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Cancer is an adaptation that selects in animals against energy dissipation

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ABSTRACT

As cancer usually follows reproduction, it is generally assumed that cancer does not select. Graham has however argued that juvenile cancer, which precedes reproduction, could during evolution have implemented a "cancer selection" that resulted in novel traits that suppress this juvenile cancer; an example is protection against UV sunlight-induced cancer, required for the emergence of terrestrial animals from the sea. We modify the cancer selection mechanism to the posited "cancer adaptation" mechanism, in which juvenile mortality is enhanced through the diminished care received by juveniles from their (grand) parents when these suffer from cancer in old age.

Moreover, it is posited that the cancer adaptation selects against germline "dissipative genes", genes that result in enhanced free energy dissipation. Cancer's progression is interpreted as a cascade at increasing scale of repeated amplification of energy dissipation, a cascade involving heat shock, the Warburg effect, the cytokine IL-6, tumours, and hypermetabolism. Disturbance of any physiological process must enhance energy dissipation if the animal remains functioning normally, what explains multicausality, why "everything gives you cancer".

The hypothesis thus comprises two newly invoked partial processes—diminished (grand) parental care and dissipation amplification—and results in a "selection against enhanced energy dissipation" which gives during evolution the benefit of energy conservation. Due to this benefit, cancer would essentially be an adaptation, and not a genetic disease, as assumed in the "somatic mutation theory". Cancer by somatic mutations is only a side process.

The cancer adaptation hypothesis is substantiated by (1) cancer's extancy, (2) the failure of the somatic mutation theory, (3) cancer's initiation by a high temperature, (4) the interpretation of cancer's progression as a thermal process, and (5) the interpretation of tumours as organs that implement thermogenesis. The hypothesis could in principle be verified by monitoring in a population over several generations (1) the presence of dissipative genes, (2) the incidence of cancer, and (3) the beneficial effect of dissipative gene removal by cancer on starvation/famine survival.

Introduction

In spite of much effort, the state of affairs around cancer remains bleak. Seyfried's book *Cancer as a metabolic disease* [1] tells that in the United States cancer's death rate is 1600 humans a day. There seems to be a failure on the fundamental level in our understanding of cancer, and new ideas may solve the permanent crisis. Here it is posited that cancer has a biological function: at the cost of shortened individual animal lives, cancer assists animal species during evolution in conserving energy by selecting against energy dissipation.

Heat engines that use heat for (free) energy generation are studied in engineering and physics, just as the reverse generation of heat from work during friction in all types of machines [2,3]. The standard example of the heat engine is the steam engine, but numerous other types exist as well, with new types continuously being proposed and developed.

The author has published theoretical models for the origin and early evolution of life in terms of heat engines [4–7]. The first organisms would have lived on thermal cycling or thermal gradients, such as present in volcanic hot springs. This process was termed thermosynthesis. The publications describe heat engines constructed from the components of the mitochondrion, which synthesizes ATP in the cell today by chemiosmosis.

The publications follow the postulated trajectory of evolution: an early paper considers ATP Synthase's β-F_1 subunit as the very first enzyme. The microorganism containing this enzyme was thermally cycled by suspension in circulating convection currents in volcanic hot springs [5]. The required amplitude of the external thermal cycling was estimated to be at least ~7.5 C [6]. A recent paper [7] models the emergence of the (metazoan) animals in

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the thermal gradients above submarine hydrothermal vents [8] during the Neoproterozoic global glaciations of the Snowball Earths which preceded the Cambrian and globally impeded photosynthesis.

Many studies mention a causal role of heat and temperature in cancer, implicitly during inflammation [9], but also directly [10–14]. Heat's carcinogenicity is however not considered as remarkable, numerous causes of cancer being known [15].

Since cancer remains extant in spite of its fatality, cancer must plausibly give a net advantage. But which, and how? It is generally held that, since cancer occurs mainly after the birth of offspring, cancer does not select.

We invoke a similarity between organisms and machines: it is posited that animal species have a mechanism to remove, or at least to diminish, heat dissipation in the body during evolution, just as engineers can deal with the heat generated by friction in machines by redesigning these machines. In both organisms and machines the enhanced efficiency by removal of friction gives a benefit. In the hypothesis, cancer is related to a mechanism of dissipation identification and pertinent gene removal in animals. The friction-generated heat is amplified by the animal body at cancer's initiation and/or later promotion. Moreover, this study posits that the detection is based on a previously proposed ancient thermosynthesis mechanism involving a filamentous mitochondrion [7]. During cancer's progression, the amplified heat is in a cascade repeatedly further amplified, resulting in "Cancer-associated Thermogenesis" (CTG), a key attribute of cancer, and a measure of cancer's aggressiveness [1].

The engineer can detect friction-generated heat in machines by the locally raised temperature observed by thermocouples and IR cameras [16]; in medicine, tumours are sometimes detected by thermography with IR cameras as well [17].

The generally assumed absence of selection by cancer was conceptually circumvented in 1992 by Graham[1] (see also Leroi et al. [19]) in his "cancer selection" (CS) model for cancer in animals. Cancer therein has an evolutionary function, and is just as regular cancer in adults still assumed to be a disease. During evolution, new traits would be selected by their inhibition of juvenile cancer.

We derive the "cancer adaptation" (CA) from the CS concept (Fig. 1): as selection gives a net benefit, cancer is not considered to be a disease, but considered to be an adaptation. The CA comprises two partial processes as main components:

(1) *Cancer progression in the (grand) parents* Cancer progression is essentially a thermal process. In the CA, multicausal free energy dissipation initiates cancer. Cancer stores the thermal signal resulting of the dissipation which, after dormancy, is repeatedly amplified late in life, accelerating death.
(2) *Weak selection on adverse genes during evolution by (grand) parental death* Cancer in the individual is separated from the object of selection, the individual's progeny: in the posited CA, cancer in the elderly has an adverse selective effect on the juveniles in the progeny through the resulting diminished (grand) parental care [20].

Until a century ago, cancer was quite rare. How to explain this rarity? In the CA, genes are selected based on the dissipation when expressed: these germline genes that result in high heat dissipation are called "dissipative genes". A selection against a gene may cause "negative hitchhiking" [21], in which genes adjacent to the target gene are also removed because of linkage disequilibrium [22]. Negative hitchhiking can be minimized by frequent recombination, which increases with the number of generations between incidences of cancer in the lineage. This benefit of a large number of generations explains the rarity of cancer under natural conditions (i.e., in humans: before the advance of medicine had diminished overall human mortality [23]).

The CA is substantiated by:

(1) the extancy of cancer in animals,
(2) the failure of the "Somatic Mutation Theory" (SMT) in explaining cancer,
(3) the observed role of the temperature in initiation of cancer,
(4) the modelling of cancer's progression as a thermal process, and
(5) the interpretation of tumours as organs that implement thermogenesis.

These items are the subject of the following chapters.

Why cancer remains extant during evolution

Consistent with an evolutionary old ancestry, cancer occurs not only in humans, but also universally in vertebrates, and in many other metazoan animals. Leroi et al. [19]:

> Cancer is a hazard that few, if any, animals escape. Unambiguous neoplasias have been recorded from molluscs, arthropods, jawless fish, cartilaginous and bony fish, amphibia, reptiles and mammals, although whether they exist in cnidarians—simple animals that include jellyfish and anemones—is more debatable.

The animal body seems prepared for the development of cancer. Oncogenes such as *src* [24] and *myc* [25] go far back in vertebrate phylogeny. Even the placozoan *Trichoplax*, a most primitive metazoan, contains the p53/mdm2 proteins of the apoptosis machinery [26].

