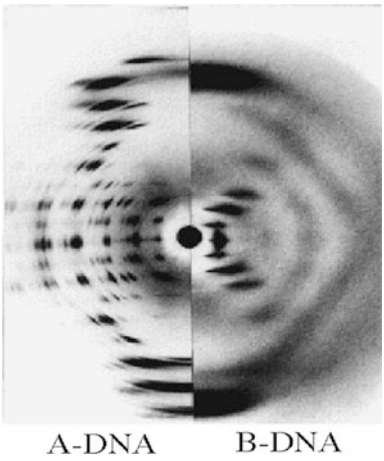

Figure 1 X-Ray Diffraction of DNA by Rosalind Franklin. The RNA/DNA complex. (A- and B-DNA X-ray diffraction patterns). http://en.wikipedia.org/wiki/Molecular_models_of_DNA#mediaviewer/File:ABDNAxrgpj.jpg by Bci21 http://commons.wikimedia.org/wiki/User:Bci21 is licensed under CC BY-SA 3.0 http://creativecommons.org/licenses/by-sa/3.0/). Reference Appendix 2, Explanations to the Figures

The primordial cellular genomes consisted of competing and cooperating RNA/DNA complexes. These ancient faculties of cooperation and competition remain preserved up to the present time. While DNA commands the genome, RNA remains the ruler of the epigenome. However, the RNAs of the spliceosomes begin their actions in the nucleus. MicroRNAs buzz all over the epigenome and in the cytoplasm.

Horizontal transfer of T-DNA (T-strand, Ti plasmid) by the Agrobacterium (the "tumefaciens") into plant cells causes the growth of large tumors recognized as "crown gall formations". The Ti plasmids incorporating the T-DNA and the *vir*-genes reproduce the natural phenomenon, as in Figure 12.1 and legend in Frederic Bushman's "Lateral DNA Transfer" (Cold Spring Harbor Laboratory Press, pp 448, 2002) [1]. The Agrobacterium oncogene transforms yeast cells. Same as in animal cells, the acetylated promoter keeps the oncogene silent; deacetylases activate the oncogene. Methylated genes are silenced; demethylation reactivates the genes. Plants are not exempted from carcinogenesis and its epigenetic control. Just now, at the concluding phase of this entire manuscript, in PLoS One, August, 2013, the emergence of the noncoding ncRNAs, small sRNAs, circular circRNAs, and antisense asRNAs of the tumefacient Agrobacterium is revealed. The inter-kingdom transfer of a bacterial oncogene into a plant cell is regulated by ncRNAs of the original host. In eukaryotes of multicellular vertebrate hosts, proto-oncogenes appear to rest or rise under the control of ncRNAs of the host (reviewed in the last issue of Int J Mol Sci, Sept, 2013). Accordingly, a postscript Table XXXV is being constructed and is attached in the text to the end of this volume.

The fundamental processes that transformed inanimate molecules into the state of the first animated biomolecules were the pairing of the purine and pyrimidine bases, adenine with uracil in the RNA, or with thymine in the DNA molecule, and guanine with cytosine in both RNA and DNA (the Chagraff rule); and the formation of a three-nucleotides codon for the encoding of an amino acid (aa). The four bases act as natural coding substances (the substitutes of C. R. Woese are cited). The sequence of the aa will then be arranged by transcription on tRNA templates into a linear strand of a polypeptid. "Organized DNA did not exist in the form of genes at the beginning of life", but even when it was formed, "the epigenetic information (was) not written in DNA and possibly (was) not coded in any symbolic fashion" and that DNA-guided reactions "gave way to life that would last for eternity". So presents, with quotations from Manfred Eigen's and R. Winkler-Oswatitsch's "Ludus vitalis", a superb alloy of philosophy and factual knowledge, the retired professor, Friedrich H. Schmidt (In: "Biological genesis; the first step from dead matter to life" Dovepress Journal: Research & Report in Biology, 2013;4:1–9).

The side by side hypercycling of the two biomolecules, Eigen's RNAs and Ghadiri's polypeptides, was not life yet, even though other ingredients, lipids and sugars, were present (generated anew, but not hypercycling). At one point, pre-cellular ribozyme-armed ribosomes (and pre-nuclear spliceosomes) must have had arisen. Heinrich Matthaei and Warren Nirenberg could work with extracellular *E. coli* ribosomes, rendering them to be functional *in vitro*. Ribozyme-armed cytoplasmic elements functioned long before the formation of nuclei. The "spark of life" of Eigen and Schmidt (*vide supra*) struck within a fragment of a second in a precellular ribosome, when some tRNAs captured some amino acids and started lining them up in chains. This occurred just once in the Universe and then only on Earth (*vide supra*)? However, once such an error-laden system was established, viroids could have been generated and from their repeated fusions, a precellular virus world and gene pool could have emerged (as envisioned by Eugene Koonin *et al*, see in the text). As protocells and cellular life emerged, the precellular viruses have become the parasites of the cells. Some of these viruses might have induced cell-to-cell fusions and even contributed to the formation of cell nuclei (see in the text).

This author's first encounter above the basics, his true acquaintance with, and admiration for, the DNA molecule, were provided and promoted by Peter J. Russell of Reed College, Portland, Oregon, in his fabulously written and illustrated "Fundamentals of Genetics" 1994 (HarperCollins College Publishers, New York); by William H. and Daphne C. Elliot of the University of Adelaide, South Australia, in their far above basics volume "Biochemistry and Molecular Biology" (Oxford University Press, Oxford, New York, Melbourne) reprinted with corrections, 1997; and by Seyhan N. Eğe's superbly basics "Organic Chemistry Structure and Reactivity" 3rd edition 1994 (D.C. Heath & Co, Lexington, Toronto). The monograph "RNA Life's Indispensable Molecule" by the Rockefeller University professor James Darnell appeared recently in 2011 (Cold Spring Harbor Laboratory Press, Cold Spring Harbor). This text ascends from the class room of college students to the most advanced laboratories of top PhDs. Its last chapter "RNA and

the beginning of life" is the light switched on in a dark room (one may say "in a dark universe"). The "Catalog of Human Cancer Genes" published in 1999 by the University of Oklahoma professor of genetics, John J. Mulvihill, with the foreword of Victor A. Kusick (Johns Hopkins University Press, Baltimore, London) is the firm foundation of our subject matter, that never will be outdated, no matter how many new oncogenes will continuously be discovered. No matter from how many new angles the inexhaustible and inventorially rich biology of the cell is looked at, each approach reveals something new and unique. Robert J. Earl and Robert A. Wallace of the University of Florida, Gainesville, published the "Biology the Realm of Life" 3rd edition, 1996 (HarperCollins College Publishers); and Gerald and Teresa Audesirk of the University of Colorado, Denver, produced "Biology Life on Earth" 2nd edition 1989 (Macmillan Publishing Company, New York). Educating this author further, other splendently written and illustrated volumes were those of Gilbert F. Scott's "Developmental Biology" 5th edition 1997 (Sinauer Associates Publishers, Sunderland); and the volume entitled "Biology Concepts and Connections" by Neil A. Campbell, Lawrence G. Mitchell and Jane B. Reese (Benjamin/Cummings Publishing Company, Redwood City Menlo Park, 1994).

