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A thermodynamic interpretation of malignancy: do the genes come later?

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Summary Current theories on cancer development focus on 'unlucky' mutations affecting oncogenes or tumour suppressor genes. In this article a theory will be developed which interprets cancer as an adaptive phenomenon – a response to cellular stress induced by an energetic overload which would ultimately lead to an increase in cellular entropy. One of these adaptive mechanisms is paneuploid polyploidization, a phenomenon frequently described in malignant tumours. This inherent property of the genome to multiply with limited sequence variability may be involved just to make new proteins which are more appropriate to manage the harmful situation of energetic overload. Another important mechanism to prevent increasing entropy is the change in chirality of proteins and carbon hydrates because the use of enantiomers with higher intrinsic energy ultimately reduces entropy of the cell. These chiral alterations in turn affect the molecular structures of proteins and DNA, resulting in abnormal function of the former and disturbances of replication, transcription and repair of the latter. Moreover, the altered proteins may – as a secondary step – induce structural changes of the DNA. Because changes in chirality affect the structure of a cell randomly, one can expect alterations of multiple genes or proteins, and this is exactly what has been described in the literature. Therefore, this hypothesis may help to clarify confusing findings of tumour genetics accumulated over the last two decades. Cancer could be seen as a reaction of a cell to entrap energy which reduces entropy, or, in other words, cancer may best be regarded as entropic devolution.

GENETIC ALTERATIONS IN MALIGNANT TUMOURS

Although a multitude of hypotheses on the etiology and development of cancer have been created, it is today generally acknowledged that genetic alterations are the key factor in carcinogenesis (1,2). These alterations are thought to be the result of mutations induced by DNA damaging agents such as radiation or radicals. The mutations, in turn, lead to either activation of so-called oncogenes, or inactivation of tumour suppressor genes within a single cell, resulting in dysregulation of the cell cycle (3). This causes a more or less unrestricted proliferation, which is one hallmark of a cancer cell. Moreover, even such complex processes as metastasis are explained by the activation of so-called metastogenes. Therefore, cancer is currently considered as a genetic disease, induced by DNA damage. But it seems that the situation is much more complex and a critical review of tumour genetics reveals problems. Until now, not a single gene has been described which is altered consistently in a given malignant tumour. On the other hand, genetic alterations which are thought to be associated with malignant tumours have also been described in normal tissues (4). Moreover, the genome has a parallel regulatory structure (5), and a parallel processing network displays the advantageous properties of redundancy,

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and consequently 'fault-tolerance' (6). Such networks tolerate multiple defects before catastrophic failure occurs (7), making it unlikely that the mutation in one or even a couple of genes would induce a malignant cell.

Epidemiological studies have calculated from the age dependence of the mortality of several of the most important types of cancers that their development requires up to twelve discrete events which, at first glance, seem to be compatible with the model of multi-step carcinogenesis (8,9). It is furthermore assumed that these initiating events are essentially at random and that interactions of the affected cells with the alterated one do not play a role. However, applying a Poisson statistic Steen (10) showed that at the single cell level the number of oncogenic events needed for transformation exceeds what is calculated by the epidemiologic data; that is, unless one assumes that every gene within a cell has an oncogenic potential or a rate of spontaneous mutations that exceeds 5×10^{-6}/gen/cell/year. Even when looking at patients with hereditary mutations such as the Li–Fraumeni syndrome, the cancer rate is much lower than predicted by the above calculation. Steen has attempted to resolve such problems by assuming that either the primary events take place not only in that one cell which becomes malignant but in more than one cell, or that much larger numbers of genes than supposed are affected. The first explanation seems to be impossible because almost all malignant tumours are amonoclonal processes. However, the important information of this calculation is that a transformed cell arises in *an area* which is affected by the oncogenic event. This is known as the 'field effect', and implies that besides the genetic alterations, intercellular interactions also have to be taken into account when discussing the development of cancer. On the other hand, if cancer is not primarily induced by genetic alterations but by a special kind of cellular stress – which induces more complex alterations within a regulatory network of a multitude of genes – the Poisson statistic and the monoclonal nature of a malignant tumour would fit.

