The cell survival pathways of the diploblastic early multicellular eukaryotic hosts contain and operate the molecular machinery resembling those of malignantly transformed individual cells of highly advanced multicellular hosts (including Homo). In the present review, the STAT/NF-κB pathway of the cnidarian Nematostella vectensis is compared with that of human tumors (malignant lymphomas, including Reed-Sternberg cells) pointing out similarities, including possible viral initiation in both cases. In the ctenophore genome and proteome, β-catenin gains intranuclear advantages due to a physiologically weak destructive complex in the cytoplasm, and lack of natural inhibitors (the Dickkopfs). Thus, a scenario similar to what tumor cells initiate and achieve is presented through several constitutive loss-of-function type mutations in the destructive complex and in the elimination of inhibitors. Vice versa, malignantly transformed individual cells of advanced multicellular hosts assume pheno-genotypic resemblance to cells of unicellular or early multicellular hosts, and presumably to their ancient predecessors, by returning to the semblance of immortality and to the resumption of the state of high degree of resistance to physicochemical insults. Human leukemogenic and oncogenic pathways are presented for comparisons. The supreme bioengineers RNA/dNA complex encoded both the malignantly transformed immortal cell and the human cerebral cortex. The former generates molecules for the immortality of cellular life in the Universe. The latter invents the inhibitors of the process in order to gain control over it.

1. Introduction

Of the genes encoding the body plane/axis/design in ontogenesis, and the stress-responses in adult life in the immense numbers of life forms emerging in the Cambrian sea, nuclear factor kappa B (NF-κB), STAT (signal transduction and transactivation), and β-catenin-dependent transcriptional activators have gained utmost and ever-lasting prominence. In the cnidarians, Toll-like receptors activated NF-κB to function as a stress response inducing cell survival pathway. The STATs are co-activators. In the advanced mammalian vertebrate hosts (including Homo), the β-catenin-based Wnt, and the NF-κB/Relp65 pathways have become the principal inflammatory STAT-associated proto-oncogenes/oncoproteins.

In the tunicate urochordate Ciona (C. intestinalis) the Wnt/β-catenin pathway regulates body design, first the trans-speciation of the swimming larva to the sessile ‘intestinal’ adult. In the decapitated hydra (H. magnipapillata/viridis), the Wnt/β-catenin (with Notch and PI3K) pathways regenerate a new head. In the other cnidarian, Nematostella vectensis (Fig. 1) next to the Wnt pathway, the NF-κB/STAT pathway fulfills essential physiological tasks. In the advanced multicellular vertebrate hosts (including Homo), β-catenin has become one of the most malignant oncoproteins, as it acts for example, in colon carcinogenesis. In Wnt carcinogenesis, the cytoplasmic ‘β-catenin destroying complex’ fails to phosphorylate β-catenin, thus, the complex does not mark it for ubiquitination. Intact accumulating β-catenin is allowed to translocate from the cytoplasm into the nucleus for the activation of oncoprotein promoter dNAs; primarily that of tcf/TCF and lef/LEF (Fig. 2). Furthermore, the Wnt antagonist Dickkopf tumor suppressor gene is forcefully eliminated. In the human genome, the NF-κB/STAT pathway has assumed the role of a
proto-oncogene. When constitutively activated, it induces B cell malignant lymphomas in the mediastinum and elsewhere. It is highly active in the Reed-Sternberg cells of Hodgkin’s lymphoma.

The rapidly expanding comb jelly ctenophores (represented here by *Mnemiopsis leidyi*) (Fig. 3) operate a physiologically defective cytoplasmic β-catenin destroying complex promoting β-catenin’s intranuclear transfer for activation of the predecessors of those genes (tcf/lef), which have become proto-oncogenes in the human genome. The ctenophore genomes do not possess ancestral Dickkopf genes, which have become tumor suppressors in the human genome. Furthermore, the ctenophore genome operates a full set of sox/Sox genes/proteins, which sustain pluripotent stem cells through the entire eukaryotic evolution, and may convert into oncogenes in the human genome. The ctenophore genome is a physiological oncogene.

2. The cnidaria class anthozoa

*Cell survival pathways.* In 2006, it was surprising that the little invertebrate basal animal, the burrowing sea anemone, *Nematostella vectensis* (Fig. 1), carried an abundance of ‘human disease genes’ (1). The numbers and positions of the introns in orthologous cnidarian and human genes reveal unusually high concordance in 47 and 69%, respectively, surpassing those of invertebrate insects and nematodes (2,3). Most of these genes are stress responder metabolism regulators (4,5). Prominent among them are oxidative stress-activated receptors and others, the aryl hydrocarbon receptor, AhR; and the hypoxia-inducible factor, HIF. Furthermore, operational are the ligand-activated nuclear receptors, ancestral predecessor of the hepatocyte nuclear factor; retinoic acid receptor (RAR); signal transduction proteins; transcription factors (including NF-κB, nuclear factor kappa B cell lymphoma); oxidizing, reducing, conjugating enzymes; oxidative cytochrome P450 enzymes (CYPs); and heat shock proteins (HSP), in several subfamilies. The cyp gene progenitor of animals (not plants) created a tandem set of duplicated genes, which utilized oxygen to modify substrate structures. Plant cells have acquired cyp genes from marine animals by horizontal transfer. Of the animal cyp gene clans, *Nematostella* possesses up to 46. Cyp genes are absent in the anaerobic *Giardia*, but are present in the aerobic *Saccharomyces*. The sponge (Amphimedon) operates 35, the amphioxus (*Branchiostoma*) has 236 cyp genes. Precursor cyp genes existed interspersed with hox, wnt and arf (homeodomain box; wingless; alternative reading frame GTPases) gene clusters (6). Later in evolution, the P450 genes lying downstream from the AhRs, will assume prominent roles, especially in hormone-dependent molecular carcinogenesis (breast cancer) (*vide infra*).

There are active efflux pumps in cnidarians operated by 64 ABC genes. The HSP (probably inherited from *Archaeoglobus fulgidus*) have assumed the evolutionary role of chaperoning oncoproteins in multicellular vertebrate hosts (including *Homo*). The descendant enzymes of the original ATP-binding cassettes (ABC) present in extant (and presumably ancient extinct) zooxantellae, act as ATP-dependent efflux transporters in pumping out molecular chemotherapeuticals from malignantly transformed (cancer) cells in multicellular vertebrate mammalian (human) hosts (as referenced in 7). Of biotransformators, there are glutathione- and sulfotransferases, but no acetyl transferases. Of antioxidant proteins, there are 6 superoxide dismutase (SOD) genes (4,5).

*Viruses-carrier algal symbionts.* Some cnidarians and para-mecia accept the intracellular invasion by chloroplast- and virus-carrier eukaryotic *Chlorella* green algae (*Chlorella vulgaris; C. variabilis*) and live with them in symbiosis (8). In the case of the Florida strain of *Hydra virilis* (in culture for over 20 years; fed with tiny pieces of brine shrimp), and the *chlorella* green alga, the symbiotic algal cells taken out from the hydra immediately succumbed to the replication of the *Hydra virilis* dsDNA chlorella virus 1, 2 and 3 (HVCV). The virus proved to be lytic to the algal cells taken from the hydra, but not to the hydra cells. Thin section of hydra cells viewed in transmission electron microscopy failed to show viral particles. These original observations remain cited in the literature of better technology; recent metagenomic studies reveal the widely spread presence of herpes-like viral agents in cnidarians, especially in *Porites* corals, but also including *Hydra* and *Nematostella*. Viral particles invade cells of the hosts and the cells of their symbiotic zoochlorellae and zooxantellae (9). The symbiotic life style and the virology of zooxantella *Symbiodinia* algae have been discussed (10). Proteobacteria and Bacteriodetes and their phages colonize various species of *Hydra*. *Myoviridae* and *Podoviridae* Burkholderia; *Siphoviridae* Staphylococcus; and *Herpesviridae* and *Phycodnaviridae* make up the microbiome flora of the holobiont (11).

The genomes of *Hydra magnipapillata* and *Nematostella vectensis* do not tolerate these symbiotic relationships, thus, reject the potential symbionts (10,11). Maltose-producing...
algae gained protection against cnidarian host cell lysosomes. Intolerant (symbiosis-free) host cells mobilized the ancient MAMP-PRR interaction (microbe-associated molecular pattern; pattern recognition receptor) (10). In this interaction, host cells release lectins that bind cell surface glycans (galactose; mannose) of the invaders.