This author was impressed by the intimate relationship of the two progenitor molecules of life, the RNA/DNA complex. In some extant genomes, long non-coding ncRNA strands harbor within their stretch, a short one-exon sequence, for example, the human stem cell *sox*2 proto-oncogene, whose product is the SOX2 proto-oncoprotein (P.P. Amaril cited in the text). Was the complimentary cDNA originally engendered inside the primordial RNA, and they preserved the relics of their original relationship, or was the DNA inserted into the RNA from an outside source (for example, as the retrotransposon of the ancient Mauriceville plasmid) (Figure 2). The reverse transcriptase of the Mauriceville retroplasmid initiates cDNA synthesis *de novo* (without primer) at the 3′ end of the tRNA molecule (cited in the text).

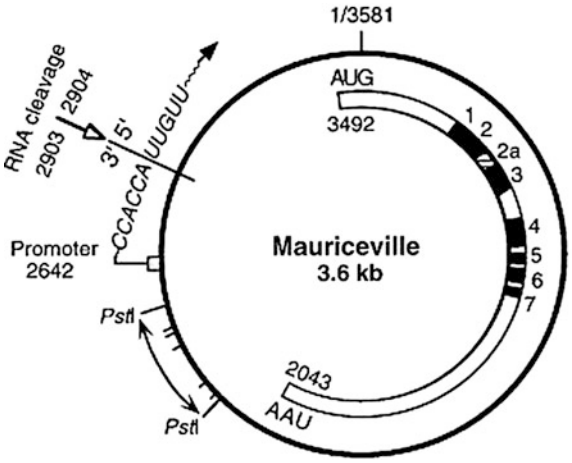

Figure 2 The Ancient Mitochondrial Mauriceville Plasmid in the Neurospora crassa. [2335] Reference Appendix 2, Explanations to the Figures

If the first DNA molecules originated within RNA strands, late in the precellular era, or thereafter within the first spheroplast-like proto-cells (described in the text), their relationship was and remains that of the "mother and son". Accordingly, this article impersonates them as "the Empress", the mother RNA, and "the Emperor", the son DNA, RNA → cDNA. A long noncoding RNA strand is the mother and within it the one exon Sox gene is the son. The name Sox derived from the Y chromosome-embedded *sox* gene (SRY, sex determining region, or box, in the Y chromosome) (Figure 3). The ancestral stem cells' *sox* gene families appeared in the protochordates, or even before. In the sea urchin and in the amphioxus, *sox* gene product proteins mediate germ-layer specification. In human malignant tumors, Sox2/Oc4/Nanog proteins abound (see embryonal carcinoma of the testis, and many others). When it pops up in the literature, that the Kaposi sarcoma virologists named the herpesviral-related shutoff exonuclease also as a SOX protein, quite different from the *sox*/SOX stem cell gene and its gene-product protein, this author's only recourse is to appeal for the readers' leniency toward the overburdened geneticists and virologists. The archaeal (*Sulfolobus acidocaldarius; Acidithiobacillus thiooxidans*) and the prokaryotic (*Aquifex aeolicus*) so-called *sox* genes and SOX gene product proteins should also be discounted from this context; those are apocytochrome B and cytochrome C oxidase subunits, and are thiosulfate sulfur-oxidizing, polysulphide reductase enzymes. However, the real primordial RNA/DNA complex remains the impersonator of the imperial majesties for all molecules, which exist and function under their reign. The DNA-binding Sox proteins de-differentiate cells into their stem cell stages. The Empress and the Emperor dance together, but whenever the opportunity arises, the Empress asserts her ancient leading role over her son, the Emperor, by issuing some ancient small

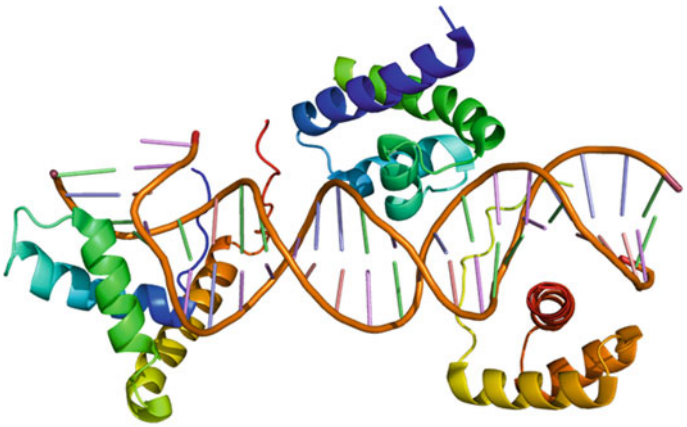

Figure 3 The sox Gene-product High Mobility Group Proteins in Stem Cells and in Tumor Cells. Reference Appendix 2, Explanations to the Figures (Structure of the SOX14 protein. http://en.wikipedia.org/wiki/File:Protein_SOX14_PDB_1gt0.png by Emw http://commons.wikimedia.org/wiki/User:Emw is licensed under CC BY-SA 3.0 http://creativecommons.org/licenses/by-sa/3.0/)

hairpin shRNAs, just as a warning: "No"! And the ribosomes will not translate the attacked mRNA into a protein.

Since the invasion of the first proto-cells by pre-existing virus-like molecules or viruses (the small viroids and large viruses formed from their repeated fusions, a presumption) up to the huge viruses that might have pre-existed and metabolized in the precellular era, multiple viral and host cell DNAs face each other in the infected cells. Different viruses interfere with each other as a rule; some viruses do away with interference and rather collaborate in order to keep the host alive for their protracted residence within. Elementary ancient virus-cell interactions replayed? (Timidly expressed in J Sinkovics: Die Grundlagen der Virusforschung, Verlag der Ungarischen Akademie der Wissenschaften, Budapest, 1955-6). There was then not even the inclination of circular herpesviral DNA genomes resting in the cellular epigenome, and periodically releasing microRNAs to neutralize host cell DNA-derived mRNAs, that would have been spliced and translated in the ribosomes into some antiviral proteins. An up-to-date text is now offered to elaborate on the battle, or reconciliation, of the viral and host DNAs and their missiles, the microRNAs.

Stem cells, haploid germ cells, somatic cells, transformed cells. The ancient unicellular life forms survived under the most adverse conditions in a chemically hostile, overheated (boiling water; pouring lava; volcanic fumes), chemically imbalanced as to excessive acidity or alkalinity, and heavily radioactive environment. The γ-rays-irradiated but radiation-resistant *Deinococcus radiodurans* (Figure 4) suffers genomic damage; it is its chaperone proteins in its proteome that perform the rescue of the genome (Mediterranean Institute for Life Sciences, Split, Croatia).