In the 19th century, Weismann proposed that aging involves a programmed death of the individual, a notion termed "phenoptosis" by Skulachev [27] and which has been related to cancer [28]. Every human eventually develops *covert* cancer [29], which is inevitable [30]. Not everyone develops however *overt* cancer—but the majority would if they lived long enough [31]:

> The cumulative risk to age 120 years for men is nearly 90% but it is just over 70% for women.

When a case of cancer occurs at an early age, it is therefore better to speak of an "acceleration of cancer" (a continuous mathematical variable), and wonder about "the cause of this acceleration", instead of "the cause of this cancer" (a discrete mathematical variable).

What is the *specific* benefit of cancer that explains its extancy? Sommer [32] sees an optimal germ line mutation rate as the benefit. This study relates cancer to germ line genes and their mutations as well.

A gene can have both negative and positive effects. The standard example is the sickle cell mutation, lethal when homozygous, but protecting against malaria when heterozygous [33]. This ambiguity has been generalized to "antagonistic pleiotropy", which has been related to several diseases [34].

Additional substantiation of the CA is given by the positive selection of cancer-linked genes [35]. Crespi and Summers [35] list the well-known *BRCA1* gene, combined with many other, less well known genes found by database studies of mice, chimpanzees and

[1] J. Graham is not a scientist, and calls himself an amateur. He has written two letters to the *Journal of Theoretical Biology* and the self-published book titled *Cancer selection* [18], cited 21 times in Google Scholar and reviewed in *Nature*. His book is certainly not dispassionate and detached, as one expects of a scientific study, but several of his arguments and conclusions are far reaching. This study modifies and extends his ideas.

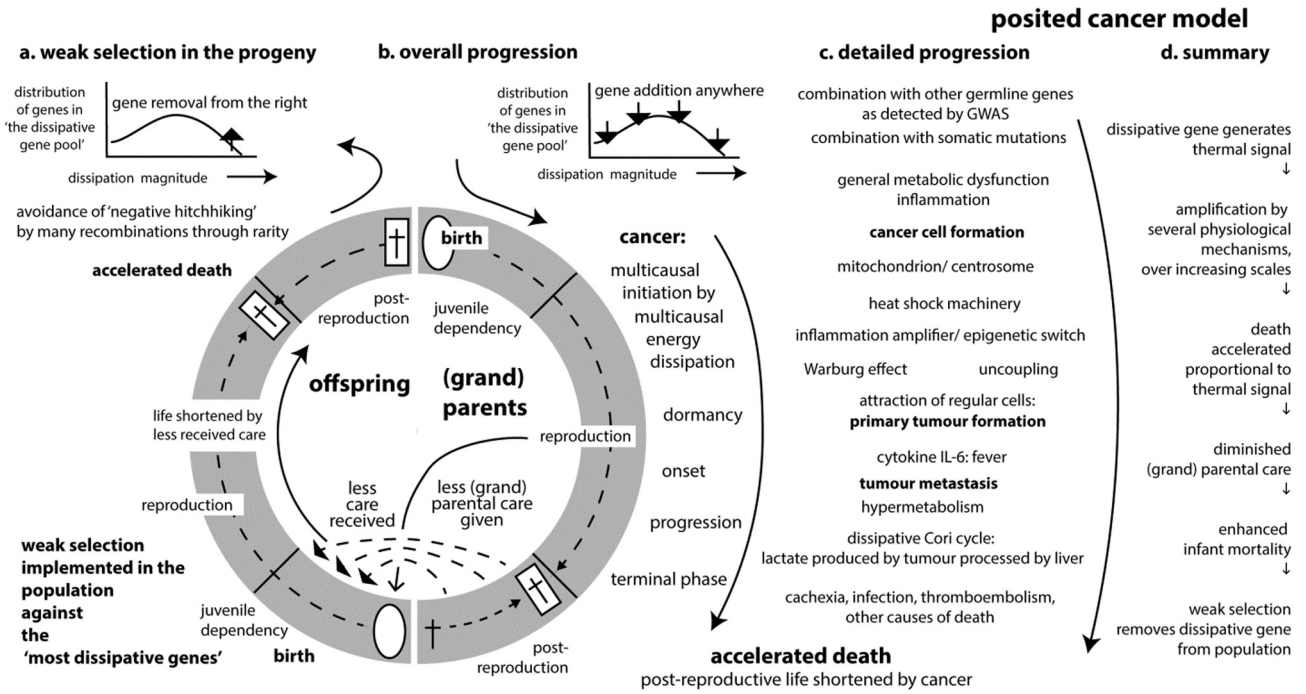

Fig. 1. The "selection against enhanced energy dissipation" (SAEED) implemented by the "cancer adaptation" (CA). Cancer selects against genes with the highest free energy dissipation and is separated in two partial processes, (a) weak-selection in the progeny and (b and c) accelerated death of (grand) parents by cancer. During evolution, new genes enter the gene pool continuously. Their place can be anywhere in the dissipative gene pool (see insets). When arranged by energy dissipation magnitude, the most-dissipative genes are found to the right, and are the main target of removal by the CA. Removed genes are not necessarily the most recently added genes, the latter are tested together with the already present genes. From left to right: (a) *Weak selection in the progeny.* This is the last step of the CA. Accelerated death by cancer diminishes (grand) parental care to the offspring. The larger the dissipation, the larger the acceleration of (grand) parent death, the less the given parental care, and the higher the infant mortality. Due to the rarity of cancer the selection is weak, and the dissipative-gene is only slowly removed from the population. This weakness allows adjacent genes on the chromosome to be saved by recombination from "negative hitchhiking", the adverse effect of linkage disequilibrium. (b) *Overall progression of cancer in (grand) parents.* Several steps are distinguished. First, new germline genes are inserted in the gene pool; somatic mutations occur during the life cycle as well. High energy dissipation inside the cells of an organ generates a signal which in turn initiates cancer. The detected heat generated by energy dissipation can have many origins: thermogenesis may be due to metabolism, inflammation, genetic dysfunction or interaction with the environment. Cancer typically occurs after dormancy, during which offspring is born. Cancer's late progression eventually shortens post-reproductive life. (c) *Progression of cancer in (grand) parents at increased detail.* The listed physiological processes constitute a thermal thread discussed in Chapter 5. (d) *Summary* The SAEED model summarized in six steps.

humans. Coevolution [36] is the evolution of mutual interactions between different species. Examples are parasitism, pollination of plants by insects, and virus-driven illnesses. Crespi and Summers propose that "antagonistic coevolution" is involved in cancer. Generalizing, they conclude somewhat obliquely:

> Such positive selection at the molecular level can be driven by diverse forms of conflict between evolutionary agents, including parent-offspring conflict, maternal-foetal conflict, sexual conflict, sexual selection, and host-parasite conflict. These conflicts lead to evolutionary disequilibrium, molecular-level arms races, and tugs-of-war over cellular resources, which generate genetic, epigenetic, and developmental systems more vulnerable to the development of cancer.
>
> and
>
> The evidence that we have presented is necessarily correlative, as the genetic systems involved have yet to be deeply investigated by both molecular-evolutionary biologists and researchers studying cancer. It is only through such multidisciplinary analyses that the study of cancer will develop its own natural history, evolutionary underpinnings, and predictive understanding of how diverse forms of selection driven molecular evolution both within and between organisms.