Proto-oncogene predecessor NF-κB. The activation of NF-κB is ancestrally TLR Toll-like receptors-mediated (4). By its RHd (reticuloendothelial viral antigen homology domain), the two alleles Nv-NF-κB proteins bind their target-dNA. The consensus sequence of the dNA recognition loop has either cysteine or serine at position 6, and the serine variants are the more potent activators. All other (including human) 440 aa NF-κB proteins have cysteine in position six in the consensus (except for one of drosophila’s four RHd proteins; there, the Relish RHD has serine). The choanoflagellates (Monosiga) do not encode RHd proteins, but the Amphimedon demosponge possesses one, thus, predating the appearance of numerous RHds after the triploblast divergence. The human genome encodes twenty RHd proteins. Some human RHd proteins may also undergo a Cys-to-Ser mutation (12,13). Both in the cnidarian and in the human RHd, serine in position six results in increased transactivational potency. It would be interesting

Figure 2. A collection of pathways operational in the human genome/proteome, which have taken their origins in primordial unicellular and early multicellular organisms. The WNT/β-catenin pathway shown in the right upper corner and the NF-κB/STAT pathway in the left upper corner is very active in the cnidarians and ctenophores, respectively. Both pathways physiological at the time of their ancestry, but function as transforming proto-oncogenes in the human genome. Other pathways are referred to in the Text. The copyright holder Creative Common Attribution-Share Alike 3.0 Unported licence granted permission for the reproduction of this document under the terms GNU Free Documentation License.

Figure 3. The ctenophore sea walnut Mnemiopsis leidyi from the New England Aquarium, Boston, MA, by Steven G. Johnson. Wikimedia Commons freely licensed media file repository. Creative Common Attribution Share Alike 3.0 License. GNU Free Documentation License Version 1.2. The ctenophore genome’s WNT pathway is physiologically defective in that, its cytoplasmic ‘β-catenin destructive pathway’ allows the transfer of β-catenin into the nucleus for the activation of the promoters of cell cycle-dependent kinase genes, and lacks their natural inhibitors Dickkopf, that are to be acquired later in evolution.
to know, if resting cells operate cysteins, vs. constitutively activated cells (including the so-called malignant transformed cells), serins, in the DNA recognizing consensus loops of their NF-κB RHDs. Ancestral ADAM (A disintegrin and metalloproteinase) exists in cnidarians; STATs, TNFα (tumor necrosis factor), and its signaling proteins, SOD and anti-apoptotic Bcl-proteins (B-cell proteins) (B-cell proteins) is functional as well. In the human genome encoding the mantle cell lymphoma, it will be ADAM that activates the TNFα/NF-κB pathway (14) (vide infra). Promoters of intranuclear translocation of NF-κB are interleukin IL-1, Ca⁺⁺-ionophore, PMA (phorbol myristate acetate and TNFα. NF-κB-inducing kinase (NIK) and the inhibitor of apoptosis (IAP) are antagonistic to each other (15-17). The cytoplasmic IkB kinase phosphorylates IkBα, thus initiating its ubiquitination, that leads to the release of NF-κB. The dominant form of the NF-κB family is its p50/p65 heterodimer, which is acetylated. Deacetylase inhibitors (trichostatin) initiate and potentiate the activation of NF-κB by TNFα, including its intranuclear entry and attachment to its numerous pro-inflammatory DNA targets. Among the NF-κB targets is the gene of its own inhibitor IkBα. The cytoplasmic IkB kinase product protein enters the nucleus, binds the NF-κB proteins and leads them back neutralized into the cytoplasm. Deacetylase inhibitors delay this process and thus increase NF-κB activity. After its release from its cytoplasmic inhibitor IkB, the intranuclear translocation and mobility of the NF-κB/p50/p65 heterodimer is dependent on the acetylation of five of its lysins; four of these residues contact the targeted DNA domains. The transcriptional activity of the NF-κB p65 subunit is further regulated by phosphorylation of its various serine residues (18,19).

The Nematostella operates at least one STAT pathway in co-existence with NF-κB (20,21). The origins of the p53 pathway date back to the ancestors of choanoflagellates and cnidarians (N. vectensis) (22,23). However, the ancestral and extant choanoflagellate, choanarian and Spongiae genomes operate without an MDM (murine double minute) pathway (24). The first signs of MDM protein appear in the placozoan Trichoplax adhaerens and in the sea squirt C. intestinalis (25). Since the placozoan T. adhaerens possesses the anti-apoptotic MDM protein (25), presumably cnidarians (N. vectensis) also have it, but no proof was found (23). Choanoflagellates (Monosiga) and spongiae (Amphimedon) are devoid of mdm/MDM possessions (24).

Cnidaria-related proto-oncogene NF-κB/STAT in the human genome. NF-κB is TCR/TNFα- (T cell receptor), IL-1β-, or mitochondrial stress-induced; calcineurin forces the release of NF-κB from inhibitor IkBα (26,27).

In the cellular transformation process, loss-of-function-mutated ikbα/IkBα (inhibitory/inducing kappaB kinase) permanently releases the NF-κB molecule. In Reed-Sternberg (RS) cells of Hodgkin's lymphoma, among others, the constitutively activated NF-κB gene/protein targets the promoter DNAs of STAT5α, chemokine receptor CCR7, cyclin D2, and inhibitors of apoptosis c-IAP2 and Bcl-xL (B cell lymphoma extra large). Interleukins (IL-13 and IL-15), macrophage-derived chemokines, and cytokines induced by NF-κB in the RS cells invoke the extraordinary cellular infiltrates which surround the RS cells (28). In the human lymphoma cell line YT, STAT3 and STAT5 are the promoters of the malignant transformation; the tyrosine- and serine-phosphorylated STAT3 is constitutively activated, but both STATs are anti-apoptotic. Neither the jak1, 2, 3/JAK (Janus kinase), nor IL-2 are drivers of STAT3, even though STAT3 expresses domains for IL-2 binding. Antisense STAT3 and STAT5 blockade induced apoptosis. IL-2 could rescue the lymphoma cells from apoptotic death consequential of STAT3 blockade, but not in case of STAT5 blockade. STAT5 depletion resulted in reduced NF-κB and TNFα activity. Helenalin, the inhibitor of DNA-binding by NF-κB, induced lymphoma YT cell death. The YT lymphoma cells resisted the blockade of the IL-2-induced pathways MAPK, PI3K, mTOR (mitogen activated protein kinase; phosphatidyl inositol kinase 3; mammalian target of rapamycin) (29). Common promoters of NF-κB-induced diffuse large B-cell lymphomagenesis are the B cell activation factor (BAF), constitutively expressed B-lymphocyte stimulator (BLyS), autochthonous B-lymphocyte stimulator ligand, and the NF-κB-inducing kinase, accompanied by the degradation of the TNF-R-associated factor (30,31). The EZH2-mediated (enhancer zeste homolog histone 3 lysine methyltransferase, Drosophila), hotspot-mutated, NF-κB-induced, mediastinal diffuse large B cell lymphomas are rare, but highly malignant (32).

In human lymphoid cells undergoing malignant transformation (RS cells of Hodgkin's disease, mediastinal diffuse large B cell malignant lymphoma, certainly; mucosa-associated lymphoid tissue MALT lymphoma, multiple myeloma, mycosis fungoides, probably), the classical NF-κB pathway undergoes amplification, or gain-of-function mutation, resulting in constitutive expression of the molecule. NF-κB remains frequently co-activated with STATs. In these entities, amplification of the NF-κB pathway is encoded by the Rel locus at 2p14-15 (reticuloendotheliosis viral oncogene homolog). TNFα phosphorylates serine Ser-471 in c-Rel for the activation of NF-κB (33-36). The activation of NF-κB in T cells is initiated by p65/RelA through triggering TCR/CD3 (cluster of differentiation) and completed by TNFα, secreted either autocrine or paracrine. TNFα induces the degradation of IkB kinase and activates the wild-type c-Rel by phosphorylation of its Ser-471. This stimulation of TNFα to activate NF-κB cannot occur in Burkitt's lymphoma T cell lines (Jurkat) with mutated Ser-471 (S471N, asparagine replacing serine) (15). In diffuse large B-cell lymphoma, NF-κB is constitutively activated by an NF-κB-inducing kinase; in addition, BAF is also constitutively expressed (but no attention was turned toward STAT) (37).

Furthermore, translocations and fusions of NIK (NF-κB-inducing kinase) and NF-κB1, two genes and gene-product proteins occur with the involvement of apoptosis inhibitor IAP (another hallmark of malignant transformation) (16,17). In evolutionarily more advanced cells (taken from mice or humans), mitochondria to nucleus stress-signaling activates NF-κB/Rel. Calcineurin-mediated inactivation by dephosphorylation of IκBαB leads to the release of NF-κB (26,27). However, the metazoan mitochondria had the time to develop genetic variations after the divergence of advanced triploblastic metazoa from the ancestral lineage of cnidarians (38,39). In the cytoplasm, the IκB/NF-κB complex is heat-labile and can be disrupted by HSP, thus, liberating NF-κB. In the nucleus,
NF-κB can target and induce the transcription of the IκB-genes (among others). The newly synthesized IκB protein can bind intranuclear DNA-bound NF-κB, and remove it from its bond. Exportin proteins return NF-κB from nucleus to cytoplasm. This interplay was observed in HIV-1-infected cells, and in HeLa cells (40). The Rel protein (reticuloendothelial viral antigen) homology domain (RHD) of NvNF-κB is 50% identical with the human p50/p52 Rel homology domain (RHD) proteins. Both the cnidian and the human NF-κB proteins interact with the Bcl-3 (B cell lymphoma; cell cycle; anti-apoptosis) and c-Myc proteins (12,13) (vide infra).