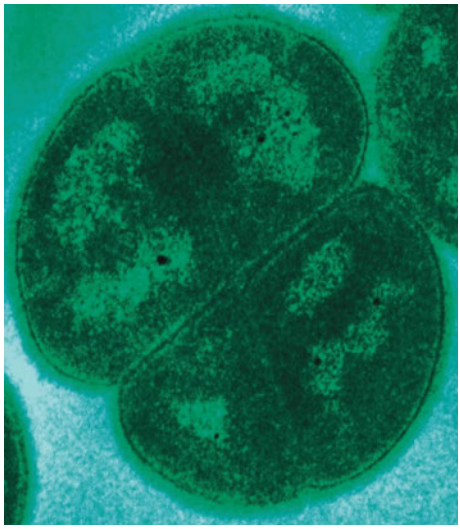

Figure 4 *Deinococcus radiodurans* and Its Survival in High Energy Radiation Fields. Reference Appendix 2, Explanations to the Figures

The heat shock proteins of the archaea chaperoned the protein molecules that were essential for life. The unicellular kinetoplastid (kinetoplastids are its mitochondria) protozoan, the trypanosoma (*T. brucei*) mobilizes heat shock proteins (Hsp) when stressed, as a cell survival pathway. No wonder, the most advanced eukaryotes undergoing malignant transformation in their multicellular hosts, enlisted these ancient proteins for their service: Hsp now protect and chaperon the oncoproteins! Geldanamycins deprive the trypanosoma of its heat shock proteins, and as the parasites die, the infected mice survive (as shown by K.J. Meyer and T.A. Shapiro of Johns Hopkins University Hospital, Baltimore, USA, in the J Infect Dis Aug 1, 2013 issue). Potent inhibitors of the human Hsp90 exist (the patented AUY922 molecules), that kill neuroendocrine cancer cells. PARP cleavage (for polyadenosine diphosphate ribose polymerase, see Table II in the text), and the suppression of ErbB, and the growth hormone-like insulin-like growth factor receptor (IGF-R) induce apoptotic tumor cell death. Similarities of the cell survival pathways between the trypanosoma (*T. brucei; T. cruzi*) driven by sugar to IGF-R, or activated Hsp, and the cancer cell offer themselves for a comparison (as Zitzmann K *et al* of Ludwig-Maximilian University of Munich published it in the Dec 2013 issue of the Internat J Oncology).

The most versatile units of the primordial RNA/DNA complex elongated, amplified, G-quadruplexed, and innovated themselves (when a duplicated extra gene mutated and became a new gene, as Susumo Ohno first proposed); further, diverged, tandem duplicated, aligned and merged, sealed end-to-end, broke and fused, or point-mutated, promptly and liberally in order to encode any new cell organelles, organs and their "cell survival pathways". The descendants of the first unicellular eukaryotes (example: the Trypanosoma) still repair their telomeres after each cell division, activate "cell survival pathways" (examples: the PI3K pathway in Giardia; the metamorphosis bordering trans-speciation in Dictyostelium, or Naegleria). The Oxytricha genome forms G4 quadruplex DNA complexes and carries the ancient piggyBacs, may be even ancestral piggyBats (see in the little brown bats in the text).

The mobile RNA elements invaded the genomes of the ancient uni- and multicellular hosts from the Volvox upward, through the choanoflagellates, Trichomonas, Dictyostelium, Saccharomyces and Candida, Tetrahymena, and Trypanosoma. Multicellular early life forms from the amphioxus (*Branchiostoma floridae*), *Suberites domuncula* Demospongiae (*vide infra*), to the heavily involved Schistosoma followed suit. In distress, the retrotransposons' provirus DNAs encoded (and still encode) the "mutator phenotype" for survival. In the human genome, in Lynch syndrome, or in chronic infections, the transposon/retrotransposon-proviral DNAs encode the "mutator phenotype", first reversibly by epigenomic interventions, then constitutively (irreversibly). The clinics diagnose "cancer." Accordingly, the text extensively reviews all forms of mutator phenotypes and retroviral oncogenesis.

In multicellular hosts, the stem cell compartments preserved most of the faculties of the ancient RNA/DNA complex. The healthy stem cells' RNA/DNA complex serves its multicellular host in its ontogenesis (in fertized egg cells, in the larvae, pupae and nymphs, or in the embryo). The pluripotent and asymmetrically dividing

stem cells generate organs: first, anlage dissolution by apoptosis, followed by organ regeneration. Examples are the morphogenesis in the cocoons of insects; the tadpole's regression of gills and formation of lungs; the coelacanth's relatives' (Figure 5) sarcopterygian fins becoming legs crawling on dry land (as imagined, the most powerful hind fins becoming the hind legs of the amphibians, the jumping frogs); and the developmental stages in the ontogenesis of the mammalian kidney. Some basic morphogenic transformations are bordering trans-speciation. Examples are the life cycles of Dd, DiDi, Dicty, the Dictyostelium (Figure 6), or Naegleria, or Theileria (see in the text). Hieronymus Bosch saw the slime molds as evil spirits in the "Garden of Earthly Delights"; the Texas cowboys suspiciously diverted the run of their herds and horses to bypass widely the huge blebs of fluctuating yellow sponges feeding on cow-manure, the slime mold colonies, off Houston, TX; and the young PhD students at Rice University, Houston, love to tender to the subject matter of their curricula, Dicty, the "social amoeba".

The artists' alleged minor distortions do not abolish Ernst Haeckel's "ontogenesis recapitulating phylogenesis" of the clade. The stem cells' RNA/DNA complex remained fully capable of encoding practically any physiological need in the onto- and phylogenesis of its multicellular hosts. The RNA/DNA complex initiated the host's natural selection under changing environmental conditions. Examples are the flying reptiles (the Archaeopteryx); flying theropod dinosaurs (the feathered birds, Aves); flying mammals (the bats, Vespertiliones). Further achievements are, **1**, the evolution of the maternal organ, the uterus, and the fetal organ, the placenta (from the egg-laying platypus up to mammals). The return of land mammals (ambulocetus → balaena) to the sea (example: the ancestral line of the pre-hippopotamus becoming whales: from a plant-eater, a meat-eater). For **2**, the evolutionarily achieved ultimate task accomplished is the encoding of the human cerebral cortex. The RNA/DNA complex proves itself capable of resolving the most complicated tasks of biological engineering. Would not the master progenitor molecules carry inherently the basic elements for the sustenance of all-resistant, independent, immortal cells, too? If some cell communities survive several thousand years (Atacarma desert shrubs in Chile; the baobab tree in Kruger National Park, South Africa; the Posidonia Oceanica sea grass in the

Figure 5 The Coelacanth Is Alive. (Latimeria Chalumnae – Coelacanth. http://commons.wikimedia.org/wiki/File:Latimeria_Chalumnae_-_Coelacanth_-_NHMW.jpg by Alberto Fernandez Fernandez http://commons.wikimedia.org/wiki/User:Afernand74 is licensed under CC BY-SA 3.0 http://creativecommons.org/licenses/by-sa/3.0/) Reference Appendix 2, Explanations to the Figures