As explanation of cancer, "antagonistic coevolution" seems abstract and vague, but the CA generalizes Crespi and Summers' role of conflict in cancer, and proposes that cancer can be accelerated by *any* dysfunction (including metabolic dysfunction), with generated *heat* being the universal intermediate agent.

The specific benefit of the CA is therefore the benefit of energy conservation: cancer implements the SAEED, a purifying selection against germline genes that cause free energy dissipation. The SAEED/CA thus identifies/replaces the benefit proposed by Sommer [32], Skulachev [27,37] and Lichtenstein [28,38], and, independently, Rew [39], which compensates for the disadvantage of death of the individual by cancer.

The somatic mutation theory

In contrast to regular diseases, cancer has many multifarious attributes: (1) universal occurrence in animals including humans, (2) occurrence in all organs, (3) multicausality, (4) variable progression trajectories, (5) involvement of many cancer-specific components (cancer-specific metabolism, cancer-specific cells (fibroblasts, macrophages), tumours, metastases), (6) numerous oncogenes, (7) robustness to many therapies, and (8) numerous interactions with physiology, including genetics, epigenetics, metabolism and inflammation. These multifariousnesses are reminding of a universal scientific principle. What is it?

The standard and mainstream model of cancer is the SMT which pictures cancer as a disease caused mainly by somatic mutations accumulated during the life cycle. This accumulation results by a to-be-elucidated pathological process in enhanced cell or tissue growth that is malignant and fatal: cancer would resemble a wart that keeps increasing in size. This common picture involving 'overgrowth' has however only a limited explanatory power. Egeblad [40]:

> Just as normal developing organs, such as liver and kidneys, have systemic consequences for the organism, so does the tumor organ. The dramatic systemic effects of the tumor organ are not limited to metastatic spread, but also include effects on immunity, coagulation and metabolism. . . . Indeed, it is these major systemic changes that cause the majority of cancer deaths, *rather than effects of the direct overgrowth* of the primary tumor or even metastases. [emphasis added]

In the SMT, the overall progression of cancer involves the stages of (1) initiation, (2) dormancy, (3) mainly in old age, promotion / onset, followed by amplification and, sometimes after spread by metastasis, (4) life termination, often by the fatal state of cachexia [41]. In the SMT, this initiation involves a genetic process, and cancer is called a 'genetic disease'.

The SMT was and is a major motivation of large scale sequencing, with the expectation that this allows the more accurate identification of oncogenes, and thus, more generally, a better understanding of this genetic disease. In 2003 the human genome project was completed, and thereafter mutations leading to cancer have been catalogued in "The Cancer Genome Atlas" (TCGA) [42]. Sequencing showed that the incidence of a few previously identified oncogenes is indeed large, and also showed the existence of an even much larger number of rare oncogenes, which are involved in a wide variety of cellular processes [43].

The recombination of chromosomes during meiosis occurs in preferred "hot spots". As a result the human genome can be divided in "haplotype blocks" of ~20,000–45,000 bps, which have been genetically marked by "single nucleotide polymorphisms" (SNPs) during the "genome-wide human haplotype map" (Hap Map) project. Individual genomes can be mapped in terms of these SNP-marked blocks [44].

During "Genome-Wide Associating Studies" (GWAS), a phenotype such as a medical condition is associated with haplotype blocks present in a population. Associated haploblock(s) can be fine-mapped and responsible genes identified. GWAS of cancer have yielded many associations (Fig. 2). Many involved previously known oncogenes, but remarkably, many weak correlations have also been found [45]. The number of germline genes (as opposed to somatic mutations) involved in cancer has increased, and may further increase [46].

The obtained massive sequence data is hard to interpret. The specific physiological effect of a mutation can in general not be predicted. The limited applicability or failure of the SMT has been discussed by many, for instance by Weinberg, Ledford, Baker (who speaks of a kerfuffle) and Heng [47–50].

Alternatives to the mainstream SMT theory have sprung up. We refer to the theories published by A. Soto and C. Sonnenschein, V. Skulachev, P. Duesberg, J. Graham, M. Greaves, T. Seyfried, A.V. Lichtenstein, S.G. Baker, H.H. Heng and P.C. Davies.

Hanselmann and Welter (2016) [51] have divided the theories on cancer initiation in four categories summarized in an unordered table, which lists seemingly contradictory observations pro and con the category. They conclude:

> . . . no one theory can claim to be the exclusive cause of cancer initiation and progression.

Table 1 contains observations taken from Hanselmann and Welter's table. For instance, although (pro) most cancer cells show (1) *mutations* (*1P1*) (which may be due to heredity (*1P2*) or artificial insertion (*1P3*)), in some cases (con) only few mutations are present (*1C2*), or mutations even seem absent (*1C3*). Moreover, many mutations may be present in the absence of cancer (*1C1*).

Similarly, (4) *aneuploidy* [52] (pro) is often present in cancer cells (*4P1*) (which may be due to chronic infection/inflammation (*4P2*)), but (con) some tumor cells show no aneuploidy (*4C1*).

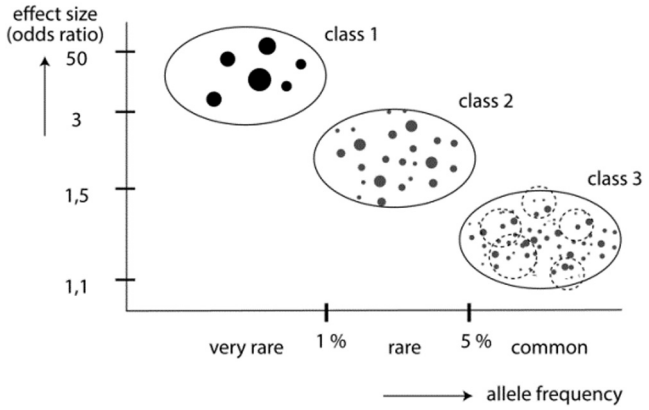

Fig. 2. GWAS and cancer (redrawn from Refs. [106,107]). Until recently, cancer was linked to the expression of a single or a few mutations (such as in the *BRCA1/2* genes linked to breast cancer), i.e., cancer was considered to be "monogenic", but GWAS have shown that it also often can be linked to multiple germline genes and thus can be polygenic. The continuum of effect (odds-ratios) and allele frequencies is commonly divided in three classes, based on gene frequencies <1%, 1–5%, and >5% [108]. Class 1: rare variants with a strong effect. This class is responsible for Mendelian disease, monogenic "hereditary" or "familial" rare high-penetrance mutations involving a high risk; Class 2: intermediate class with uncommon variants with intermediate odds-ratios; Class 3: common variants with a low effect. Through polygeny, a significant risk of cancer can be caused by the combined (indicated by circles) expression of genes that on their own give only a minor contribution to the cancer risk and have a small odds ratio.

Again, just as for mutations, aneuploidy may be present (in the brain) in the absence of cancer (*4C2*).

The (3) *mitochondrion* plays a central role in cancer [53]: (pro) the metabolism of cancer cells is different. Cancer shows the Warburg effect (*3P1*), intense fermentation of glucose (just as in yeast) but in the presence of oxygen (contrary to yeast) [54]. Mitochondrial toxins can induce cancer (*3P3*). Nucleus/cytoplasm (=mitochondrion) transfer experiments [1]—which should receive much more attention in cancer research than they are receiving—contradict several current cancer initiation theories since cancer goes with the mitochondrion, and *not* with the nucleus. Mutations and aneuploidy, i.e. genetic changes, cannot be a single initiator of cancer (*1C5*, *3P2*, *4C3*).