The ancient combined TNFα, STAT and NF-κB pathways recur in the pathogenesis of human malignant lymphoma. Phosphorylation of human cytoplasmic inhibitory IκB releases NF-κB for its intranuclear transfer. In the nucleus, the NF-κB/RHD complex activates directly or indirectly some of its 140 DNA targets, including proinflammatory interleukins (IL-1, -2 and -6). Point-mutated codon S525P serine to proline human pro-inflammatory microRNA-155 cluster carries a NF-κB responsive site. The miR-155 promoter is a target gene for the NF-κB/Rel family members (vide supra)(42). Physiologically, miR-155 positively regulates the immune response of CD8+ T cells (43). The promoter of the human pro-inflammatory microRNA-155 cluster carries a NF-κB p50/p65 responsive site. The miR-155 promoter is a target gene for the NF-κB protein. Activation of miR-155 (by NF-κB) is essential for optimal CD8+ immune response (42,43). In the human cutaneous T cell lymphoma mycosis fungoides, miR-155 suppresses STAT4 expression by targeting its mRNA for its neutralization, and thus canceling the Th1 NRF-kB/STAT acti

NF-κB/STAT/P13K proto-oncogenes in virus-carrier human cells. In the human genome the NF-κB/STAT association is prominently active in infectious processes, and in the malignant transformation of selected cells. STAT4 and NF-κB (p65) were expressed highly in tuberculoid leprosy, according to immune reactions induced by interferon-γ (46). N. vectensis is not known to possess IFNγ (3), but as a predecessor of the system to come, it expresses alternatively spliced mRNAs to bind tRNAs and GAIT element RNAs (interferon-γ-activated inhibitor of translation) (47).

As a distant upward derivative of the viral-carrier N. vectensis genome (vide supra), retrovirally and herpesviral infected human mesenchymal cells frequently express NF-κB/STAT/P13K (phosphatidyl inositol kinase) co-existing pathways, often constitutively and in cells malignantly transformed. In RS cells, STATs and NF-κB co-exist. STATs act in antagonistic terms: STAT6 anti-, and STAT1 pro-apoptotically. RS cells operate constitutively activated JAK/STAT pathways; the DNA-binding STAT proteins entering from the cytoplasm to the nucleus, activate their targets for the malignant transformation of the cell (here, not by the stimulation of the cell cycle, since RS cells are known for long periods of rest) (48,49). It

is the gene bcl-3 (B-cell lymphoma) at chromosome 19q13, which encodes elements IκB of the NF-κB pathway. The IκB molecules form complexes with the five NF-κB/Rel family member proteins in the cytoplasm. Degraded IκB molecules release NF-κB proteins for their translocation into the nucleus, in order to accomplish their DNA-bindings. Aberrant Bcl-3 protein constitutively releases an excess of NF-κB proteins for intranuclear transfer, where they bind the promoters of their target genes, which encode chemokines, cytokines and their receptors; anti-apoptotic molecules and various transcription factors, including persistently activated STATs (50). Viral DNA (herpesviral, HHV4, HHV6 and HHV8) (51-55), and RNA (retroviral, HIV; HTLV-I) (56) infections can force the cytoplasmic IκB inhibitors for the release of NF-κB molecules. In particular, open reading frame ORF-1 (referred to as disease-related DR7) of the extent HHV6 encodes a p53-binding protein, which renders it anti-apoptotic. In RS cells, DR7B is an oncoprotein; it downregulates p53 and activates NF-κB (54). The herpesvirus-carrier N. vectensis does not operate a pro-apoptotic p53, but has its ancestral predeces-sors, p63/p73 (23). In the human genome, p53 eliminates mutated cells by apoptosis. In the process of malignant transformation, it is acting as a tumor suppressor gene, unless, the cell eliminates the MDM-bound p53 protein by ubiquitination (vide supra).

The genomes of herpesvirally infected human cells (HHV4, EBV; HHV8, KSHV) readily respond with NF-κB/STAT activation (51,52,55,56). Human malignant cells transformed by circular dsDNA papillomaviral genomes resist apoptosis, gain immortality (the HeLa cells), and chemo-radiation resistance (58). Could the DNA virom-carrier Hydra and Nematostella cells be driven by constitutively activated NF-κB/STAT pathways, thus, resembling cells in the process of malignant transformation higher up on the evolutionary scale?

NF-κB/STAT-inhibitors. Dexamethasone, pyrididine dithiocarbamate, BAY-11-7082; the sponge-derivative marine natural product microsclerodermin inhibit or alter the excretions of inflammatory chemokines (CXCL8/10) and interleukins (IL-1β, IL-6 and IL-8), but have not been enlisted as effective anticancer agents (59-61). Anti-NF-κB RNA-aptamers (specifically target-binding short ss nucleotides) and siRNAs are powerful NF-κB inhibitors (62), not yet in clinical use. In gram-negative septic shock, lipopolysaccharide endotoxins degrade IκBβ and liberate NF-κB, which may induce an interleukin (IL-1β, IL-6 and IL-12p) storm (63). In gram-positive septic shock lipoteichoic acid LTA, activates toll-like receptor TLR2, which induces the proto-oncogene cascade of Raf/MEK/ERK/NF-κB. LTA promotes the transfer of NF-κB from cytoplasm to nuclei; this is inhibited by propofol (64). The sesquiterpene lactone partenolide inhibits NF-κB by alkylating p65 at Cys (65). Synthetic epoxyquinone A monomer is a potent inhibitor of NF-κB resulting in the cessation of growth of human lymphoma cells (66,67). The NF-κB inhibitor partenolide induced apoptotic death of p31 ras- and P13K/Akt-driven malignantly transformed cells (rat sarcoma oncogene; phosphatidylinositol-3 kinase; AK mouse thymic lymphoma retroviral oncogene). This effect was mediated by downregulation of the inhibitor of apoptosis IAP2, and degradation of polyadenosine-diphosphate-ribosyl-
transf erase (PARP). In p210 BCR/ABL-transformed cells (breakpoint cluster region; Abelson mouse retroviral oncogene), parthenolide treatment failed to induce apoptotic deaths due to antagonism by STAT5 and BCL-xL activation (B cell lymphoma extra large) (32). Under natural circumstances (in the cell) siRNA and RNA aptamers (specific target-binding nucleotide or peptide biomolecules) disable NF-κB mRNAs. In the RNA-induced silencing complex (RISC), helicases unwind the dsRNA molecules, thus, the antisense RNA strand can align with the receptive UTR (untranslated) domain of the mRNA strand and neutralize it (62). In contrast, O-linked N-acetylglycosamine by glycolysation (oligosaccharide; N-terminal) post-translationally activates the NF-κB molecule by acetylating its serine 350. Interacting are TCR and TNFα in encoding NF-κB target gene IkBo. TCR and TNFα may activate NF-κB with or without O-GlcNAcylation (OGT, O-linked GlcNAc transferase; N-glucoseamine acetyl) (68). The Cys-to-Ser mutated human NF-κB RHDs are not only gaining translational activity, they become resistant to their natural inhibitors sesquiterpenes and possibly to cures (vide supra). The post-translationally functioning nucleo-cytoplasmic protein for O-GlcNAcylation first appeared in prokaryota, and remained functional in the low-branching Giardia and in the placozoan Trichoplax adhaerens (69), cultured and fed by red alga Rhodomonas salina. The ancient system O-GlcNAcylation was discovered in the Drosophila (70), but it must have been present at the beginning of cellular life and remains active in every cell. It is overexpressed in mitotic cells. Further physiological blockade of NF-κB is brought about by the p53-neutralizing protein, ubiquitin ligase MDM2 directed at p65Rel (71).