THE SECOND LAW OF THERMODYNAMICS AND CANCER DEVELOPMENT

The human organism is a thermodynamic open system, in a state far from equilibrium, which has a much higher degree of organization compared to its environment. According to Boltzmann's theorem, the maintenance of this organization necessitates a permanent production of energy, which in most human cells under physiological conditions happens by oxidative phosphorylation. However, this kind of energy production is associated with increases in temperature and production of damaging oxygen radicals, which both increase entropy. Anyhow, according to the second law of thermodynamics irreversible processes which are characteristic for thermodynamic open systems are associated with increasing entropy. Under normal conditions the increase in entropy is minimized by utilizing the work value of energy as best as possible, because both are associated by an inverse relationship (11). Moreover, a permanent export of entropy is absolutely necessary to maintain the highly organized structures of life. Unfortunately, the dispatch of entropy is far from being perfect, which results in a constant increase in entropy during life which has been regarded as the 'final reason' for aging.

To understand cancer from a thermodynamical point of view one has to consider the relationship between thermodynamical equilibrium and dissipative structure. In cases when a thermodynamical open system is pushed away from the equilibrium, it can reach a critical point where its state changes abruptly towards more complexity, in what is called 'dissipative structure' (12). I think that a malignant tumour can be seen as a dissipative structure arising within the thermodynamical open system of the human body. Doing so one has to answer the question about the force driving a system to such a critical point. In my opinion such a critical situation arises when a localized *surplus* of energy exists and there is no possibility to export entropy. An energetic overload in most malignant cells is indicated by their abnormally high phosphorylation state. Furthermore, a relationship between abnormal storage of energy and malignancy has been suggested earlier (13). The abnormal phosphorylation state is the result of an enhanced activity of kinases or the reduced activity of phosphatases. Generally speaking dissipation of heat and photons can balance excessive energy production. But if not, an increase in entropy is unavoidable and the possibility exists that the affected cells will ultimately form a new system – a dissipative structure. There is currently no answer as to the question of how the formation of such a new system happens, although suggestive parallels have been made to incipient embryonic/developmental structures. Although unproven, it is very likely that an increase in entropy is a cellular stressor that induces a *stress reaction* in the affected cell. It is well known that malignant cells show signs of stress like enhanced content of heat shock proteins (14).

But there are probably other and even more harmful ways for the cell to reduce entropy. One of these possibilities is that metabolism uses structural components with higher intrinsic energy content. This can be achieved simply by a change of chirality. Higher biological life is dominated by L-amino acids and D-sugars forming enantiomerically pure molecules (15,16). The energetic content of a protein can be enhanced without modifying its amino acid sequence by the use of D forms of amino acids as their energy content is higher than that of

the L form (16). Therefore, it is necessary to investigate whether homochirality is broken in malignant tumours. Homochirality, however, appears to be indispensable for the regular function of enzymes and nucleic acids (15). A mixture of D- and L-amino acids inhibits the alpha-helical folding of proteins (16), and an exchange of enantiomers within a protein results in conformational change. Joyce et al. (17) were able to show an enantiomeric cross-inhibition of optically homogenous template-directed oligomerization of nucleotides, and the handedness of amino acids determines the winding of a peptide nucleic acid double helix, a DNA analogue with a backbone consisting of N-(2-aminoethyl)glycine units (18). Whether comparable changes occur when the deoxyriboses within the DNA undergo chiral alterations is unclear so far, but it would be not surprising if the promotor activity of genes and the chromatin structure are also sensitive to the enantiomeric composition. Therefore, heterochirality probably would have significant influence on many cellular functions. In this regard it is interesting to note that chiralic changes occur spontaneously during life. The reason why this happens is that the overall metabolic rate decreases with age, and amino acids which do not participate in metabolism slowly racemize towards chiral parity. The degree of chiral lability differs between the various amino acids but is most pronounced in asparagine (19). Once formed, chirons will accumulate because they are degradation resistant (20). This means that during life there is a progressive change in chirality, and that most of the common cancers have an increasing incidence with age is well known. Moreover, free radicals which are thought to be involved in carcinogenesis are believed to affect chiral conversion (21). Taken together, chiral alterations induced to prevent increasing entropy could induce severe alterations of multiple cellular structures and functions.