The (2) *microenvironment* category owes its existence to the observable initiation of cancer by hormones and a low pH (*2P1*).

The Cancer Adaptation In the SMT, cancer has remained a mysterious phenomenon, but in the CA, cancer has a comprehensible function. The CA considers the selection of dissipative germline genes the main, evolutionary relevant process—it relates to hereditary cancer *(IP2)*. Whereas cancer by somatic mutations is the main process in the SMT, it is just a side-show in the CA. Somatic carcinogenic mutations would be handled similar to germline dissipative genes, as the CA cannot distinguish them.

Our Table 1, obtained by modifying Hanselmann and Welter's table, names and numbers their categories as (1) *mutations*, (2) *microenvironment*, (3) *mitochondrion* and (4) *aneuploidy*, which are incorporated in the CA framework in a single entity, the "Sequence":

$$(1 \rightarrow 2 \rightarrow 3 \rightarrow 4 \rightarrow \textit{further progression}),$$

wherein distinct initiators from a category (say category 3) can initiate cancer in the absence of initiation by preceding categories (here, categories 1 and 2).

The Sequence starts with (1) *mutations*. The hereditary cancer (*1P2*) therein is the fundamental cause of cancer: cancer during evolution continuously removes dissipative germline genes. In the CA these genes/mutations, germline or somatic, upon expression generate heat—sometimes after interaction with the local (2)

Table 1
Four, apparent contradictory, categories of cancer initiators, here named the '(1) *mutations*', '(2) *microenvironment*', '(3) *mitochondrion*', and '(4) *aneuploidy*' categories. From Hanselmann and Welter [51], with reformulated text and rearranged rows; their study also gives references. The rows—initiator categories—in their unordered table have been arranged in the temporal order posited in the CA. Two columns list the summarized arguments supporting and contradicting the evidence for the category. Entries have been numbered (*1P1*, *1C1*, ...) in order to simplify their discussion in the text.

Hypothesis/model category	Pro (*P*, supporting) evidence	Contrary (*C*) evidence
(1) *mutations*	(*1P1*) Most cancer cells show mutations. (*1P2*) Hereditary cancer (=cancer due to germline genes) (*1P3*) Targeted mutation causes cancer. (*1P4*) Mutation can cause aneuploidy.	(*1C1*) Normal tissue shows many mutations. (*1C2*) Mutation rate is too low for cancer emergence. (*1C3*) Cancer can occur without mutations or with only a few ones. (*1C4*) Frequently long dormancy between mutation and cancer (*1C5*) Mitochondrion and nucleus transfer experiments
(2) *microenvironment*	(*2P1*) Microenvironment can cause cancer (for instance by hormones and low pH)	(*2C1*) Hereditary cancer (=cancer due to germline genes)
(3) *mitochondrion*	(*3P1*) Warburg effect is detectable in all tumours. (*3P2*) Cancer induction by mitochondrion transfer (*3P3*) Cancer induction by mitochondrial toxins.	(*3C1*) Hereditary cancer (=cancer due to germline genes) (*3C2*) Hereditary mitochondropathies that increase cancer are unknown. (*3C3*) Cancer by substances that disrupt the mitotic spindle and induce aneuploidy.
(4) *aneuploidy*	(*4P1*) Most tumours show aneuploidy. (*4P2*) Pre-cancer stage, and chronic infection/inflammation show aneuploidy.	(*4C1*) Some tumor cells show no aneuploidy. (*4C2*) Normal brain shows constitutional aneuploidy. (*4C3*) Mitochondrion and nucleus transfer experiments.

microenvironment—heat that is detected by the (3) *mitochondrion*, leading to its transformation to a carcinogenic state.

Feedback to preceding between categories however complicates the simple picture of the Sequence. The *progression* may result in (4) *aneuploidy*, which itself may change the (2) *microenvironment*, by a feedback process through metabolic changes (4 → 2). The started cancer may also result in additional (1) *mutations*, another feedback process (*further progression* → 1). Due to these feedbacks following the basic progression, the transformation to cancer would be irreversible on the cellular scale; stopping cancer requires cell death, apoptosis.

The Sequence in detail:

(1) *Mutations*: (*1P1*, *1P2*, *1P3*) mutations can cause cancer if the metabolic changes by the expressed proteins result in sufficiently high thermogenesis. As just mentioned, a*neuploidy* (*1P4*) may be an intermediate step in this thermogenesis, the result of genetic changes driving metabolic changes. Mutations that do not result in high thermogenesis would however not cause cancer (*1C1*). Where the mutation rate is too low for cancer emergence (*1C2*), or even seems absent (*1C3*), cancer may be due to activation of following steps of the Sequence:

(2 → 3 → 4 → *further progression*).

In mitochondrion transfer experiments (*1C5*) the pertinent process is:

(3 → 4 → *further progression*).

The frequently long dormancy (*1C4*) between mutation and cancer assists the CA in delaying cancer until the post-reproductive period. This delay diminishes cancer's incidence, which in turn diminishes negative hitchhiking.

(2) *Microenvironment:* Cancer initiation by the microenvironment (*2P1*) is attributed to the resulting changes in metabolism, which cause thermogenesis. Hereditary cancer (*2C1*) is not seen as contrary evidence, but would instead be a cancer initiator from the preceding initiator category in the Sequence, (1) *mutations*.

(3) *Mitochondrion:* The Warburg effect that characterizes cancer (*3P1*) is linked to enhanced thermogenesis by the mitochondrion during this metabolic condition; the thermogenesis follows amplification of metabolic thermogenesis. This mitochondrial cancer initiation also explains cancer induction by mitochondrion transfer experiments (*3P2*) and mitochondrial toxins (*3P3*).

The absence of hereditary mitochondropathies that increase cancer (*3C2*) is explained by the requirement for a proper functioning mitochondrion in order to effect amplification of the metabolic thermogenesis signal during initiation by the (2) *microenvironment*.

(4) *Aneuploidy:* Substances that induce aneuploidy (*3C3*) are carcinogenic because in the CA, aneuploidy enhances the disorder of the gene expression machinery, which in turn results in enhanced thermogenesis in the (2) *microenvironment*. This (4 → 2) feedback accelerates cancer's progression. Since aneuploidy is a late step in the Sequence, cancer can be initiated without it *(4C1, 4C3)*. Aneuploidy can be an early stage of cancer (*4P2*), and is indeed present in most cancers (*4P1*).

The posited role of intracellular thermal gradients

The recent unexpected discovery of ultralow heat conductivity inside the eukaryotic cell is a key element of the newly posited CA. It can be a factor 10^5 smaller than predicted [55–59]. Although 100,000 is by all accounts a huge number, the discrepancy has attracted little attention, and remains unresolved: "intracellular thermal gradients" (ITGs) of ~1 C should in theory decay quickly but in practice they endure [59,60].

In daily life we have internalized that the smaller an object, the faster it adopts the temperature of its surroundings. Because of their extreme smallness, we expect the internal constituents of a cell to be isothermal. The existence of significant ITGs is both a surprise and an opportunity to find new explanations for observed phenomena.

This study accounts for the paradox by postulating that on the intracellular scale, heat conduction deviates from Fourier's classical law: $J = \kappa^{dT}/_{dx}$ (where J is the heat flow and κ the thermal conductivity); instead, heat conductivity would have to be described by the quantum mechanical concept of phonons, used in the emerging discipline of phononics[2] [62], which investigates processes such as signalling driven by thermal gradients. Until now, phononics has been applied to a few inanimate systems.