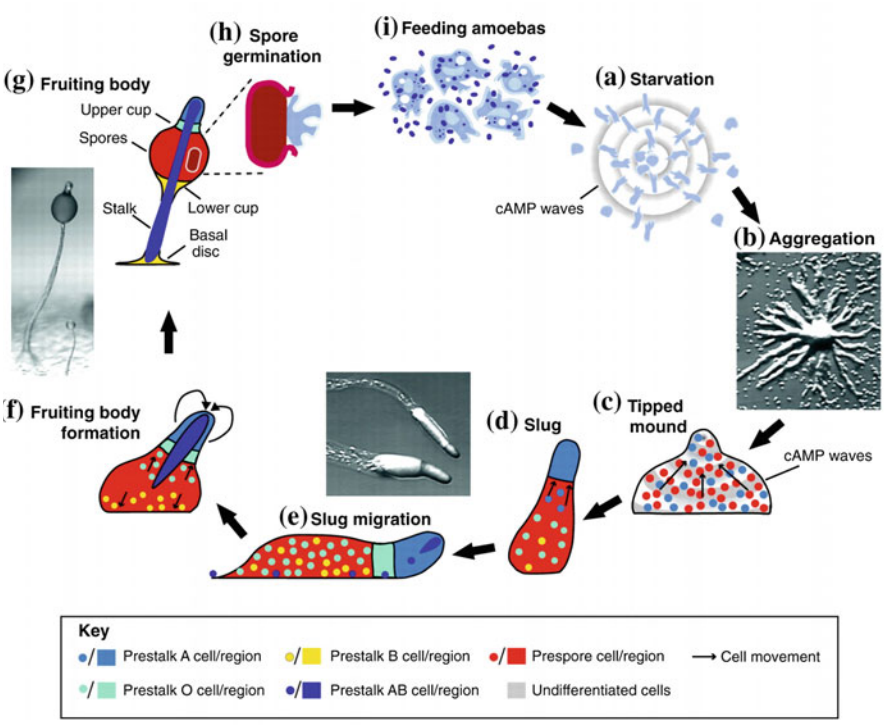

Figure 6 The Amoebozoan Dictyostelium discoideum and Its Cell Cycle. [2336] Reference Appendix 2, Explanations to the Figures

Mediterranean Sea; the cyanobacterial stromatolits of Western Australia) that does not necessarily mean that their individual cells were immortalized (see in the text); or are they living in a biological entity free of senescence, but different from "malignant transformation"? (Rachel Sussman: The Oldest Living Things in the World", University of Chicago Press, 2014).

It is not so that the RNA/DNA complex possesses a foresight, as to what environmental changes to expect; for these, it has no premonition to prepare for in advance. Evolution is not supposed to have any foresight. However, one of the multiplicities of its products is able to adapt to the changed environment, and select out its progeny, whereas, the other competitors perish. The elements of these new faculties appear to have been present in a small subpopulation, even before the full folding out of the new environmental changes. The close to omnipotent RNA/DNA complex refrains from, or fails to, catching up with the new environmental changes in retroactively re-adjusting the inadequate faculties of the left-behind hosts. The inexhaustible mutability, the driving force of the Darwinian selection process, rendered the host in advance to be best fitted to survive under any new circumstances. The faculties enabling the host to adapt happened to be "in the waiting."

For survival, the fittest individuals of a cell colony under attack in a changing environment (an infectious process; a gross metabolic change in the host; the aging process) will be those, which already carry a subtle minor difference in deviation from the uniformed vast majority. These are the cells, which rapidly will undergo the genomic transformation and prove themselves to be the immortal survivors. In a vast cell community, the transformation begins just in one (or in only a very few highly selected) cell(s).

In the multicellular hosts, the subservient somatic cells are under the control of the immune system, first innate, then adaptive, then united. The entire biological system of the multicellular host is set for the prevention of a reversal of its somatic cells to the life style of their independent and immortal unicellular ancestors. Ironically, some enzymes working in the process of somatic hypermutation in antibody generation, as to insert the newly created light chain immunoglobulin genes into the heavy immunoglobulin gene, miss-nick instead, and thus liberate, a proto-oncogene. The adaptive immune system may commit an error in promoting the fusion of a gene, from the compartment of the stem cells (c-*myc*), or from the cell survival pathways (*bcl*-2), with the heavy immunoglobulin gene (*IgH*). Thus, a fusion protein (an "oncoprotein") is generated dictating cell survival constitutively. The affected lymphoid cell, due to the "mistaken installation" of one of the most sophisticated biological machinery, assumes the semblance of immortality. An armada of "tumor suppressor genes" and immunoreactive genes arise to eliminate the maverick cell. The success rate of this intervention, the silent expunging of the maverick cell before its expansion, is not known (but Sir Macfarlene Burnet guessed it just right, in: "The concept of immunological surveillance" (Prog Exp Tumor Res 1970) (see in the text). In contrast, the success rate of the expanding transformed cells is well known, as it is measured as the incidence of malignant tumor generation in the life time of various multicellular hosts (prominently including *Homo*). Once the driving mutations (PI3K/Akt/mTOR; Wnt, see in the text) are set, the genome is triggered to initiate hundreds (or more than a thousand) somatic mono(uni)genic gain-of-function mutations. These are for any unforeseen environmental constellation into which just one in a thousand of the mutated cell will have to fit, in order to be able to faultlessly metabolize in it. Permission to re-publish pending, a text-figure will show how so-called defensive enzymes, the APOBECs, can also induce such mutations.

When the RNA/DNA complex can generate "by mistake" cells transformed into the life style of their ancient unicellular ancestors, it reveals its inherent aboriginal potency to generate such individual cells "intentionally". It is a display of a faculty for the preservation of cellular life in mortal multicellular hosts under stress (a chronic infection), or under any other threat of extinction. The clinics diagnose the inherent natural process as the fatal malady "cancer" (Siddhartha Mukherjee: "The Emperor of All Maladies" 2010, Amazon.com). In the multiple forms of gain-of-function re-arrangements, there are no exact criteria for the distinction between an accidental genetic deviation from norm, and an encoded inherent process initiated for the same purpose. An example of the former is the "balanced chromosomal rearrangement", due to misaligned chromosomes in the spindle

(that may result in aneuploidy). An example of the latter is the strategy of the oncogenome with sequential gains of cellular vitality: elimination of auto-apoptotic processes, serial gain-of-function point-mutations and gene fusions meticulously avoiding nicks within protein-encoding sequences, and generating new proteins (the "oncoproteins") exempt of ubiquitination. Are here the characteristics of the cell known at the clinics as "the cancer cell" displayed?