STABILITY OF THE GENOME

Because genetic instability is regarded as a hallmark of malignancy it is necessary to discuss the stability of the genome in general, as well as the direction of flow of information within a cell. It is noteworthy to say that the DNA sequence is not as stable as usually believed. Individuals are born with genes that are naturally unstable (22), and the fact that cells have an extensive capacity of DNA repair suggests that genetic instability is an essential biological constant (23,24). After the first complete sequencing of a plant genome the remarkable dynamic nature of the genome stands revealed – one in constant motion and one undergoing constant rearrangements. Nature allows structural DNA variations to some degree, indicating that DNA is in a dynamical state, and the degree of DNA sequence variability depends on the activity of DNA repair enzymes.

Another important ability of genes that impacts evolution is their tendency towards additivity, creating a redundancy that is free to mutate. That means that amplification of a gene gives the cell the possibility to maintain the original set of genes and to alter the structure of the additional copies just to test whether better structures have been created. This is underlined by the finding that mutation rate increases under stress – enhancing the potential to evolve rapidly when needed (e.g. genomic shocks may activate transposable elements). In the germinal centres of the lymph nodes, mutation of the immunoglobulin light chains are induced *permanently* to create the diversity of antibodies necessary to survive, and hypermutation within the immune system is used to fight off novel pathogens. Therefore, mutations are not always 'accidents', but are useful in some situations, indicating that genetic variability is an indispensable property of life. In a more general sense, Lunine stated that 'without the imperfection and vulnerability of the genetic code . . . evolution would not be possible' (25). With animal evolution, the recent discovery of hierarchical genes such as the homeobox genes has shown that slight changes can cause severe alterations, as characteristic for non-linear, chaotic processes. A cell also has the capacity to multiply the complete genome, a process called polyploidization. Polyploidization may be regarded as a buffer for the genome to absorb deleterious gene alterations, while providing creative power. Such a multiplication can be induced by regeneration, as with the polyploidization of tissue around human wounds (26).

Biological information must also conform to the second law of thermodynamics. Consequently, informational entropy of the genome will increase over time, and its correlate is genetic instability (24,27). Thermal noise has been suggested to be an unalterable baseline modulator of genetic instability (28). Therefore, genetic instability increases in the event of energetic overload. Moreover, it is known that certain regions of the genome are inherently more unstable than others (29), such as cis-regulatory DNA controlling gene expression. Therefore, an increase of entropy leads to random losses of information in DNA and affects regulation of gene expression.

Beyond the molecular level, there are questions regarding the flow of information within the cell and between cells. It is important to recognize that the genome is not a sovereign power enthroned in the cell. Genome and other cellular functions are inextricably intertwined, for example the torsion of the helical DNA formation is controlled, or when RNA is further edited by the cell. As noted earlier, environmental stress targets specific genes and causes 'hypermutation at vulnerable sites', increasing the variants most likely to survive stress.

Likewise, Wright has hypothesized that there are very sensitive directed feedback mechanisms which are initiated by stress to accelerate a type of directed adaptation (30). As evolution can be regarded, at least partially, as adaptive mechanisms to dissipate or resolve stress (31), so can the genetic changes associated with malignant tumours be seen as an 'adaptive' approach to survive a particular form of cellular stress. While cancer is negative to the survival of the individual organism, it could also be put in the larger context of life's dynamic capacity to change and evolve.

Taken together, I believe that cancer is a special kind of adaptation to energetic overload, characterized by multiplication and mutation of genomic DNA (generation of new biomolecules which enhance the probability of survival under harmful conditions), and by chiral alterations (reduction of entropy by entrapping energy) leading to abnormal configurated biomolecules. In this regard the genetic alterations are probably secondary changes. Cancer serves to dissipate energy in a type of developmental process but one in which the results are harmful to the whole organism – an entropic devolution.

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