Helicobacter pylori activates in gastric epithelial cells the expression of IL-8, Jak1/STAT and NF-κB (72). In the targeted cells several ligands bind their receptors, as shown in Fig. 1 of the cited article (20). The physiological inhibitor of the Jak/STAT pathways is SOCS (suppressor of cytokine signaling). The ancestral Jak proteins appear in the invertebrate H. symbiolongicarpus (42). In H. symbiolongicarpus (42), and its reappearance during regeneration. This study shows that the hydra Kazal(-) phenotype mimics autophagic mammalian pancreatic cells with non-functional trypsinogen-inhibitor SPINK1/3 (citing the literature on the mouse experiments). The pancreas upregulates SPINK3 expression in the gland regenerating after injury (82-84). The ancient serine protease inhibitor (SPINK, Kazal type 1) reappears in the fluid contents aspirated from human pancreatic cysts; these aspirates are analyzed for carcinoembryonic antigens CEA and CA 19-9, but it is the high SPINK content that indicates the

**Autophagy.** Under stress, Saccharomyces and Dictyostelia assume an autophagic stage of existence. Autophagy has become an evolutionarily conserved process extended to every eukaryotic species. Its potential reversal indicates that autophagy is not a self-destructive process, but it is a homeostatic phase in cellular life (75). Mitochondrial autophagy (mitophagy) (76) indicates that the origin of the process predated the appearance eukaryotes. The wild hydra may live in a steady stage of autophagy and eventually recover. The mTOR inhibitor rapamycin induces, wortmannin and bafilomycin inhibit autophagy. In the hydra during starvation for weeks, myoepithelial cells form autophagic vacuoles. Endodermal digestive cells with knocked-out Kazal gene (serine peptidase inhibitor Kazal, SPINK, *vide infra*) die, whereas ectodermal epithelial cells survive in autophagy (77,78). Break-down of the symbiotic relationship between host cnidarian and symbiont dinoflagellate alga leads to autophagy and apoptotic death of the host. Drastic environmental changes (temperature; ultraviolet light; reactive oxygen species, ROS; loss of antioxidant defenses; water pH changes; microbial invaders; combination of unknown factors) induce the process. The process could be induced by the TOR inhibitor rapamycin (target of rapamycin). Hyperthermic-stressed (HTS) anemones released larger number of symbionts than subjects kept on termed control temperature (CT); however, exposure to rapamycin induced symbiont release in CT anemones. It was either autophagy or apoptosis that dominated, and possibly spingosine kinase and PI3K signaling regulated a see-saw relationship between the two outcomes (79). Alloreactivity after transitory fusion of hydractinia (H. symbiolongicarpus) colonies with minor incompatibilities is another cause of irreversible autophagy terminating not in apoptosis, but in necrosis (observe electron microscopic pictures in the cited article) (80).

The Wnt pathway remains dominant for the regeneration of a new head in the decapitated hydra (81). The enzyme Kazal (*vide supra*) in the hydra prevents autophagy and promotes self-preservation; after amputation, it encodes de-differentiation and transdifferentiation, blastemal transition, and activates the ontogenic organizer pathways, for example those of the head regeneration. View color pictures of Hydra proteomics (metalloproteinases, thrombospondin, tubulin network, mitochondria, and Kazal type 1 enzyme expression: its disappearance in autophagic cells after its dsRNA knock-out (by feeding, and its reappearance during regeneration. This study shows that the hydra Kazal(-) phenotype mimics autophagic mammalian pancreatic cells with non-functional trypsinogen-inhibitor SPINK1/3 (citing the literature on the mouse experiments). The pancreas upregulates SPINK3 expression in the gland regenerating after injury (82-84). The ancient serine protease inhibitor (SPINK, Kazal type 1) reappears in the fluid contents aspirated from human pancreatic cysts; these aspirates are analyzed for carcinoembryonic antigens CEA and CA 19-9, but it is the high SPINK content that indicates the
presence of malignant transformation (it is to be differentiated from chronic pancreatitis by biopsy) (85). The Kazal type 1 serine protease inhibitor SPINK1 gene is subject to point-mutations N34S and P55S (asparagine, proline and serine) in patients with chronic pancreatitis, but not in healthy controls (86). The SPINK1 N34S mutation is considered to be a high risk factor for cancer, especially when increased numbers of pancreatic stellate cells (PSC) co-exist; PSC release proliferation and colony formation inducing molecular mediators to the parenchymal or ductal cells (87).

3. The primordial cell survival pathways become proto-oncogenes

Proto-oncogenes ascend to the human genome. In the human genome, all these cnidarian genes and gene-product proteins can function as proto-oncogenes, oncoproteins.

SPARC. The primordial SPARC glycoproteins (secreted protein acidic rich in cystein) forms the mesoglea in between the ectoderm and endoderm of the diploblast cnidarians. In N. vectensis, the Ca++-binding glutamic acid-rich acidic domain at its N terminus is absent. Even in the absence of frank mesenchyme, N. vectensis operates the primordial winged helix transcription factor forkhead/and zink finger transcription factor snail gene-product proteins. Snail formats the endodermal cells from invaginating ectodermal cells (88). The N. vectensis larva practices the evolutionarily conserved epithelial-to-mesenchymal transition (89). SPARC proteins in advanced multicellular vertebrate eukaryotes (including human cells) are encoded by the genes snail and act as major contributors to epithelial-to-mesenchymal transition of invasive cancer cells-in-lacomotion; co-activated are the ligands and receptors of TGFβ and ERK kinase (extracellular signal-regulated kinase), while miR-29b acts as an inhibitor of the process (90). Prominent examples are non-small cell lung cancer and pancreatic and breast cancers expressing melanoma antigen Mage (91-93).

RUNX. The runt-related Runx transcriptional regulatory factors bind the CAAT box (Runx/core binding factor CBFβ genes) which appeared even before the cnidarians and sponges and continued to evolve in triploblasts and bilateralia. In the figures of the cited article (94), the ancestral eukaryotic protists appearing first 987 mya are compared with the cnidarians (Anthozoa and Hydrozoa) and sponges (Porifera), appearing first 867 mya. The study presents the genes as boxes connected with introns as lines and gives the exon-products in amino acid numbers. These are 35-284 for the Nematostella and 35-219 for the Hydra. Depictions of the groucho-binding motif and the runt domain (RD) are given. Nucleotides 56-434 are shown with digoxygenin labeling. DNA and protein bindings are shown in three dimensions. The NvCBFβ protein is in 59% identical and in 79% similar to the HsCBFβ protein. The sponge AqCBFβ protein in 54% identical with the HsCBFβ, and in 47% identical with the NcCBFβ proteins. As 'packages of stem cells', cnidarians and sponges are able to regenerate from single cells of adult hosts (the archaeocytes of the sponges), including the regeneration of the nerve cells (94). (Further referenced in 7).

The ancestral Runx-CBFβ-DNA complex remained evolutionarily conserved in advanced vertebrate hosts including Homo. In the human genome, runx/RUNX may promote, induce, or obliterate target genes as a multifunctional transcription factor. The expression of FoxP3 in Treg cells is susceptible to suppression by the Runxl/CFβ transcription complex (95). In the human host, CBF-leukemias arise due to inv(16) (p13.1q22) or t(8;21)(q22;q22) involving the NF-κβ family kit (tyrosine kinase receptor) gene (96). The Runx1 gene (of the Runx family Runx1, 2, 3, same as AML1, acute myelogenous leukemia) forms fusion product with CBFβ. Further fusion of the amino terminus of AML1 with MLL (mixed linkage leukemias), carrier of histone methyltransferase activity at its C-terminus, SET (suppressor of variegation, Su/vari enhancer of zeste; trithorax, Drosophila) maintains lysine 4 (K) trimethylation of histone 3 (H3K4me3) in the AML1 target gene PU1 (same as Spi, spleen forming-retroivirus proviral integration oncogene). The ternary complex consisting of RUNX1/AML1, CBFβ and MLL regulates hematopoiesis, but when mutated and constitutively expressed, it induces leukemogenesis (AML or B-ALL) (97). The fusion oncogene EWS/FL1 t(11p22;q24) (Ewing's sarcoma; Fos-like immunoreactivity; Finkel osteosarcoma retroviral oncogene; Friend leukemia insertion; here: Friend leukemia insertion at 11q24.3) binds RUNX2 and prevents its action. Runx3 protein promoted oncoprotein EWS/FL1-stimulated target gene responses, and Runx2 and transcriptional co-activator core binding factor β (CBFβ) promote invasiveness (98). Runx2 and bone morphogenetic protein (BMP, member of TGFβ family) upregulated snail-induced lung cancer cell migration and epithelial-to-mesenchymal transition (99). The RUNX3 promoter in inv(16)(p13.1q22) acute myelogenous and lymphocytic leukemias (AML; ALL) is hypermethylated with adverse prognosis. In contrast, non-inv(16)(p13.1q22) and not hypermethylated leukemic patients experienced relapse-free survival. Demethylator decitabine restored RUNX3 mRNA and protein levels with expectation of improved prognosis (100). In the human embryo, the runx/Runx proteins work in hematopoiesis (R1), osteogenesis (R2) and neurogenesis (R3). Gene/protein runx2/RUNX2 is very active in embryonic life in regulating endochondral ossification. Metastatic osteosarcoma with amplified region 6p12-p27, the locus of runx2, remains a lethal tumor; this locus operates two promoters, which constitutively release high mRNA levels of the large DNA-binding protein RUNX2. Directly and by cascading targeted major genes are IGF, BMP, P33K/Akt, TCF/LEF, FGF, iHh, Wnt (insulin-like growth factor; bone morphogenetic protein; phosphatidyl inositol kinase 3; AK mouse thymus retroviral oncogene; T-cell factor, lymphoid enhancer-binding factor, fibroblast growth factor, Indian hedgehog, wingless/integrated). Suppressed are CDK4/kip/cip; and p53 by MDM (cycline-dependent kinase; wild-type p53-activated fragment; cycline-dependent kinase interacting protein; murine double minute protein) (101). Osteosarcoma tumors readily outgrow standard chemotherapy of high dose methotrexate with leucovorine rescue; doxorubicin and ifosfamide; cisplatin. A STAT3 molecular inhibitor (S31-201) inhibited growth, and induced apoptosis of human osteosarcoma cell lines (102). The licensed multikinase inhibitor sorafenib in reduced dosage in combination with cisplatin suppressed phosphorylation of
extracellular signal-regulated kinase ERK, thus, inhibiting the growth and inducing apoptosis of human osteosarcoma cell lines (103) (see comments in Discussion). The fact that patients with chordo- and osteosarcomas generate immune T- and NK cell-mediated attacks on autologous osteosarcoma cells (104) raises high expectations that CAR cell (chimeric antigen receptor), and checkpoint inhibitor (PD-1/PD-1L) therapy might induce clinical remissions, especially when the tumor cells express NY-ESO antigens (105).