The stem cell ascending in the crypts of Lieberkühn in the colonic mucosa is the star. This stem cell divides asymmetrically, thus creating the differentiating epithelial cells of the colonic mucosa, while it also renews itself. The ultimate result of differentiation is at the end of the trajectory. It is the epithelial cell of the intestinal lining, a subservient somatic cell. In the colon, this cell is bathing in liquid feces, that is populated by the natural microbiome, which is engaged in a balancing act with its phages, and with its host's tolerance. The epithelial lining is shed and regenerated practically daily. The clockwork of the genomics disallows any de-differentiation (for the time being). However, a clone of bacteria becomes invasive (an enterotoxigenic Bacteroides), and the environment suddenly changes. The host mobilizes a chronic and protracted immune reaction. Some of the $CD133^+$ stem cells in the bottom of the crypt sense a signal, conveyed by accident, or by the inherent rules. The stem cell refuses to ascend, and to asymmetrically divide; no differentiating somatic daughter cells will be released. This stem cell divides symmetrically producing two stem cells in each division. This stem cell puts all its ancient genome to full alert. By deacetylating their promoters, it liberates the cell survival pathways encoded by the proto-oncogenes. The activated genome dictates full symmetric mitoses (no asymmetric mitoses). Some genes try to encode inhibitors of the cell cycle; the promoters of these genes will be immediately silenced at their CpG residues by hypermethylation (the so-called "tumor suppressor genes" are inactivated, among them first APC). The guardian of the genome, the wild type p53 gene, rises to induce apoptosis. Its protein product will be neutralized by the MDM protein, and sent to ubiquitination. The rapidly dividing stem cells demand a blood supply by generating VEGF-R. The host obliges and provides a network of blood vessels. In response, the stem cells activate their β-catenin/Wnt/Hedgehog pathway (Figure 7). Accordingly, the suppressor gene dickkopf is silenced and β-catenin is released from the cytoplasm for transfer to the nucleus. The ancestral wnt/hedgehog proto-oncogenes exist in the universal eukaryotic genomes from the choanoflagellates (Monosiga), and the cnidarians (Nematostella) on, with a side way to the drosophilas' *notch* gene. The evolutionarily vertically transferred genes reach up to Homo. The cell survival pathway of the sea anemone (Nematostella), the genes regenerating the cut-off head of the hydra, become oncogenes in the human stem cell.

By now, the transformed cells form a large conglomerate in the colonic wall, from where they will disseminate (Figure 8). In addition to the stem cells, some of the somatic cells are also induced to de-differentiate into stem cells. At the bottom of the crypt, a set of stem cells continues to divide symmetrically, in a set sequence. Their *snail/slug* proto-oncogenes change their epithelioid cytoskeleton into a slick mesenchymal-sarcomatoid structure. Fibroblast-like cells (some of them of bone

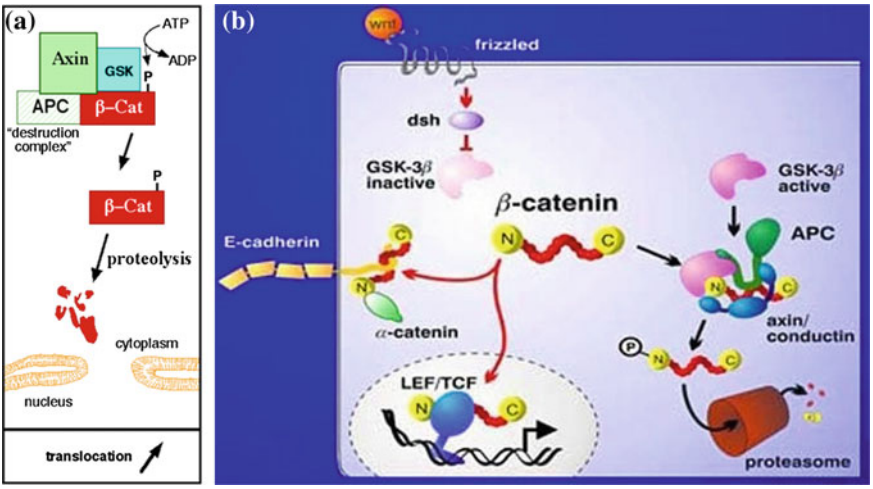

Figure 7 **a** The Wnt Pathway for Body Image in Ontogenesis, and for Malignant Transformation in Oncogenesis. (Wnt doesn't bind to the receptor. Axin, GSK and APC form a "destruction complex," and β-Cat is destroyed). http://en.wikipedia.org/wiki/Wnt_signaling_pathway#mediaviewer/File:Axindestructioncomplex.png by JWSchmidt http://en.wikipedia.org/wiki/User:JWSchmidt is licensed under CC BY-SA 3.0 http://creativecommons.org/licenses/by-sa/3.0/). **b** The Wnt Pathway for Body Image in Ontogenesis, and for Malignant Transformation in Oncogenesis. With kind permission © Walter Birchmeier, Max Delbrück Center. All Rights Reserved 2015. [2337] Reference Appendix 2, Explanations to the Figures

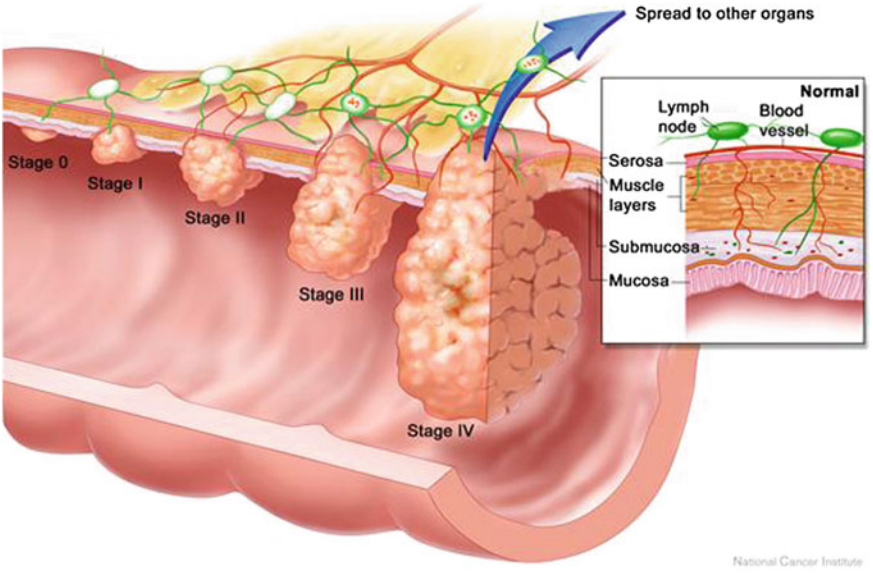

Figure 8 Staging in Colon Cancer. © Terese Winslow. All Rights Reserved 2015

marrow-derivation) induce further the epithelial-to-mesenchymal (ETM) transformation. The elongated cells sneak through lymph- and blood vessel walls, travel, and occupy lymph nodes and parenchymal organs, with preference to the liver. There, subverted macrophages, Kupffer cells, mast cells and vascular endothelial cells welcome and feed them; the T lymphocytes and NK cells recognize them as their own "self", and refrain from attacking them. If immune T cells reacted to them, chemokines (stromal cell-derived factor, SDF) calls in regulatory T (Treg) cells to put an end to that reaction. The invaders exhibit great resistance to chemical and radiation exposures (like their primordial ancestors on Earth did). These cells could exist long in the state of autophagy, and regain an accelerated malignant behavior years later (see in the text). The recurrent tumor lost its brake, the microRNA-451; it produces ATP-binding cassette ABC protein pumps (as their ancestral unicellular eukaryotes, the dinoflagellate algae, do, *vide infra*) to immediately exude ("pump out") chemotherapy drugs. Thus, a full resistance to FOLFOX/FOLFIRI (5-fluorouracyl; oxaliplatin; irinotecan) is gained. These cells eventually kill the host. Newly discovered antibiotics (salinomycin) and anti-CD133 monoclonal antibodies may eliminate them (Table I). To switch off billions of years of differentiation in a few cells living in the police state of a well-organized cell community is a challenge only primordial forces conserved in the RNA/DNA complex can measure up to.