[2] The origin of phononics lies in the "thermal diode" discovered in 1936 that conducts heat preferentially in one direction. The explanation in 2002 was followed by the construction of the "thermal transistor": in a thermal diode with blocked heat flow, additional heat entry can lead to a heat flow increase across the blocked interface. Complex *thermal* systems such as the "thermal computer" [61] that are analogues to complex *electronic* systems are easily imagined. The applications of phononics to the life sciences may be numerous.

Similar to the explicit statements of Baffou et al. [55,58], it was implicitly assumed in previous studies by the author that the high thermal conductivity inside the cell precludes the existence of intracellular thermal gradients. The discovered presence of ITGs suggests a role in cellular physiology. As mentioned in the Introduction, the minimal amplitude of the thermal gradient to effect thermosynthesis was in a previous study by the author estimated as ~7.5 C. The invoked thermal cycling and thermal gradients were macroscopic and external to the organism considered. Inside our own cells, these ITGs would plausibly not have the function of generating free energy as ATP: the ITGs of ~1 C seem too small.

Although the ITGs observed today cannot plausibly generate power, they still could however sustain intracellular signalling. Only future investigations can tell what role ITGs play in the signalling involved in cell regulation. Although the specific details of the functions performed are still unknown, it is clear that ITGs might be generated and detected.

This plausible detection capability is of high principal interest. All physiological processes dissipate free energy because of the universal applicability of the Laws of Thermodynamics [2,3]. Friction in machines results in heat generation and diminishes efficiency. The ITG may permit the detection of intracellular dissipation, and therefore of cellular inefficiency.

Friction, and most free energy dissipating processes, i.e. entropy-generating processes, result in thermogenesis, which is a good (but not a perfect) measure of dissipation (we disregard entropy-generating processes that take up heat such as relatively rare highly endothermic chemical reactions or processes linked to the physical process of transpiration). Minimization of energy dissipation must maximise energy conversion efficiency, which gives a selective advantage.

The previously mentioned carcinogenicity of a macroscopic thermal gradient [10–14] by the resulting ITG is linked to the (2) *microenvironment* cancer initiator category mentioned in the previous chapter. Examples are body parts in regular contact with heaters—stoves, the Indian kangri earthenware bowl, the Japanese kairo tin box, the skin in contact with infrared radiation and heat [11,12,14], including reports of burn wounds and scars, and the oesophagus in contact with hot beverages and hot food [13].

Consistent with this notion of the initiator role of a high temperature generated *externally* to the body, a high local temperature generated *internally* to the body, which must have been generated by thermogenesis, has indeed been reported as a first sign of breast cancer [63]. Etehadtavakol and Ng [64]:

> An irregular thermogram is indicated as a significant biological risk marker for the presence *or growth* of breast tumours. [emphasis added]

Polygeny can similarly be explained by combined thermogenesis. The numerous "cancer susceptibility genes" [65] found by GWAS have led to a change from single-gene to polygenic modeling of cancer. Polygeny deals with combined effects of genes and is commonly invoked in GWAS studies [66]. A standard example is body length, associated with dozens of genes [67]; the contribution of each single gene may be small but is quantifiable as a number of mm's height.

What is the physiological mechanism of the additivity seen in polygeny? In the case of cancer, how can there be so many cooperating weak oncogenes? Schadt (2009) has explained the aetiology of polygenic diseases found by GWAS by special attributes of the metabolic networks sustained by the pertinent genes [68]. Wallace (2010–2013) has proposed links between "GWAS & common diseases" to "bioenergetics & mitochondria" [69]. Garraway and Lander recently (2013) remarked on the numerous found oncogenes [43]:

> . . . many of the newly discovered cancer genes affect global processes whose precise connection to cancer remains obscure. These cancer genes act by deranging gene expression (through changes to chromatin and DNA methylation), RNA splicing, protein synthesis and degradation, and cellular metabolism. . .. Presumably, these global changes propel cancer by affecting one or more specific *targets* [emphasis added] involved in cancer processes—activating or repressing specific genes, altering the isoforms of specific mRNAs, and increasing or decreasing steady-state levels of specific proteins. The key targets are likely cell type specific, accounting for the presence of specific subsets of driver genes in particular cancer types.

In the CA, these mentioned specific "targets" are redundant: the numerous recently found weak oncogenes with their very low-odds ratio are linked to cancer by the additive effect of enhanced thermogenesis. A large enough combination of weak oncogenes would generate sufficient heat to significantly accelerate cancer.

The thermal thread during cancer's progression

After the model in Table 1 for the initiation of cancer, we model its progression with a core role for heat and temperature. In all organs, cancer stem cells would continuously check their microenvironment for the carcinogenic initiating thermal signal. The detected dissipation, linked to an adverse germline gene through the associated ITG, is after dormancy amplified late in life; the progression eventually results in fatal hypermetabolism, followed by gene removal by (grand) parental and offspring death. The thread is composed of a large number of partial thermal processes, comprising many entities:

> *presence of dissipative germ line gene* (Table 1: 1. Mutations: *1P2*) → (2. Micro-environment: high local temperature) → *the centrosome/mitochondrion* (3. Mitochondrion; 4. Aneuploidy) → *the heat shock machinery → thermal sensing by other cellular compounds → chronic inflammation → inflammation amplification → the Warburg effect and uncoupling → tumor formation → hypermetabolism → individual death → diminished (grand) parental care → enhanced death of offspring → removal of dissipative germ line gene from the lineages*

Interference of each of these entities/processes with the temperature or by a mutation may cause initiation of a downstream cancer progression, another explanation of cancer's multicausality (where we found a reference of a possible causal link between the entity/process and cancer, we give this hereafter as the literature reference for the entity).

The given sequence of the cascade is tentative, and additional investigation may lead to its rearrangement. In particular it is considered possible that eventually mitochondrion-related processes will be found to precede centrosome-related processes. Keeping this uncertainty in mind, we start with the centrosome.

(1) *The centrosome* The uncertainties surrounding the centrosome demonstrate that the physiology of the cell is far from completely elucidated [70]. Since microtubules lead to the centrosome, also called the "microtubule organizing center" (MTOC) [71], Kong has proposed that microtubules carry information that is processed therein, making it "the cell's brain" [72]. A raised temperature [60] has been observed in the centrosome and it therefore can sustain an ITG.

As mentioned in Footnote 2, many analogues of electronic devices have recently been proposed in phononics including the "thermal computer" [61]. Combining the just mentioned ideas and observations, we hypothesize that the centrosome is a thermal computer which processes thermal signals carried by microtubules. Disturbance of this thermal computer is another conceivable cause

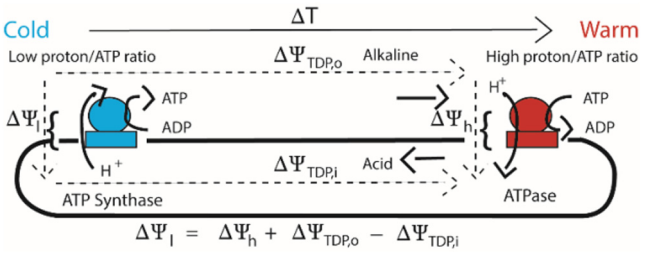

Fig. 3. The previously proposed thermonerve, a progenitor of the nerve [7]. The thermonerve gained energy from a thermal gradient by a biological analogue of the well-known thermocouple, in which two different alloys are placed in a thermal gradient which generates different electrical potentials in the alloys. In the thermonerve, electrical potentials $\Delta\Psi_{TDP,i}$ and $\Delta\Psi_{TDP,o}$ are instead generated by means of the Soret-effect in two solutions with different composition, present inside and outside a filamentous membrane [7] (the idea extends Skulachev's cable model for the mitochondrion [109]). The difference in potentials drives two different ATP Synthases, each type localized at one of the filament's end points. One is forwards active, at a low proton:ATP ratio, the other backwards active, functioning as a proton-pump at a high proton:ATP ratio. The circulating current generates net ATP from the thermal gradient. It is posited that a filamentous mitochondrion placed inside a eukaryotic cell can similarly detect ITGs: the possible relic of the thermonerve does not function as heat engine but uses the ITG for thermal signalling during carcinogenesis.

of cancer. Microtubules are often adjacent to mitochondria [73], which can yield the heat required by phononics.