Hedgehog. The first Hog domain proteins appeared in dinoflagellate algae. The hedgehog (Hh), notch, sox and Wnt genomic pathways operational in the cnidarians remained highly conserved by the triploblastic bilaterals up to vertebrate mammalians (including Homo). The Nematostella Hh orthologs are among other cnidarian precursors (Wnt, TGFβ/BMP and FGF) of bilaterian genomic pathways. Here, the Hh ligand-receptor patched (Ptc) represses smoothed (Smo), the inhibitor of Gli (glioma). Capturing the ligand by Ptc, releases Smo, that liberates Gli (glioma-associated oncogene homolog 1). The Nematostella genome contains six genes encoding Hh ligands and receptors, and genes coordinating Wnt, Hh, TGFβ and FGF (106-108). The role of sensory cilia in Hh signaling emerged in the sea urchin (Strongylocentrotus) and was conserved up to vertebrates. The kinesin motor proteins originated in the chlamydomonas (C. reinhardtii). The choanoflagellates (Monosiga brevicollis) operate an elementary Hh pathway in expressing receptor Ptc (109). Various co-expressions of these genes guide the cell through its ontogenesis and final differentiation. The enriched mammalian genomes operate three Hh pathways (sonic, desert and indian), that evolved through gene duplication. In chronic lymphocytic leukemia, the Hh pathway enlists PI3K (110). In hepatocellular carcinoma of whatever etiology (B&C) of bilaterian genomic pathways. Here, the notch/Notch signaling pathway was functional in the embryos, larvae and planula of the Branchiostoma floridae (vide infra) and was conserved up to vertebrates. The ancient Notch cascade (vide supra) is essential for the transactivation. The process was duplicated in the ancestral cnidarians from the yeast to the human genome, where it is a notch/Notch activator (and RBPIk as a Notch effector), and as such it is overexpressed in some tumors (Kaposi sarcoma; adenocarcinomas). Co-opted by KSHV, Pin1 by direct binding, enhances the viral Rta transactivational functioning and protects Rta from auto-ubiquitylation, thus, contributing to Notch activation (view Fig. 6 of the cited article) (116). In primary effusion lymphoma cells KSHV and EBV commonly co-exist and activate the Notch signaling pathway (117). In HPV-induced squamous cell carcinomas activated Notch may be an aggravating or an alleviating factor (118). Observe: Kaposi sarcoma virologists use abbreviation vSOX for viral shut-off exonuclease, that has no connotation none whatsoever with eukaryotic stem cell proto-oncogene sox/Sox (vide infra).

The human oncogenic dsDNA viruses activate notch/Notch. Human herpesvirus 8, Kaposi sarcoma herpesvirus (HHV8; KSHV) uses the Rta protein (replication transcription activation) as its lytic switch and RBPIk (recombination signal-binding protein-1 immunoglobulin kappa J region) is essential for the transactivation. The protein-folding cellular peptyl-prolyl cis/trans isomerase, ‘never in mitosis’ (Pin1) had been conserved from the yeast to the human genome, where it is a notch/Notch activator (and RBPIk is a Notch effector), and as such it is overexpressed in some tumors (Kaposi sarcoma; adenocarcinomas). Co-opted by KSHV, Pin1 by direct binding, enhances the viral Rta transactivational functioning and protects Rta from auto-ubiquitylation, thus, contributing to Notch activation (view Fig. 6 of the cited article) (116). In primary effusion lymphoma cells KSHV and EBV commonly co-exist and activate the Notch signaling pathway (117). In HPV-induced squamous cell carcinomas activated Notch may be an aggravating or an alleviating factor (118). Observe: Kaposi sarcoma virologists use abbreviation vSOX for viral shut-off exonuclease, that has no connotation none whatsoever with eukaryotic stem cell proto-oncogene sox/Sox (vide infra).

Gamma secretase and ADAM proteases (A disintegrin and metalloprotease domain) cleave the Notch receptor; Delta and Jagged ligands activate it so, that its intracellular domain translocates into the nucleus. The ancient Notch pathway had been evolutionarily conserved. A major Notch target gene is the RBP-Jk (vide supra). NF-κB activation is mediated by protein interaction with IKKα (inhibitory kappa kinase). Notch negatively interacting with tumor suppressor protein PTEN (phosphatase tensin chromosome ten), liberates PI3K/Akt from suppression, and opening up a pathway to mTOR activation. View Fig. 1 of the cited article (119). Hypoxia is a major activator of proto-oncogene Notch in glioblastoma (vide infra).

Sox. N. vectensis utilizes the ortholog of the coral Acropora millepora's six sox/Sox pathways (sex determination region Y, SRY box). These transcription factor genes encode high mobility group proteins (HMG) functioning in a wide range of developmental processes, gastrulation; and laying down ectoderm and endoderm. The sox genes co-exist in pluripotent stem cells with stem cell genes kfl (Krüppel factor-like); oct (octamer), c-myc (myelocytosis) and Nanog (rejuvenating celtic tribe). The Sox8 stem cells of N. vectensis are positioned interstitially and encode three neural cell types: sensory neurons, ganglion neurons and nematocytes. Sox and Fox (forkhead box) genes cooperate in N. vectensis in germ layer specification and in the regulation of gastrulation (120-123).

The stem cell promoter proto-oncogene sox/Sox family members (SRY-related sex-determining factor on Y chromosome high mobility group box) are ancient transcription factors which exist in a family of over twenty proteins in the human genome/proteome. The Sox proteins functionally sustain stem cell pluripotentialities and act as generators of tissue anlagen.
in embryonic life, and as proto-oncogenes/ oncogenes (example Sox2/9) or tumor suppressor genes (example Sox7/15), or alternatingly both (example Sox2/4/9) in adult life. Some Sox proteins (Sox9/21) activate the oncogenic pathways Wnt; Gli; Hh; Notch. Sox15/20 inhibit the Wnt pathway in pancreatic and other (testicular) cancer cells by dimerising with other oncproteins (124).

Wnt. Unicellular eukaryotes do not operate the Wnt pathway. The Wnt pathway (wingless; Drosophila; integrated, mouse) in the ontogenesis of Ciona intestinalis was recently reviewed (125). Cnidarians and ctenophores in their ontogenesis utilize the Wnt pathway. Wnt ligands are secreted glycoproteins specific to their transmembrane receptors frizzled that trigger the β-catenin cascade by first liberating the β-catenin destroying unit from the control of disheveled. The β-catenin destruction unit consisting of proteins axin, glycogen synthase kinase (GSK) and an ancestral adenomatosis polyposis coli gene product in the cytoplasm is able to phosphorylate β-catenin, thus, marking it for ubiquitination. The cell rests. However, if unphosphorylated β-catenin is allowed to accumulate, it will translocate from the cytoplasm to the nucleus. There, it will by domain-attachment activate its target genes. Of numerous β-catenin target genes, genes tcfTCF/lefLEF are activated first (T cell factor; lymphocyte enhancing factor). (Evolutionarily reviewed and extensively referenced in ref. 126,127).