The differentiated somatic cell of the integument (a keratinocyte) obeys proper biochemical orders (in the form of proto-oncoproteins with or without chemo-, cyto-, and lymphokines) to reverse its trajectory and become a stem cell, and then to re-differentiate into a nerve cell (Shinya Yamanaka's Nobel Prize, 2012). Improperly stimulated, it may become a basal cell carcinoma, or a squamous cell carcinoma. The ancient RNA/DNA complex will de-differentiate the mature somatic cell to its ancestral stage of existence. A fatal event mistakenly installed? A process of re-juvenation inherently installed? Is this a blind duty of the genomic retrotransposons for the maintenance of the living matter in whatever formation or shape (see in the text)?

In the highly chemo- and radiotherapy-resistant malignant peripheral nerve sheath tumors (MPNST), the tumor suppressor genes, the apoptosis-inducer p53; the PI3K/Akt oncogene-suppressor PTEN; the ras oncogene-suppressor NF-1 are lost (phosphatidyl inositol kinase 3; phosphatase tensin deleted on chromosome ten; AK mouse thymic lymphoma oncogene; rat sarcoma oncogene; neurofibromatosis), but the major promoter oncoproteins, the EGF-R and the IGF1-R (receptors, epidermal and insulin-like growth factors) are amplified without a gain-of-function mutation. Szokol B, Gyulavári P, Baska F et al of the Semmelweis University, Budapest, and the Max Planck Institute, München, just announced the discovery of new EGF-R small molecular inhibitors. Will they work in patients with lung cancer, where gefitinib and erlotinib have failed? The cascades of the ancient cell survival pathways of PI3K/AKT/MAPK (mitogen-activated phosphatase kinase), and those of EGF-R, c-MET (hepatocyte growth factor receptor) continue. Is it an ancient, and neither expunged, nor domesticated retroviral LTR of unknown relationship to microRNAs

Table I Oncogenic Stem Cells

In the crypts of Lieberkühn asymmetrically dividing stem cells release a somatic daughter cell and renew themselves. The somatic cell may de-differentiate into an asymmetrically dividing stem cell with mutated APC (in the GSK-3β/Axin complex) allowing cytoplasmic β-catenin to enter the nucleus to activate proto-oncogenes *tcf/lef* and notch. This is the Wnt ligand → Frizzled → Disheveled oncogenic pathway. The malignant cells (colorectal adenocarcinoma) respond to the FOLFIRI protocol: remissions are induced. Another population of stem cells in the bottom of the crypt begins to divide symmetrically (producing two stem cells) and rest long between divisions. These stem cells lose miR-451 control (miR-451 is downregulated), overproduce CD133, and ATP-binding cassette (ABC) transporter proteins, invite fibroblasts of bone marrow derivation, perform the conversion ETM, metastasize late; exhibit full resistance to FOLFIRI and XRT. May be forced to re-differentiate into asymmetrically dividing stem cells by salinomycin, BMP4 (bone morphogenetic protein) and anti-IL4 mcab.[1]
Similar transformed stem cell invasions occur in breast cancers induced by paclitaxel and avascular ischemic hypoxia due to bevacizumab.[2] Notch protooncogene emerges as a major luminal breast cancer stem cell up-regulator.[3] NFκB drives breast cancer stem cells.[4]
ATP-binding ABC proteins protected unicellular eukaryotes (dinoflagellate algae) from ingestion of toxic substances; same for vertebrate multicellular (fish) and mammalian hosts. Malignantly transformed cells revert to overproduction of ABC proteins. ABC proteins neutralize oncogene-antagonist curcumin. Verapamil, cyclosporin, erlotinib, marine products (agosterol, bryostatin, ecteinascidin, sipholane, triterpenoids) reverse the effects of ABC proteins in restoring cell susceptibility to cytotoxic drugs. Bromoditerpene parguerenes I/II of red algal derivation force the intracellular retention of doxorubicin, paclitaxel, vincristine better, than verapamil, thus promote cell death by toxins (chemotherapy in clinical oncology).[5]
1 Puglisi MA et al World J Gastroenterol 2013;19:2997–3006. 2 Conley SJ et al PNAS 2012;109:2784–9; Polyak K & Vogt PK PNAS 2012;109:2715–7. 3 Lafkas D et al J Cell Biol 2013;205:47–56; Suman S et al Br J Cancer 2013;109:2587–96; Peng GL et al J Huazhong Univ Sci Technol Med Sci 2014;34:195–200. 4 Zhang W & Grivennikov SI Breast Cancer Res 2013;15(5):316; Yamamoto M et al Nat Commun 2013;4:2299. 5 Abraham I et al Mar Drugs 2012;10:2312–21. Hawley TS et al Am J Hematol 2013;88:265–72. Huang XC et al Biochem Pharmacol 2013;85:1257–68. Lainey E et al Cell Cycle 2012;11:4079–92. Liu S et al PLoS One 2013;8(5):e63895. Sakulterdkiat T et al Anticancer Res 2012;32:5337–42. Wang DZ et al PLoS One 2013;8(5):e3659. Yamada A et al Breast Cancer Res Treat 2013;137:773–82. Zhang DM et al Mol Pharm 2012;9:3147–59.

(miR), that is responsible for these gene amplifications? Oncogene-activator host cell genomic LTRs (long terminal repeats) are discussed in the text.

The stem cell practices self-preservation by dividing asymmetrically in almost unlimited numbers of divisions, with the release of a somatic daughter cell on each occasion. Since stem cells are singularly distributed in the parenchyma, they must build up that daughter cell within their nucleus and cytoplasm from nutrients received by diffusion; unless, there are special stem cell compartments (in the Lieberkühn crypts in the gut), where stem cells may receive blood supply. In contrast, the differentiated somatic cells of the multicellular hosts are allowed only a limited number of cell divisions. The somatic cells of the multicellular host are instructed to leave their chromosome ends uncapped after each mitosis. This is in contrast to many extant free-living, or parasitic unicellular life forms, which diligently recap their chromosomal ends after each of their divisions (*Trypanosoma*

brucei in culture). Theileria-infected host lymphocytes are forced to do so (see in the text). The ancestral unicellular eukaryotes probably practiced telomere re-capping after each cell divisions. The regular enlisted-for-service somatic cells of the multicellular hosts are allowed not more than approximately 30 cell divisions in their life span (the Hayflick rule). Thus, they undergo senescence and eventually die. They may be replaced by new somatic cells, as newly generated daughter cells of the ever-present resident stem cells provide them. In contrast, the somatic cells' gain-of-function point-mutations may reverse their course toward immortality. These cells now repair their chromosomal ends with an overactive telomerase, and activate in a constitutive manner their cell survival pathways. The notorious PI3K pathway is activated upon the elimination of its arch-enemy suppressor, the PTEN gene (see in the text). Loss-of-function mutations, or deletions, abolish the tumor suppressor genes, or by ubiquitination, their gene product proteins, respectively. These faculties were installed in multicellular hosts in order to prevent constitutively activated cell survival pathways, the rebellious stem or somatic cells may revert to. The clinical textbooks read: "loss of the tumor suppressor genes occurred, and the malignantly transformed cells replicate constitutively and unopposed".