The functioning of the centrosome is easily linked to aneuploidy since the centrosome moves the chromosomes during cell division: it is plausible that centrosome disturbance breaks them.

(2) *The mitochondrion* Cancer is strongly linked to the mitochondrion [53]. Transplantation experiments show that cancer goes with the mitochondria-containing cytoplasm and does *not* go with the nucleus [1]. Regular mitochondria suppress cancer.

The mitochondrion is the cellular site of oxidative phosphorylation. Its impediment is the only metabolic pathway, from a large collection of tested pathways, which negatively affected survival in a study of the link between chromosomal instability and cancer [74]. It seems a most suitable organelle for detecting errors in energy conversion.

IR radiation is associated with heat. It can elicit "the retrograde response," a signal from mitochondria to the nucleus that has been linked to cancer; its name follows from its direction opposite to the regular information flow direction from nucleus (DNA) to cytoplasm (protein) [75].

In a previous paper [7] the author described a theoretical heat engine called the "thermonerve" which consists of a filamentous membrane that generates ATP in a thermal gradient (Fig. 3). It was considered a progenitor of today's nerve that worked on thermal gradients of biomembrane size. During the global glaciations of the late Proterozoic, the thermonerve would have generated ATP for the first animals in the thermal gradients above submarine hydrothermal vents.

Today's mitochondrion can undergo dynamic fusion-fission transitions between (1) a fragmented or spherical shape, and (2) an extended, filamentous or network-like shape [76]. A filamentous mitochondrion spanning an ITG could detect a thermal gradient similar to the thermonerve, and little or no modification of the mechanism may suffice to initiate cancer.

(3) *The heat shock machinery* A macroscopic high temperature affects mitochondria, as was noticed by the first investigators of heat shock [77]. This Heat Shock process, activated by an externally applied high temperature could plausibly be activated by ITGs as well: the first report [78] mentions that the externally applied high temperature can be mimicked by the uncoupler dinitrophenol, which must generate an ITG near the mitochondrion. Heat Shock involves the promotor Heat Shock Element (HSE), and the synthesis of RNA and proteins, such as transcription factor Heat Shock Factor 1 (HSF1) and heat shock proteins (Hsps, including Hsp60 and Hsp90). HSF1 binds to the HSE promotor of Hsp genes and can drive tumorigenesis [79].

(4) *Thermal sensitivity of cell components* Temperature sensitivity is found in the plasma membrane [80], intermediate filaments [81], and even DNA and RNA [82]. The "high-temperature-required proteins A" (HTRA*n*) are involved in several processes, some related to cancer. Another thermal sensitive protein linked to cancer is the H2A.Z histone [83], a major component of the epigenetic machinery.

(5) *Chronic inflammation* Chronic inflammation stimulates cancer [9].

(6) *The inflammation amplifier based on an epigenetic switch* Recently, Murakami et al. [84] have proposed the notion of the "inflammation amplifier" for cancer, which relates to the "inflammation feedback loop" (Fig. 4) [85,86]. An epigenetic signal can drive carcinogenesis [87], and Struhl et al. [85,86] have modified Murakami's idea to such an epigenetic switch (H3K27-trimethylation) [86,88].

In some "predisposed cells" a transient activation of Src lasting 5 min turns them into cancer cells [85]. Struhl [86]:

> . . . activation of this inflammatory regulatory circuit is insufficient to trigger transformation of normal cells. Instead, this inflammatory circuit is likely to be relevant in "predisposed" cells that are genetically altered to be at an intermediate stage in the transition between a primary cell and a cancer cell. In such predisposed cells, anything that activates the positive factors (NF-κB, Lin28, IL-6, STAT3, miR-21, mir-181b-1) or inhibits the negative factors (let-7, PTEN, CYLD) will trigger the inflammatory feedback loop that induces and maintains the transformed state. As such, the triggering event does not have to be an inflammatory signal (e.g., Src) per se, *but can be any genetic or environmental change that affects the activity of factors in the inflammatory feedback loop.* [emphasis added]

The loop could combine many causes of cancer, including causes which are at the moment only partially resolved, such as the carcinogenicity of RNA. The intensity of the enhanced feedback loop can enhance dissipation quantitatively by cytokine IL-6, which is involved in inflammation, and negatively correlates with patient prognosis [89].

(7) *The Warburg effect* Warburg discovered that cancer cells have a distinct metabolism: excessive glucose fermentation in the presence of oxygen [54]. His observations were ignored by the mainstream of cancer research after the 1950s, but they are nowadays reconsidered. In the standard cancer paradigm the inefficiency of ATP generation during the Warburg effect is puzzling [90], but in the CA it is naturally linked to CTG, and thus simply explained. Excessive glutamate consumption during cancer's progression is similarly explained.

(8) *Uncoupling* CTG can also occur by other mechanisms. During cancer, mitochondria show high proton leakage [91]; the uncoupling of oxidative phosphorylation produces heat. Uncoupling can be effected in many ways, including the so called "uncoupling proteins" of varying types (UCP*n*s) [92], of which the activity increases during the progression of cancer.

(9) *Tumours and tumor cells have a high temperature* The high temperature [93] was already noted by Galen and Avicenna in ancient times. Today, CTG has been observed from the scale-range of cells [94] to the whole organism [95]. Generation of CTG by *cancer tissue* has been observed by microcalorimetry: the generated heat can be a factor 10 larger than the heat generated in regular tissue [96]. In *tumor cells* the heat production can also be much higher; Van Wijk et al. give values of 15–50 pW/cell [97].

