Senescence, cancer and ‘endogenous parasites’: a salutogenic hypothesis

ABSTRACT—The integrity and health of an organism can be considered as a state actively imposed by specialised ‘salutogenic’ mechanisms (immune, endocrine, paracrine etc) on an innate tendency towards internal conflict. One major source of internal conflict arises from the operation of natural selection upon replicating sub-organismal components such as cells, organelles and gene sequences. From this perspective cancer is seen not as a pathological process arising in a healthy organism but as caused by the capacity of replicating cells to evolve ‘selfish’ adaptations and elude the finite repertoire of integrative mechanisms. Cancer can therefore be regarded as one instance of a more general tendency towards senescence due to the failure of salutogenesis and accumulation of endogenous parasites. This may provide a new and potentially fruitful approach to framing, analysing and understanding the aetiology of the degenerative diseases of senescence.

Cancer research has led to a massive expansion of knowledge at the genetic level. A great deal of detailed information has emerged, but also a few simple principles. The model of neoplasia is roughly as follows [1–3]. Cancer is defined as uncontrolled cell replication, and the process that causes it is natural selection. Cancer arises from a single ancestral cell with enhanced replicative capacity due to a gene mutation or serial mutations. The mutation may either enhance the growth of the cancer cell itself (eg activation of oncogenes) or remove the inhibitory restraints on cell growth (eg inactivation of tumour suppressor genes). Mutations favourable to the promotion of uncontrolled replication accumulate progressively among progeny of the original ancestral cell, and lineal descendants will undergo adaptive evolution (tumour progression).

Knowledge concerning the genetic lesions which may contribute to the cancer process can be seen as filling in detail within this general framework. To use Mayr’s terminology [4], the ultimate causes of neoplasia are clear in outline, while cancer research has been mainly a matter of delineating the proximate causes—those mechanisms that give rise to particular cancer diseases in particular situations.

What follows should be seen not as supplying novel theories of cancer, nor as a review of the latest information concerning mechanisms, but as suggesting a broad perspective in which to view neoplasia. Cancer is seen not as a qualitatively distinct entity but as an instance of a more general senescence phenomenon named endogenous parasitism. It is a perspective that embeds the modern, gene-centred, evolutionary view of the nature of the cancer process into a human-centred view which concentrates on the evolution of the organism and the nature of health.

Endogenous parasitism

The evolutionary process by which endogenous cancers are generated can be seen as inevitable where there is replication of genes in a context of selection pressure. Natural selection will act such that gene mutations associated with ‘selfish’ phenotypic adaptations will differentially be favoured [5]. For instance, mutations coding for adaptations that enhance cell replication will be retained, while mutations coding for phenotypic functions that have a role in maintaining organismal functions (the ‘somatic duties’ of the cell [6]) will progressively be discarded. This tendency must continually be thwarted by the organism if health is to be maintained.

The process of within-organism natural selection for ‘selfish’ phenotypes is not, however, limited to cells, and applies equally to any gene-bearing component (or ‘vehicle’ [5]) that codes for its own reproduction—such as an organelle [7]. For example, it seems plausible to speculate that evolved selfish adaptation in mitochondria might explain the progressive decline in the performance of mitochondrial ‘duties’ of oxidative phosphorylation, combined with increased replicative efficiency due to chromosomal shortening [8,9]. A similar example could be the proliferation of non-coding ‘selfish DNA’ in the genome when there may be no direct phenotypic consequences, merely a differential survival of DNA on the basis of its capacity to self-replicate [5]. Such changes would not usually be referred to as ‘cancer’ but would nonetheless explainable as a result of the same basic process of natural selection.

This tendency for natural selection at sub-organismal levels of organisation can be described as parasitic, in that phenotypic evolution is in the direction of exploiting the organismal environment rather than contributing to its functional integrity. Parasites will pursue replicative goals at the expense of organismal fitness. I have therefore suggested the term endogenous parasitism to describe the process of natural selection at the sub-organismal level [9].

There is also a close analogy between the selective process that generates endogenous parasites (eg tumour progression) and the process of within-host
evolution of ‘exogenous’ parasites such as pathogenic bacteria [10]. Because a rapidly replicating parasite can evolve but the host cannot, parasite variants are selected that have the greatest resistance to the host’s immunological defence mechanisms. Although the parasite may initially be held in check by the immune system, the selective accumulation of adaptive mutations within the parasite genome means that host defences are progressively eluded by new generations of parasites, and ultimately overwhelmed. This has been suggested as a possible cause of senescence [10].

Possibility of organisms

Organisms arise owing to natural selection acting upon the germ line genome [5–7]. The organism is necessary to the germ line because the sex cells are the only route by which the whole set of cooperating genes are able to reach future generations of new organisms. Selection pressure at the level of the organism will therefore favour the evolution of mechanisms that maintain integration and harmonious functioning at least until reproduction has occurred [7].