In full activity, the somatic cells' glycolytic pathways are those of oxygenation through the mitochondria with high energy (ATP) yields. However, upon "malignant transformation", one form or the other of the ancient Warburg type pre-mitochondrial glycolysis is re-activated. The Warburg's switch is recalled from the past to engineer the return to one or to another form of the ancient Embden-Meyerhof-Warburg type glycolysis (Figure 9). This form of glycolysis

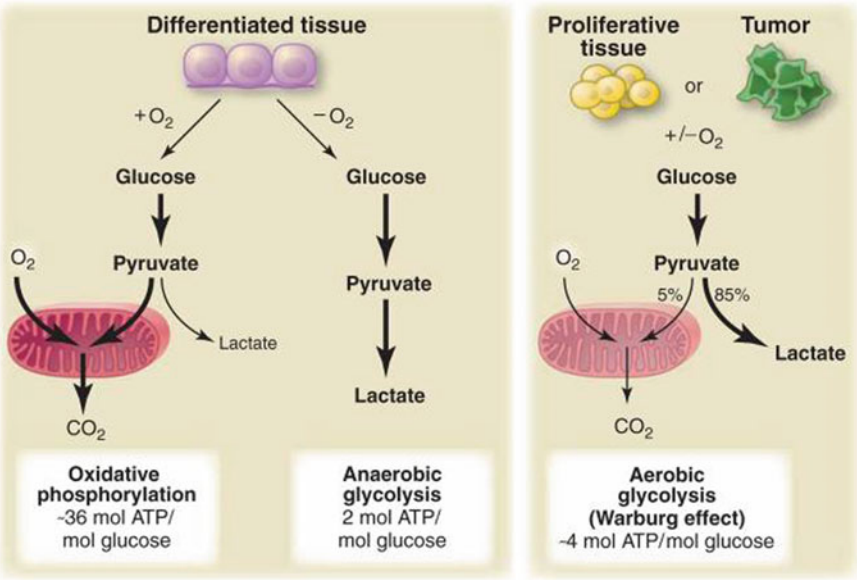

Figure 9 Warburg's Aerobic Not-mitochondrial Glycolysis. [2338] Reference Appendix 2, Explanations to the Figures

served unicellular life forms in the ancient anaerobic (or even aerobic) environments prior to the acquisition of mitochondria. Nevertheless, it is an oxidative form of glycolysis, but with a very low energy (ATP) yield. The transformed cells practice it even in the present aerobic environment by-passing their mitochondria. However, in many ways, the transformed cell will eventually switch to a form of glycolysis of high energy yield. Examples of such maneuvers are known in the glioblastoma-, or in the mantle lymphoma-cells (documented in the text).

The coding capacities of the cell-transforming RNA/DNA complexes follow a serial and consequential pathway in eliminating apoptosis-inducing genes first (the "tumor suppressor genes"), and activating "cell survival pathways" by expropriating all physiological growth factors (even erythropoietins) and their receptors in autocrine or paracrine circuitries in multicellular hosts. The oncogenic RNA/DNA complex of transformed single cells exhibits most of the faculties of the ancient primordial RNA/DNA complex of the stem cells. Cells of the marine hydrozoon cnidaria, *Hydractinia echinata,* are able to bud off new individuals, or to undergo meiosis resulting in either ovum- or sperm-forming cells, thus preserving either stem cell, or germ cell faculties. However, when the individual cells form colonies, some cells differentiate into epithelial cells of the "gastrointestinal or vascular network" shared by the entire colony. Retained in the interstitium are the stem cells. In these cells, the polynem (Pln) gene (equivalent to the Oct4 human stem cell gene) may suddenly dictate a reversal to the pheno-genotype of the primordial individual cells. The differentiated cells of the gastrointestinal and vascular network suddenly begin to de-differentiate. De-differentiated Hydractinia and Medusozoa cells practice reverse ontogenesis. They may re-differentiate into mature organs. They may uncontrollably proliferate, transform into large tumors and actually kill their host (see cited in the text).

The ancestors of some of the most hidden proto-oncogenes in the vertebrate mammalian hosts served in the uro- and protochordates and in the cnidaria. The amphioxus separated a minuscule central and an extensive peripheral nervous system. There, and in the anemone, and the hydra, appears for the first time, the basic helix-loop-helix protein gene *ash*, to encode some early nerve cells. These genes under the name achaete scute homolog (*ash*) become a proto-oncogene clade in the mammalian vertebrate hosts' neuroectodermal/neuroendocrine cancer cells (chaete, bristle in the drosophila larva; a-chaete, no bristle, due to a gene mutation). The human *ash* genes encode the malignant tumor of the olfactory ganglion known as esthesioneuroblastoma, or transdifferentiate lung or prostate adenocarcinoma cells into highly chemo- and radiation-resistant neuroectodermal-neuroendocrine cancer cells (described in detail in the text).

In contrast to degenerative monogenic (one gene and "loss-of-function" type) germline mutations, every one of the multigenic serial and sequential mutations in the somatic cell is one of the "gain-of-function" type, thus increasing the cell's vitality. There are driver mutations as conserved cell survival pathways from the distant past; these notoriously occur in the cancer stem cells. In addition, there are numerous somatic cell one-gene mutations, all of them the gain-of-function type. The textbooks say that these are fundamentally random events. May the question be

asked: could not the DNA initiate such gain-of-function mutations by the thousands in its progeny made to fit into just one of millions of not foreseen environmental changes. These changes are to come, and in which just one in thousands of the mutated cells will be able to fit into and survive in it?

Some of the stressed unicellular life forms (the protists, the ciliate, *Oxytricha trifallax*, etc.), as well as the "oncogenes" in multicellular host cells (c-*myc*), convert their linear DNA into a G-quadruplex (propeller) formation. What occurs in a human oncogene (c-*myc*), occurs normally, or under 'stress', in the genome of a ciliate. In the "oncogenome", distant genes travel within the genome from chromosome to chromosome, to form unisons by fusion with another gene. The fused genes encode the oncoprotein for an irreversible cell survival pathway. So do the genes of the potato-pathogen oomycete Phytophthora for increased virulence and pathogenicity (see in the text). Did similar proteins drive the ancient unicellular life forms through blasts of UV and ionizing radiations (the DNA-repair enzymes of *Deinococcus radiodurans*), or in water close to its boiling temperature (the heat resistant polymerases of the *Sulfolobus acidocaldarius/solfataricus*, or *Thermus aquaticus*, Taq), and/or in potentially lethal chemical reactions? A chemical reaction of this type is the high concentrations of sulfuric acid and pH < 3 in pyrite ores, the environment in which the archaea, *Ferroplasma acidarmanus,* thrives (see in the text). The transformed extant cells (referred to as "cancer cells") possess extraordinary abilities, not only to pump out from the cytoplasm harmful chemicals, but also to neutralize them within the cytoplasm. Cisplatinum forms intrastrand cross-links (adducts) in the DNA molecule. Before that, the cancer cell neutralizes the cisplatinum molecule (diammine-dichloro-platinum) in the cytoplasm by conjugating it with metallothionein, or glutathione; after that, by enzymatically excision-repairing the platinum-DNA adducts. The defense mechanisms of unicellular "radiodurans" life forms and transformed single cells of multicellular hosts toward chemical- and radiation-induced damage are quite comparable.