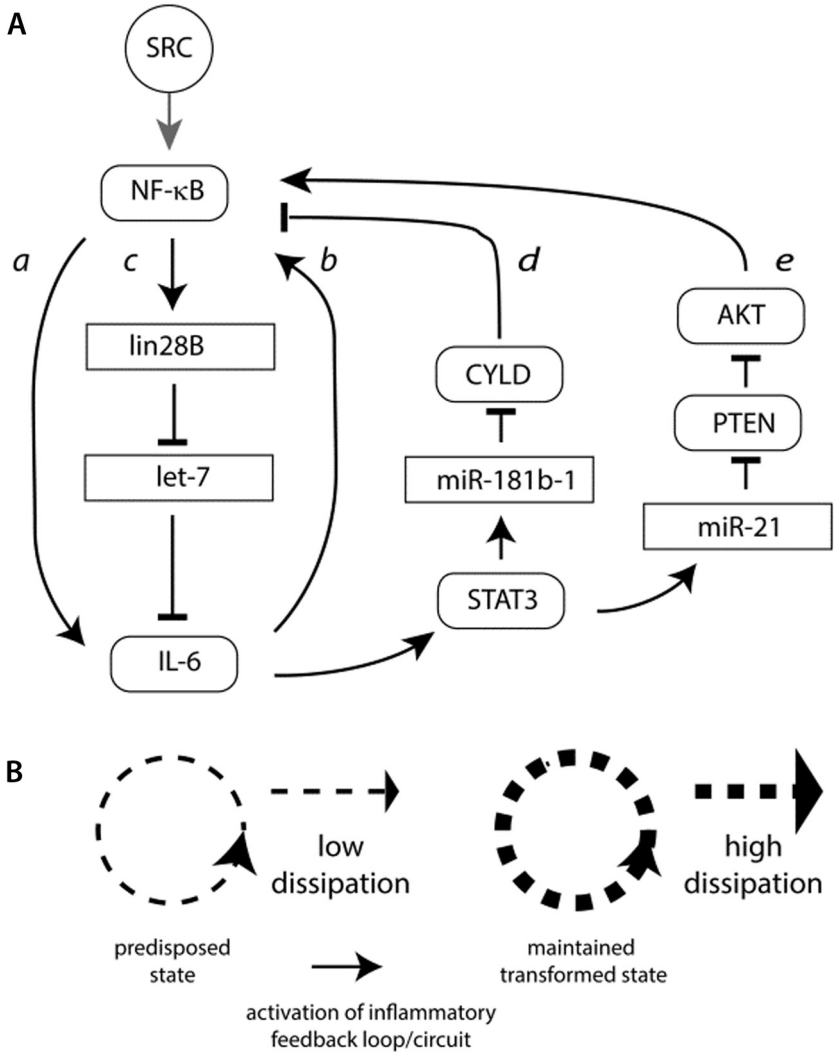

Fig. 4. The inflammatory feedback loop/circuit between the "nuclear factor" NF-κB (a transcription factor) and the cytokine IL-6 (redrawn from Fig. 7E in Ref. [85] and Fig. 7G in Ref. [86]). Rectangles indicate RNA molecules, ovals proteins. The feedback loop/circuit transforms "predisposed cancer cells" into regular cancer cells. The signal starts with SRC oncogene. *A.* The inflammatory loop/circuit consists of the composite signalling channels *a*–*e*. Channels *d* and *e* are activated through STAT3. *B.* Increase in the feedback loop signal as a result of the opening of additional signal channels may result in enhanced dissipation. For additional discussion and references see the main text.

(10) *Hypermetabolism at the end stage* At the end of cancer's progression in the patient, different cancer cell types converge to a similar end state [98]. On the organism scale, cancer types seem to converge as well. During cachexia, a frequent end stage, thermogenesis is enhanced by the "energy-wasting syndrome" [95] which comprises a diverse collection of highly dissipative processes, from an enhanced inter-organ Cori (lactate) cycle between the tumor and liver, down to uncoupling by UCP proteins.

We consider thermogenesis of the individual cancer patient. The "resting energy expenditure" (REE) is the energy spent by an individual human at rest. Recent studies in healthy humans by Pontzer [99] show that the possible increase of *daily* "total energy expenditure" (TEE) is constrained, from the base REE_{start} of REE of ~2300 kcal/day, TEE reaches a plateau of 2500 kcal/day. The main cause of variation is "physical activity" (PA): when this exceeds 200 kcal/day, REE decreases, and body mass diminishes.

The REE has been widely investigated in cancer research. A recent (2016) meta-analysis by Nguyen et al. [100] of 27 REE studies states that in cancer patients REE is on average enhanced by 8–9% (although the reported confidence interval is large).

Tumours would therefore increase the energy expenditure of the entire body. As a result, REE approaches TEE_{max}, and less energy is available for PA, which explains the fatigue reported by cancer patients [101]. We divide REE into a non-cancer and a cancer part:

$$REE = REE_0 + REE_{cancer}$$

As REE_{cancer} increases, and REE reaches its limit of TEE_{max}, REE_0 must decrease, as is observed during cachexia, and body mass becomes lost: instead of by a high PA, by a high REE_{cancer}. Because of the progressed cancer, there is insufficient energy available to maintain body mass.

(11) *The terminal phase* About 50% of cancer deaths is due to cachexia. We quote Egeblad for the second time, now emphasizing the fatal role of systemic effects [40]:

> Just as normal developing organs, such as liver and kidneys, have systemic consequences for the organism, so does the tumor organ. The *dramatic systemic effects of the tumor organ* are not limited to metastatic spread, but also include effects on immunity, coagulation and metabolism. . .. Indeed, it is these *major systemic changes that cause the majority of cancer deaths*,

rather than effects of the direct overgrowth of the primary tumor or even metastases. [emphases added]

In addition to cachexia, with severe fatigue and weight loss, Egeblad mentions infections, and thromboembolism as specific causes of death.

(12) *The removal of the dissipative germline gene from the population* As a result of this death, (grand) children of the individual receive less (grand) parental care, and their mortality must increase. Infants under 6 years old may be especially vulnerable. In rural Gambia, an undeveloped country where conditions may still resemble the conditions of humans living under natural conditions in natural environments, it has indeed been observed that infant death increases upon the death of (grand) mothers [102].

This infant death is the last step of the dissipative gene removal which is posited to constitute the essence of cancer. In the spirit of phononics, the germline gene removal can be interpreted as the processing of a thermal signal which was detected and transmitted. Because of the involvement of progeny, the whole process of the SAEED takes many generations, and surpasses the time scale of the life cycle of individual organisms.

Tumours are organs that implement thermogenesis

Tumours, primary tumours as well as metastases, appear late during cancer's progression. Tumours increase the metabolism of the entire body, and thus cause the hypermetabolism of the end stage of cancer's progression [100]:

> The presence of tumor is proposed to elevate energy expenditure. However, there is uncertainty surrounding this. It has been suggested that the tumor itself is unlikely to be the direct cause of elevated energy expenditure as tumor rarely contribute more than 5% of body weight. *A plausible explanation may be that the presence of tumours can exert an indirect effect on energy expenditure*. The production of biochemical mediators stimulated by tumor growth may alter metabolism and promote the inflammatory response which could contribute to hypermetabolism. [emphasis added]

Tumours are formed upon the attraction by cancer cells of regular cells; the resulting complexity varies strongly. Some are simple, and seem to consist of only a few cancer cells that have attracted many regular cells, such as the lymphoma of Hodgkin's disease. Other tumours are highly complex, and resemble organs [40]. Lichtenstein highlights common misunderstandings of the tumor-organism interaction, in which the tumor host is seen to support the tumor [38]:

> The tumor and organism relationships are intuitively (perhaps by analogy with infections) perceived as antagonistic. It seems that this does not correspond to reality. If tumor elimination were the real priority of the "host", it would be simply enough to ignore it. Most likely, the organism not only does not struggle against tumor, but on the contrary, it helps the tumor in all possible ways and the tumor exists exclusively due to the support from the immediately surrounding and remote normal tissues. Fibroblasts, tumor-associated macrophages, tumor-infiltrating neutrophils, stroma, bone marrow, and remote organs are involved in the "escape action". Inflammation cells are an obligatory growth stimulating component of a tumor focus. Owing to the help from the outside, tumor cells get blood supply, grow, form metastases, and mutate at a higher rate. In response to the tumor produced granulocyte colony stimulating factor, synthesis in bone marrow of angiogenic peptide Bv8 increases, and as a result, myeloid cells are mobilized and rush to the tumor focus where they induce angiogenesis.