Hh/Wnt. The hedgehog pathway is active in several human cancers and is potentially susceptible to small molecular inhibitors. Vismodegib induces remissions in advanced basal cell carcinoma due to inhibiting the Hh receptor smoothened (128). The antifungal itraconazole inhibits chemotherapy-resistant pancreatic adenocarcinoma cells (129). Natural products (cyclopamine, curcumin, epigallocatechin-3-gallate, genistein, norcantharidin, resveratrol and zerumbone) exert blockade in the sonic Hh pathway (130). The STAT/NF-κB pathway is suppressed by curcumin and epigallocatechin gallate (131). The basic nature of malignant transformation is to advance in several pathways, thus, rendering monotherapy often ineffective. The Hh/Gli and the Wnt/β-catenin pathways appear in combination (132). The sponge Amphimedon releases the antifungal cyclic peptide microscleroderm (61). NF-κB is constitutively activated in pancreatic adenocarcinoma cells. Microscleroderm block NF-κB production in pancreatic adenocarcinoma cells and forced cell death in the form of apoptosis (61). In the Wnt pathway, β-catenin and DNA methyltransferase (DNMT) co-localize in tumor cell nuclei. Lysine-specific demethylase (LSD), the regulator of DNMT, becomes a component of the complex. The DNMTs usually hypermethylate CpG islands and LSDs demethylate histones. The complex represses tumor suppressor genes and activate oncogenes (133).

CYPs. Cytochrome oxygenizers are expressed by the ligand-activated AhRs. CYP1 family proteins are overexpressed in ER+ human breast cancer cells. Considered to be co-carcinogens (breast cancer) due to their positive involvement in estrogen metabolism, production of procarcinogenic estrogen metabolites and induction of nucleotide polymorphism (134,135).

ASC. Ernst Haeckel's works from 1876 are recently cited for placing the amphioxus (represented by the Branchiostoma floridae) (Fig. 4), at the base of vertebrate evolution (136). The amphioxus without duplicating its genome preserved the body image of its ancestors living 550 mya. It is not only being a cephalocordate that makes it unique. It has developed a large repertoire of TLRs, retained a large supply of transposable elements, and acquired the most ancient transposable elements of the adaptive immune system of vertebrate mammals, one of the recombination activating genes, the RAG transposon (reviewed in ref. 137). The achaete scute (ASC, Drosophila) neurogenic pathway has taken its beginning in the Nematostella and reached an advanced stage in the amphioxus represented by the Branchiostoma floridae (112,113). The human homolog of achaete scute encodes esthesioneuroblastoma, the malignant tumor of the olfactory ganglion, and converts adenocarcinoma cells into radiochemotherapy-resistant neuroectodermal
cancers (138,139). The neuroectodermal small cell broncho-
genetic carcinoma was treated long ago with cyclophosphamide,
vincristine and doxorubicin. Short lasting remissions were
induced at the price of toxicity; all remissions were lost to
relapses. Immunosimulation with BCG (Bacille Calmette-
Gurén) failed to improve results (140). Cisplatin improved
remission rates, exerted toxicity, but failed to cure the disease.
Targeting the causative oncogene/oncoprotein hASH with
small molecular inhibitors and monoclonal antibodies raises
the possibility to cure (141).

MicroRNAs exert post-translational control. The genomics
and proteomics of the cnidaria cell enable it to practice siRNA
inhibition of the NF-κB mRNA, and O-linked glycosylation of
the NF-κB protein molecule (vide supra), but all the target
molecules thus diminished or overexpressed have not as yet
been reported or even identified. In clinical medical oncology,
naturally occurring and synthesized molecular inhibitors are
applied for treatment (and encounter strong resistance by the
NF-κB/STAT-transformed cancer cells) (59,60).

The non-protein-coding RNAs (micro miRNAs; small
interfering siRNAs; piwi-interacting piRNAs) exist and
function in all eukaryotic cells primarily in post-transla-
tional downregulation of mRNA expression. Drosha, Dicer
and Ago-piwi (argonaute; P-element-induced wimpy testis,
Drosophila) RNase, helicase and RNA polymerase enzymes
carry out the specific alignment and degradation of the
targeted mRNA molecules (142). Of the oldest miRs, only
one, the miR-100 possessed by the cnidarian, *N. vectensis*,
was passed through evolution to the human genome. Others,
miR let-7 (the ancestor of the let family miRs), appeared in
the first true bilaterians, the annelid Platynereis. Its
antagonist Lin-28 expressed itself in the nematodes
*Caenorhabditis elegans* (143-146). All other genuine miRs the
cnidarians preserved for themselves, and the descendant
organisms generated their own new miRs. So much so, that
the Hydra does not have miR-100. The hydra PIWI protein/
piRNA association represses transposon expressions that
might threaten genomic integrity (147,148).

In the human genome, the major effect of miR-100 is
tumor growth suppression. In colon cancer, downregulation
of miR-100 results in accelerated tumor cell growth (149,150).
The epithelial-to-mesenchymal transition of tumor cells
(breast cancer) is an adverse prognostic event, except when
it is induced by miR-100, in which case cessation of tumor
cell growth follows (151). Uregulated expression of miR-100
attenuates glioma cell growth due to decreased expression of
ATM (ataxia telangiectasia mutated) (152). In urothelial
cancer of the urinary bladder, miR-100 suppressed oncogenes
of ATM (ataxia telangiectasia mutated) (152). In urothelial
cancer cells (155). In HeLa cells, an antagonism exists between the
p53 and NF-κB proteins, in which the former blocks the latter
in its intranuclear binding to the upstream sequence of the
miR-100 gene (156). The presence of some of these elements
in *N. vectensis* (miR-100), allows the presumption, that the
entire human reaction originated in, and was inherited from,
the cnidarian.

The miR let-7 and Lin28 antagonist-collaborator did not
exist in the cnidarians; it was acquired and expanded to a family
in the first true bilaterians and their successors, exhibiting itself
in full in the nematode *Caenorhabditis elegans* (146), from
where it continues its competition-collaboration in the human
genome (157). There, it determines if chronic inflammatory
processes will eventually terminate in oncogenesis (158). The
oncogenic cascade is initiated by src/SCR, Lin-28 and IL-6;
let-7 is depleted; STAT3 and NF-κB are co-activated and the
process becomes irreversible (159).

See images of cnidarian pyruvate dehydrogenase kinase
and hypoxia inducible factor in the internet (or in the original
literature). The presence of STAT/NF-κB and STK, the src-
type kinase, in the cnidarian cytoplasm (160) enables cells to
live in the state that is recognized in the mammalian host as
a chronic inflammatory process (the inflammasome) (158). Observe miRNAs regulating the relationship between host
(scleratinian corals) and the Red Sea-isolate symbiont alga
(Symbiodinium microadriaticum) forming a holobiont (161)
(viral involvements received no comments in the study).

4. Ctenophores

Genomic proteomics of basal metazoans. At the stage
of baseline diploblastic metazoans, beneath Cnidarians
and *Spongiae* (162-164) lie the Placozoans, represented
by *Trichoplax adhaerens* (165,166), and the comb jelly
Ctenophores, here by *Mnemiopsis leidyi* and *Pleurobrachia
piles/bachei* (167). These ctenophores are best characterized
by missing genes, which are prominently present in other
diploblastic metazoans. Ctenophores are devoid of Toll-like
receptors and MyD88 signals. Hedgehogs and JAK/STATs are
absent, but the numbers of homeodomain genes are in excess
of other diploblasts. Acetylcholine, adrenaline, dopamine,
histamine and serotonin are missing. Glutamate is a major
signal molecule; it induces action potentials and currents.
G-protein coupled neuropeptide receptors exist (without
neurons). Ion channels carry stimuli. DNA methylation and
demethylation are practiced. Argonaute units with dicer are
functional in the cytoplasm (167). The non-duplicated placo-
zoan and cnidarian genomes carry the ancestral P450 cyp/
CYP sequences; so do the *Spongiae* (Amphimedon) (168).
The unicellular choanoflagellates (Monosiga) do not show
the presence of Runx genes/proteins. Single Runt domain
Runx gene-product proteins are present in the placozoan
Trichoplax, in the cnidarians and *Spongiae* (Amphimedon).
While the *Amphimedon* genome encodes a Groucho protein,
its Runx protein is devoid of the Groucho recruitment motif
amino acid sequence WRPY (tryptophan; arginine; proline;
tyrosine). Figs. 1 and 3 of the cited article (169) show that
all the other listed organisms encoded this motif. The larva
of the sea anemone *Edwardsiella lineata* parasitizes the
ctenophore *M. laidyi*. The *Edwardsiella* NF-κB is ancestral
The ctenophore Wnt pathway imitates malignant transformation. Referenced in the Appendix of the volume in print (7), the ctenophore genome is shown encoding glycoprotein hormones (without glands), bone morphogenetic protein (BMP, without bones), platelet-derived growth factor (without platelets), nerve growth factor (without a nervous system), and the Wnt activator and BMP/TGFβ-inhibitor norrin. Norrin is the ligand of the leucine-rich repeat-containing G protein-coupled receptor. The ctenophore Wnt pathway acts in an upregulated state driven by ligand-bound Frizzled and lipoprotein receptor-related protein receptors, and dishevelled, that can inhibit by phosphorylation GSK-3 (glycogen synthase kinase). In the cytoplasmic ‘β-catenin destructive complex’, the active GSK-3 phosphorylates cytoplasmic β-catenin, thus sending it to ubiquitination. However, the inhibited GSK-3 allows excessive cytoplasmic accumulation of non-phosphorylated β-catenin, which translocates into the nucleus. There, it activates the promoters of its target genes, primarily tcf; tcf/lef develop into T cell factor and lymphocyte enhancing factor (without lymphocytes being in existence). In mammalian cells, TCF/LEF have become proto-oncogenes/oncoproteins. There, the target genes of the TCF/LEF proteins are stimulatory to the cell cycle by PI3K/AKT and inhibitory to apoptosis by survivin (171). The complete vertebrate mammalian β-catenin destructive complex consists of GSK, axin and APC (adenomatous polyposis coli) gene product proteins. The ctenophore β-catenin destructive complex is deficient in that it is devoid of axin expression, and its GSK may act downregulated. The advanced mammalian Wnt pathway is antagonized by the tumor suppressor proteins Dickkopf (Drosophila). In Wnt carcinogenesis, the mammalian cell undergoing malignant transformation eliminates the Dickkopf genes (which suffer loss-of-function mutations). The ctenophores do not possess the Dickkopf genes. Thus, the ctenophore Wnt pathway is similar to that magnificently transformed vertebrate mammalian cells: operate: the β-catenin destructive complex is weak in antagonizing the intranuclear transfer of β-catenin, thus, β-catenin readily translocates. Furthermore, natural inhibitors of the process, the Dickkopf proteins, are non-existent (172,173).