In the oncogenes of the multicellular hosts, the elementary basic structure of the genes encoding cell survival pathways and accelerated cell divisions in the extant descendants of the primordial unicellular ancestors can be recognized. In a form of human leukemia cells, the descendant of the yeasts' cell-division accelerator *bub* gene (budding uninhibited by benzimidazole) and that of the trypanosoma's *nup* gene (nucleoporin) form a fusion oncoprotein. Bub protein overexpression in itself is an inducer of aneuploidy and Aurora B kinase hyperactivation (see text). Through these measures, the ancient unicellular life forms were endowed with the faculties of close to non-surmountable physico-chemical resistance, and the faculties of cell divisions in young mature age, thus escaping by prevention senescence and natural death. Some 'malignantly transformed' individual cells of the multicellular host are able to revert to the metabolism of their distant ancestors.

Some malignantly transformed cells in the multicellular hosts behave like those unicellular life forms, which have become the parasites of the multicellular hosts. These unicellular life forms (Plasmodia, Theileria, Trypanosoma) alter their cell surface antigenicity, induce tolerance by masquerading as "self", and subvert mesenchymal cells of their host for their active support in producing the appropriate

chemo-, lympho-, and cytokines for the growth factor receptors of the invaders. The CD47 ligand of leiomyosarcoma cells in acting on the signal regulatory protein receptor of M1 naturally defensive host macrophages, convert them into tumor-friendly M2 Mϕs. At the Stanford University Medical Center in California, antibodies neutralizing CD47, secure that M1 macrophages remain naturally defensive and will engulf and digest leiomyosarcoma cells (PNAS April 24, 2012). The transformed cells (cancer cells) of the multicellular hosts (the human host) repel the host's immune defenses (especially those mediated by immune lymphocytes and NK cells) exactly the same way as unicellular parasites overcome their hosts. Epithelial cancer cells may undergo alterations bordering trans-speciation by assuming the phenotype of vascular endothelial cells ("vasculogenic mimicry"), or that of elongated mesenchymal cells (fibroblasts, monocytes) for accelerated locomotion toward forming metastases ("epithelial-to-mesenchymal transition"), as illustrated widely in copyrighted figures in the literature.

The malignantly transformed cell and the syncytiotrophoblasts learn from each other. The fetal trophoblast of the placenta utilizes ancient defensive reactions similar to those of unicellular eukaryotic parasites and/or tumor cells, in order to evade its rejection; more than that, it is frequently invasive in provoking full tolerance by the mother. The placenta utilizes defensive reactions similar to those of tumors and parasites, in order to evade its rejection: thus, it was referred to as a "pseudomalignant organ", and its features as such were tabulated. Here is that Table reproduced. At The University of Texas M.D. Anderson Hospital's 56th Annual Symposium in 2003, held on the topic "Cancer Immunity: Challenges for the Next Decade", J.C. Horvath, H. David Kay and this author presented the two extreme means by which ancestral NK cells protected the Botryllus colonies from fusion with incompatible colonies, or how placental trophoblasts deal with maternal invariable iNKT cells for the protection of the fetus against rejection. It is the opposite of what secured the individuality of the Botryllus colony; it is a reconciliation in the interest of the fetus. The fetal trophoblasts and tumor cells learned each others' defensive (and aggressive) strategies. In many malignant tumors, especially teratomas and lymphomas, or in autoimmune diseases, latent endogenous retroviruses become reactivated (as documented in the monograph of Joseph Sinkovics "Cytolytic Immune Lymphocytes..," Schenk Buchverlag, Passau & Budapest, 2008). Many of these endogenous retroviruses are fusogenic (promote cell fusions), a faculty probably preserved from primordial ancestors. Fusogenic retroviruses were instrumental for the evolution of the placenta. In the superb Springer Verlag textbook of the editor György Berencsi III, and his co-author, Mária Takács, under the title "Maternal Fetal Transmission of Human Viruses and Their Influence on Tumorigenesis", these concepts were presented a-new in 2012 in great details. What was not re-cited in that volume from the precursory literature is being summarized here (with the generous permission of the editor, Demetrios Spandidos). Indeed, endogenous retroviruses and the fetal trophoblasts changed the course of the evolving adaptive immunology, by imitating the tumor cell, and then, *vice versa*. The inserted RNA-to-DNA proviruses become from pseudogenes to functional genes (F Bushman) [1].

Table (a modified reproduction*) "**Placenta as a "Pseudo-Malignant Organ"**

Placenta features expressed/acquired	Trophoblast	Malignant Cell
Chronionic gonadotropin	++++	+++
TGFα↑EGF-R	++	+++
TGFβ antagonizing Immune T cell expansion	++	++
Placenta GF	++++	++
GM-CSF	++	++
VEGF/VEGF-R	+++	+++
bFGF/FGF-R	+++	+++
MMP (matrix lysis for invasiveness)	++	++
Cox (subversive prostaglandins)	++	++
PP-A-R (growth factors for deciduas/placenta/tumors)	++	++
Mϕ MIP 1 (attracts inhibitory NKT cells)	++	++
Th-1 induction (INFγ TNFα[a] IL-2)	↓	↓
Th-2 induction (IL-4 IL-10)	↑	↑
B cells antibodies, cytolytic	↓	↓
ADCC	↓	↓
enhancing	↑	↑
MHC-expression	↓	↓
Immune T cells	Evasive	Maneuvers
Treg cells (antagonizing immune T cells)	↑	↑
NK/NKT cells	↓	↓
FasL ('counterattack' on Fas $^{+}$ immune T cells)	↑	↑
IDO (depleting tryptophan)	↑	↑
Vascular mimicry (replacing spiral arteries)	↑	↑
IGF (activated by endogenous retrovirus in the placenta)	↑	↑
Proto-oncogenes (wnt, fms, etc. activated)	Reversibly ↑	constitutively ↑
Endogenous retroviruses (fusion protein syncytin)	++++	++

a, added ADCC, antibody-directed cellular cytotoxicity COX, cyclooxygenase FGF, fibroblast growth factor IDO, indol-amino-2,3-dioxygenase IGF, insulin-like growth factors MIP, monocyte inflammatory protein PP-A-R, peroxisome proliferator-activated receptor
* Sinkovics JG & Horvath JC Internat J Oncology 2005;27:5–47

The human cerebral cortex. The consummate bioengineer RNA/DNA complex finally encoded the human cerebral cortex, endowed with trillions of nerve cells (Figure 10). The human brain has evolved to the competence of encompassing a limited but rapidly expanding comprehension of the universe and life within it. There are some 5000 to 200,000 synapses per one mature neuron. The entire human brain is the site for expression of the widest scale of emotions, from generous altruism to devastating anger and revenge; to pleasant amusements, artistry, logical thinking, imagination (often beyond logics), but nevertheless with keeping the faith in the transcendental, planning in advance, premonitions, and driving curiosity.