In 2010, Egeblad et al. published a study titled "Tumors as organs" [40]:

> Solid tumours are not random mixtures of cells and ECM [extracellular matrix], but rather resemble organs, ...
>
> They contain multiple cell types and extracellular matrix components and develop through complex interactions between these different components of the tissues using processes that often resemble those used by developing organs. Tumors interact with the rest of the organism, similarly to normal organs. However, whereas normal organs have functions that support the survival of the organism, the systemic effects of the tumor organ often are what ultimately kill the patient. Thinking of tumours as organs may allow us to better understand the processes that govern how solid tumours develop and progress.

The frequent protection of tumours by the immune system is often seen as a paradox [103]. Egeblad notices that the interaction between a tumor and the immune system differs strongly from the interaction during a regular disease [40]:

> Whereas the cells of the innate immune compartment are primary tumor-promoting, the adaptive immune compartment (B and T cells) can be tumor suppressing.... Though the role of the adaptive immune compartment in suppressing cancer is well established, there is also evidence that it plays a role in promoting cancer.

In the CA, this tumor promotion by the immune system is explained by the "tumor organ" being an organ that has the function of killing the individual—in the CA, there is no paradox.

The observation that cutting the nerve to a gastric tumor impedes this tumor [104] is hard to explain from the point of view that cancer is a disease, as the effect of denervation must involve a complex mechanism. In the CA model, it is however reasonable that the progression of cancer is well regulated and under control of the entire organism, including the central nervous system.

The similarities between tumours and organs are interpreted as evidence that a tumor is indeed an organ, with the function of killing the animal in a controlled way, in agreement with the posited role of cancer in the CA.

Discussion

A comprehensive new model for cancer has been presented in which cancer is a major component of the evolutionary machinery of animals. The SAEED/CA hypothesis posits a major change in the fundamentals of cancer. Due to lack of space, we can only list a few of the numerous ramifications. Some items of the following list are summaries, others are corollaries or speculations:

(1) *What is cancer?* Seyfried has lamented the absence of a [1]:

> ... unifying theory that can integrate the diverse observations on the nature of the disease. Without a clear idea on cancer origins, it becomes difficult to formulate a clear strategy for effective management and prevention.

Here we propose such a unifying theory. Instead of the common assumption that the essence of cancer is a disease which involves the loss of control of cell division, cancer is posited to be an adaptation that permanently implements energy conservation by selecting germ line genes.

The model naturally explains the multicausality of cancer and the numerous oncogenes found by sequencing and GWAS. The multicausality [1,15] is linked to energy dissipation and the universally applicable Laws of Thermodynamics. The model explains why "everything" can be a cause of cancer, or, why, in the colloquial, "everything gives you cancer".

(2) The CA is unusual in the invoking of (grand) parental care, which falls outside the disciplines of physiology, biochemistry and molecular biology commonly called on in cancer research.

This study modifies Graham's CS, which is based on a selection mechanism involving

accelerated death of juvenile animals by cancer,

and yields the CA, with the SAEED involving

accelerated death of juvenile animals ***through accelerated death of their (grand) parents*** *by cancer*.

Animals can roughly be divided in those that give parental care (*K*-selection) and those that do not (*r*-selection) [105]. The existence of *r*-selection is no counterexample of the CA. The number of gametes produced during *r*-selection is already a good measure of metabolic efficiency, which makes a complex CA that selects against inefficiency redundant.

(3) A tumor is an organ that has the function of killing the individual by amplified thermogenesis on the short evolutionary term, so that in the long evolutionary term energy dissipation is minimized.
(4) The rarity of cancer before the 20th century permitted slightly beneficial genes to escape through recombination from "negative hitchhiking" while the adverse dissipative genes were removed.
(5) The (1) Warburg effect, (2) enhanced glutamate metabolism, and (3) uncoupling work through the heat they generate.
(6) The heat shock machinery and uncoupling proteins are components of the CA.
(7) The aggressiveness of cancer relates to the magnitude of its acceleration of death. The aggressiveness of an oncogene or of polygenes has been related to the magnitude of thermal dissipation. This death acceleration-aggressiveness-dissipation correlation is observable and verifiable. It may be therapeutically important: if heat generation is not detectable or small, treatment may be less urgent. Moreover, the efficacy of a treatment may be testable by the effect on the observed dissipation.
(8) At present, the hypothesis is only conceptual and theoretical. The many organs, animals, and historical periods in which cancer may have occurred allow for several combinations of applicability: the hypothesis may apply (1) to all cancer types in all metazoan animals, (2) to only some or a few cancer types in all animals, (3) to only some cancer types in some animals, (4) to only some animals in the past (for instance, in the first metazoans), or (5) may even not apply anywhere in the present—nor (6) having applied anywhere in the past.

Future experimental work by observers, experimenters and clinicians can clarify this uncertain applicability of the hypothesis. Such work could involve the determination of the presence of dissipative genes in a population of animals or humans, the occurrence of cancer as related to these genes, and the effect of changes in reproductive rate on the survival of intermittent starvation/famine.

In summary, an evolutionary-physical hypothesis for cancer is presented with a wide explanatory power. Cancer is posited to be an adaptation and not a disease. Selection by cancer diminishes in *the species* the energy dissipation that according to the Laws of Thermodynamics is inherent to any system, animate or inanimate. The function of cancer in *an individual* is posited to amplify in old age heat dissipation that occurred at an earlier age due to germline mutations, and thus to accelerate death, which results in a minor selection against the mutations by death of the progeny.

The hypothesis presents a complete new point of view on cancer, and can be called a truly new paradigm. Numerous reinterpretations of observations become possible. This study already explains cancer's overall progression, its complexity, its multicausality, its extancy in humans and animals, the heat produced and the correlation with its aggressiveness, its rarity in humans in the past, oncogenes, its polygeny by numerous weak oncogenes found by GWAS, the role of the centrosome, aneuploidy, the role of the microenvironment, the carcinogenicity of external high temperatures, the role of intracellular thermal gradients, the inflammation amplifier, the epigenetic switch, the role of the mitochondrion, mitochondrion transfer experiments, fusion-fission of the mitochondrion, the role of metabolism, the Warburg effect, glutamate metabolism, uncoupling, the tumor organ, hypermetabolism, the apparent paradoxal role of the immune system, and the apparent paradoxal effect of denervation.

Cancer metabolism is a currently quickly evolving discipline, also because of the many investigations of the distinct thermogenesis by brown, white and beige fat. Since the state of knowledge in this area is in this flux and also due to lack of space, we have not referred to them, but it shall be clear that the CA may be highly relevant for these studies.

The presented hypothesis cuts the Gordian knot of a vast, fast expanding, extraordinarily confusing, extensive and disorganized body of observations and experimental studies. It yields a simple explanation of cancer in terms of a few well-established notions from physics, engineering and biology such as heat, temperature, thermogenesis, energy conservation, energy conversion, (grand) parental care and natural selection. Until now, cancer has been seen as a major pathological process; this study asserts instead that cancer also may foremost be a major constructive agent of animal evolution. Cancer may be a necessity in a complex species—complex extraterrestrial life might also need cancer.

Confirmation of the presented hypothesis on the fundamentals of the cancer will most plausibly lead to improvement in cancer therapy.

The presented progression of cancer can be linked to its phylogeny: this study adds cancer to the biological phenomena of which the emergence can be modelled in terms of thermosynthesis. This study therefore gives additional corroboration to the author's tenet that thermal processes play a fundamental and central role during evolution.

Conflict of interests

The author declares no competing interests.

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