The sox/Sox transcription factors maintain stemness of their host cells and operate by encoding high mobility group proteins. In the so-called tumor stem cells, they are active in association with other stem cell genes and proteins (Kruppel-factor; c-Myc; Nanog; Oct4) (vide infra). In the embryonic larval stage of ctenophores (Mnemiopsis; Pleurobrachia), several members of five major Sox gene groups perform essential regulatory functions for the directives of orderly ontogenesis (174). Extraordinary cell proliferations leading to deformities have not been observed. If some functions are constitutively encoded due to sox gene amplifications or gain-of-function point mutations, that has not been as yet observed. However, in mammalian cells, the sox genes (and several other stem cell genes) are known to convert into proto-oncogenes (vide infra).

Wnt and Sox oncogenesis in human cells. Within the Wnt/β-catenin oncogenic pathway in hepatocellular carcinoma cells, the mRNA of the tumor suppressor gene, Bednarek’s WWOX (double tryptophan domain oxidoreductase), is demolished in the AGO complex by miR-153, which by aligning specifically to the WWOX mRNA 3'-untranslated region (UTR), destroys it. The cell cycle inhibitory protein WWOX will not be translated. The uninhibited intracellularly transferred β-catenin binds to its target DNA gene promoters of the cell cycle (primarily to tcf/lef, vide supra) and constitutively activates them, to produce their oncoproteins TCF/LEF and others (175). WWOX plasmid induced WWOX protein expression in ovarian cancer stem cells. WWOX plasmid-treated ovarian cancer stem cells reduced, or ceased, the expression of stem cell markers as follows: CD133, CD117, ATP-binding cassette G member2 protein, Nanog, Oct4 (octamer-binding transcription factor 4) and breast cancer resistance proteins (for which specific antibody is available at Chemicon, Billerica, CA, USA; cat. no. #254515). A sign of differentiation induction was the increase of E-cadherin presentation (taking control of β-catenin at the inner cell membrane). The WWOX plasmid-treated cancer cells failed to grow in xenografts and lost their chemotherapeutic resistance. The DNA-binding WWOX protein of ancient derivation is naturally released from the mitochondria and translocates into the nucleus, where it interacts with TNF-related genes, oncogene Jun N-terminal kinase (reticuloendothelial virus 17 oncogene; in Japanese 17 is jun), being either inhibitory (to proto-oncogene jun) or promotional (to pro-apoptotic TNF and p53) (176).

In advanced multicellular organisms (including Homo), the cellular programing of twenty-some Sox gene-product SOX proteins regulate the development of hematopoietic and central nervous systems in the embryo, and sustain pluripotency in their resting stem cells. Expressing their faculties constitutively, some sox/Sox proteins (human Sox2/9) transform individual cells into immortal and independent life forms (cancer cells), which overgrow and eventually kill their multicellular host. Other sox/Sox proteins (human Sox7) undergo methylation silencing it, so they may act as tumor suppressors. Such SOX proteins bind oncoproteins β-catenin or TCF, thus neutralizing them. If the sox/Sox protein resides its cell polarity signaling, that is physiological in embryonic cells, in mature cells of a multicellular host, those cells will become metastasizing tumor cells. Tumor cells with certain downregulated sox/Sox proteins gain malignant potential, whereas tumor cells with overexpressed sox/Sox undergo attenuation (124). It is not known as yet which microRNAs influence translational expression of sox/Sox15. Many tumor-promoting or inhibitory circulating microRNAs are recognized in patients with cancer (177). Examples: miR-21 downregulating tumor suppressor PTEN (phosphatase and tensin homolog) and activating oncoprotein Akt (v-akt murine thymoma retroviral oncogene); the differentiation-inducer tumor suppressor miR let-7 (letter, lethal) are downregulated in many cancers (lethal when deleted); but SOX15 regulator miR has not been named as yet. In the early multicellular bilobular life forms (cnidarians; ctenophores), sox/Sox proteins serve in ontogenesis and in several cell survival pathways of their hosts. It appears that the ctenophore genome operates a weak β-catenin inhibitory system without inhibitors. If sox/Sox proteins sustain undifferentiated stem cells, the ctenophore genomes assume the imitation of an oncogene arising in selected individual
cells of an advanced multicellular host (including Homo). The sox/Sox2 stem cell proto-oncogene promoted self-renewal, proliferation and chemoresistance in head and neck squamous carcinoma cells (178). Chemoradiotherapy-resistant stem cells arise in hypoxic regions of glioblastoma tumors. Hypoxia inducible factors, vascular endothelial growth factor (VEGF) and erythropoietin (EPO) accumulate in these regions. The tumor cells assume stem cell characteristics and upregulate notch/Notch proteins (179). Notch activation in hypoxia may be a fundamental ancient reaction of the cells living in anaerobic environment. When this fundamental faculty is resumed in single cells of a multicellular host, it may de-differentiate them to their ancestral pluripotentiality, physicochemical resistance, and independence from the community manifesting in incessant replicatory activity.

5. Discussion

Concerning the resistance of the Hydra and the Nematostella to algal symbionts, what has not been investigated and recognized is the ability of the invader Symbiodinia cells to inactivate the NF-κB pathway of the tolerant cnidarian host cell. One should conclude, if not proven otherwise, that zoochlorellae and zooxantellae cannot overcome the defensive host cell. One should conclude, if not proven otherwise, that NF-κB and Sp1 (stimulating protein encoded from 12p12-q13.1), and thus NF-κB/Spl induce KIT overproduction. Spl inhibitor mithramycin, and NF-κB inhibitor Bay 11-7082 reduced KIT expression. Bortezomib induced Spl ubiquitination, and thus disrupted Spl/NF-κB interaction. Transactivation by the kit promoter Spl/NF-κB unison was abrogated, and thus KIT overproduction ceased. Bortezomib further inactivated oncoproteins STAT3, AKT, and ERK by appropriate serine and tyrosine phosphorylations. Codons 822- and 816-mutated KIT proteins are inhibited by imatinib and dasatinib, respectively. Furthermore, Spl was found to repress miR-29 transcription and so acted as antago-miR29, resulting in rising Spl levels; consequently, KIT was upregulated. In reverse, bortezomib, mithramycin, or Bay 11-7082 downregulated KIT and Sp1 and increased miR-29 expression. Spl and NF-κB have binding sites on the primary enhancer element of the miR-29 transcript on chromosome 7, and thus reduce miR-29 expression. In reverse, siRNA-induced knock-down of Spl and NF-κB (p65) resulted in miR-29 upregulation. Bortezomib blocked the binding of Spl/NF-κB to the miR-29 regulatory element on chromosome 7, and thus induced miR-29 production; it also reduced c-Myc expression. Bortezomib downregulated Spl/NF-κB, and upregulated miR-29b by disrupting the Spl/NF-κB/HDAC complex. The hypophosphorylated KIT protein lost its leukemogenic potency. Furthermore, Spl/NF-κB and histone deacetylases (HDAC) interact. Enrichment of HDACs and Spl/NF-κB on the miR-29 regulatory sequences occurs in concert. In effect, HDAC inhibition by its specific siRNA, or OSU-HDAC42 and MS275 resulted in upregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in downregulation of miR-29 transcription, with concurrent drop of Spl and KIT levels. Whereas HDAC expression resulted in...
expressed (184). The natural substance capsaicin is an NF-κB inhibitor (185). Several synthetic small molecular PI3K inhibitors are ready for clinical trials (186). The FDA approved the small molecular PI3K inhibitor idelalisib first for lymphoma, lymphocytic leukemia, and as an investigational agent for metastatic breast carcinoma (187). Molecular kinase inhibitory therapy for the PI3K-driven rapidly replicating cancers (breast carcinoma) is to follow. The complex oncogenome of the breast cancer cell will not be switched off by single agent monotherapy (view Fig. 2 in the cited article) (188).

While the first cellular life forms succeeded in populating the ancient Earth by using the ancestors of the extant proto-oncogenes as cell survival pathways, the small molecular inhibitors synthesized now against the human cancer oncoproteins would probably render them defenseless first; but subsequent mutations could rescue their new small subpopulations to begin replicating again. Advanced protocols of combination chemotherapy and targeted therapy readily induce remissions, that are lost to relapses. Hundreds of million years of evolution superimposed an adaptive immune system over the preserved innate immune system (reviewed in refs. 90,137). Yet, infectious diseases are eradicated not by natural herd immunity, but rather by external interventions, such as preventive vaccinations. Is it possible that malignantly transformed cell populations could be eradicated by the immune system, even if the defensive cellular elements are the malignant cells themselves? The treatment modalities graft-versus-leukemia (189) and HSCT (hematopoietic stem cell transplantation) induce remissions in survivors of treatment mortality, especially when re-enforced with NK cell, targeted chimeric antigen receptor- CAR-armed T cell, PD-L1-directed (programmed death, ligand) monoclonal antibody, or immunotoxin therapy (190). The best examples are the adoptive immune T- and NK lymphocyte-mediated protocols, the application of which eradicates malignant lymphomas and lymphocytic leukemias (191). In the leukemia-afflicted host, the native immune system does not mobilize an effective reaction for the rejection of malignantly proliferating cells. The elements for the rejection of the malignant cell population are there, but they are not assembled and are not self-applied. Properly assembled in the laboratory and administered sequentially, host immune reactions are capable of dissolving large masses of tumors (so much so that the patients are to be protected from life-threatening lymphokine storms and tumor lysis syndromes).

Predecessors of cnidarians and ctenophores survived physicochemical insults in the ancient Earth in a stage of autophagy. Malignantly transformed human cells (cancer cells) resist the effects of chemical and radiological agents in the stage of reversible autophagy followed by constitutively activated proto-oncogenes for survival and recovery. These cells will resist exposure to the same agents that induced the assumption of the autophagic stage. The clinical oncologists diagnose chemotherapy-resistant relapsed cancer. The practice of autophagy by the malignantly transformed cells in advanced multicellular hosts is a return to an atavistic physiological reaction widely exercised by the ancestors of cellular life on Earth.

The intracellular environment with operational p53, but absent MDM in the choanoflagellates, cnidarians and Spongiae might have been chronically inflammatory, and thus hyperactive, but not antiapoptotic. Their semblance to the malignantly transforming cells higher up on the evolutionary scale is comparable to the Wnt and NF-κB/STAT pathways, but not to the MDM anti-p53 pathway. Environmentally stressed predecessors, the virus-resistant cnidarians (Hydra magnipapillata; N. vectensis) might have initiated for their survival the scenario that occurs in advanced stages of the evolution, and manifests in cell survival by the Wnt, and NF-κB/STAT co-activation, and the inhibition of pro-apoptotic p53/p60/p70 by MDM generation. That would be physiological metabolism in a stressed Ciona or amphioxus. When activated in some selected individual cells of arthropod, nematode, vertebrate piscine, reptilian, avian or mammalian (including human) hosts, these reactions may be viewed as a reversal to inherent ancient faculties conserved in their genomes (7,125). The terminology for this condition in vertebrate hosts is the malignant disease cancer.

What was not available to deal with for the unicellular eukaryotic ancestors, is the multicellular host in which somatic cells, germ cells and stem cells coexist. There, if the malignant transformation was induced by an external pathogen (an oncogenic virus), the malignant cell has to withstand an immune attack by the host. Should the malignant transformation be induced endogenously by a LINE transposon, as referenced in (7), the malignant cell induces no immune reactions, or if it does, it is able to suppress them by the mobilization of stromal cell-derived factor chemokine CXC and its ligand CXCL12; Treg cells; myeloid-derived suppressor cells, and dendritic cells remaining undifferentiated and tolerogenic. Macrophages assuming M2 phenotypes, fibroblasts and endothelial cells rise for direct defense and support of the transformed cell. The transformed cell establishes cell-to-cell communications by surface membrane-to-surface membrane contacts, or by the release of microvesicle endosomes, all for its favor, within its microenvironment with fibroblasts, vascular endothelial cells, and M2 macrophages; microvesicles of tumor cell derivation de-activate immune T cells or even NK cells (125). The tumor cell evokes host tolerance by the production of IL-6, IL-10, IL-1β generating T17 lymphocytes, TGFβ, prostaglandins and other factors regularly produced by syncytiotrophoblasts of the placenta, including IDO (indoleamine 2,3-dioxygenase) (192,193). Thus, endogenously induced tumor cells receive full support for their growth and spread from their multicellular hosts. Human tumor cells grown in vitro in cultures, or as xenografts in athymic mice, lose this support. When tested for susceptibility to chemotherapeutical agents, or oncolytic viruses, these cells are defenseless and display deceivingly high sensitivity. No wonder, most of those treatment regimens fail to induce complete remissions in the environment of the natural hosts of the malignantly transformed cells in clinical trials conducted for the cure of cancer.

6. Conclusion

The primordial cell survival pathways that were assembled in the life forms in existence before and during the era of the the Cambrian sea enabled the establishment and expansion of eukaryotic cellular life on Earth. In extant descendants of all eukaryotic cells continuing in unicellular, or arranging for multicellular embodiments of life, the life survival pathways...
rendered basic services for the individuals in their ontogenesis and adult life, including the designs of body plans, generating haploid germ cells and retaining stem cells for the construction of organs, including a peripheral and a central nervous system, and for the replacement of aging somatic cells. In these advanced multicellular organisms, the cell survival pathways may revert to their phylo- and ontogenetically ancestral structure and function in a point-mutated constitutive manner, create new genes by fusions, and keep the cell in an immature, undifferentiated, individually independent and immortalized condition. Occurring in advanced multicellular hosts, these structures are recognized as proto-oncogenes and oncogenes and their gene products as oncoproteins. In becoming parasites of their differentiated multicellular hosts, these cells extract full support from their host, while exacting mortal consumption. The clinics diagnose the malady of cancer. The academic laboratories maintaining these immortal cell populations in culture recognize a close to indestructible ancient form of eukaryotic cellular life.

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Note added in proof

An extraordinary observation concerns the evolution of tumor necrosis factors (mentioned among Death Factors in Fig. 2). The human TNF-α, as the ligand of its receptors R1 and R2, activates different cytoplasmic pathways. R1 releases NF-κB from its cytoplasmic anchor IκB, thus allowing its transfer to the nucleus for the activation of its numerous pro-inflammatory and proto-oncogenic target genes. This receptor activates also cytoplasmic MAP3K (mitogene-activated protein kinase). Further, commands emanating from R1 travel either toward SODD (silencer of death domains), or to FADD (factor apoptosis stimulator Fas-associated death domain), and to activation of caspases 8/3. This latter effect culminating in apoptosis induction was responsible for the unforgettable sensational first introduction of the newly discovered ‘tumor necrosis factor’ molecule in the mid-1970’s (194). Pathways activated by R2 are those of VEGF-R2 (vascular endothelial growth factor receptor) and PI3K (phosphatidylinositol kinase) (195). The ancestor of the human system was installed in the pre-Cambrian cnidarian corals Acropora, and remains conserved throughout over 550 million years of evolution in both the cnidarian and human genomes. The human TNF-α induces apoptosis by myosin fragmentation in the extant cnidarian coral cells, and vice versa: the cnidarian TNF equivalent remains an apoptosis-inducer in human (WT-immortalized Jurkat T-lymphocytes) cells, both operating through the FADD pathway (196). The derivation and the evolutionary conservation of proto-oncogenes, from the ancestral unicellular eukaryotes on, have been recognized early: yeasts and amoebae (the Dictyostelium) operate the ancestral ras proto-oncogenes (197).

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Addendum

Int J Oncol 19: 473-488, 2001; DOI: 10.3892/ijo.19.3.473

The authors would like to acknowledge that the Coriphosphine O stain shown in the upper panel of Figure 8 was a kind gift from Dr T.P. Loughran of the H.L. Moffitt Cancer Center, Tampa, FL, USA.