Multicellular organisms commence life as a somatic clone, but the operation of natural selection upon random mutations in succeeding generations of cells will mean that organisms progressively evolve into chimeras composed of the original zygotic genome plus newly evolved cell lineages [6]. The integrity of a clone is easily explained on the basis of identical cellular genomes having identical replicative interests, but the different genetic compositions of different cells in a chimera are a potential source of intercellular conflict.

The tendency to generate endogenous parasites means that natural selection operates in a sequential fashion, first to create the organism, then to destroy it. Organism-level selection dominates until the usual age of reproduction, after which the balance progressively tips away from the need to maintain organisinal integrity and towards ‘allowing’ sub-organism selection [11]. This sequence may seem paradoxical, futile, or even tragic, from an organism-centred viewpoint. However, from the gene-centred perspective of natural selection, the organism is ‘merely’ a vehicle for producing further copies of the germ line genome [5]. Because maintaining organisinal integrity is costly, a ‘disposable’ organism is the most efficient way of ensuring gene survival and replication [9,11].

Salutogenic mechanisms

Traditionally medicine has assumed health and sought to explain disease. The study of disease is pathology, and the processes that cause disease are described as pathological. Cancer has generally been interpreted, from an organism-centred perspective and within the pathological framework, as an ‘abnormal’ event arising in the context of an integrated organism and disrupting its state of health [12]. In other words the occurrence of cancer is seen as the state that requires explanation.

However, an organism is not intrinsically harmonious and is a site of potential conflict at every level of organisation [13]. Health should be seen as something that cannot be assumed and must itself be explained [14]. To rephrase Dawkins [15], there is an infinite number of ways to be unhealthy, but only a few ways of being healthy. Health, not disease, is the state that requires explanation, and disease may most plausibly be considered a consequence of the failure to maintain health.

The study of health and its determinants has been dubbed salutology, and the processes by which organisinal health is created and maintained may be considered salutogenic [14] (the name was coined by Antonovsky [16] and derives from ‘salutary’, meaning health-promoting or beneficial). Salutology is not merely the reciprocal of pathology [14,17], since the processes that ‘cause’ health are often different from the processes or events that ‘cause’ disease.

The ultimate, foundational salutogenic processes that ‘cause’ (or enable) health will include the evolutionary history, the organism’s developmental history from fertilised egg to adult capable of reproduction, and—in humans—a vast range of social processes [6,7,16,17]. The proximate salutogenic causes would include the whole spectrum of mechanisms that have evolved to create and sustain organisinal integration.

Proximate mechanisms range from organism-wide systems (such as immune, endocrine and nervous systems) to a large and growing number of described intercellular control and signalling mechanisms to regulate cell reproduction, differentiation etc, such as those coded for by the various ‘tumour suppressor genes’, and the signals to induce apoptosis or programmed cell death [1–3,18]. An analogous role may be surmised for many transcription regulating processes, eg the control of intragenomic conflict [19]. Another vital class of salutogenic mechanisms is that which monitors and repairs damaged DNA [7].

The value of a salutogenic perspective is heuristic. I suggest that it is often useful to consider health and disease as alternative outcomes of a dynamic conflict between salutogenic forces (which act to maintain organisinal integrity) and pathological forces (which cause disintegration or destruction). This may have implications both as a framework for research and as a background theorem for therapeutic intervention [9,14,17].

Senescence and degenerative disease

Slow maturation and a lengthy period of development means that transmission of genes in a human depends upon many years of good health leading to reproductive maturity. Following reproduction the need to look after dependent infants likewise places a premium
upon an extended lifespan. Such selection pressures have led to the evolution of highly effective salutogenic mechanisms to control the endemic threats to organismal integration, including neoplasia. Human health and longevity [20] are therefore byproducts of the constraints on effective human reproduction.

Although multicellular organisms have ‘solved’ the problem of controlling endemic neoplasia well enough to enable organisms to reproduce and pass on their genes to future generations, this solution is temporary for each organism. Natural selection is constantly operating on dividing cells, and cancer can only be held in check by salutogenic mechanisms which will inevitably develop imperfections.

The production of endogenous parasites is a phenomenon of senescence, the effects of which accumulate with time. This implies that cancer is not a distinct entity. Cancer is a particular instance of the generalised phenomenon of natural selection acting upon organismal components. This is important because the same process that gives rise to cancer cells may be expected to give rise to other deleterious outcomes both at the cellular level (including the various ‘pre-cancerous’ states) and in other subcellular replications such as organelles and gene sequences.

Cancer is likely to be a major problem the longer an animal lives and the lower its death rate from accident, predation or exogenous parasites. Natural selection of sub-organismal components will eventually lead to variants able to elude any conceivable integrative system. This is consistent with the observation that cancer becomes a relatively more common cause of death among humans as average lifespan increases.

A consideration of natural selection within organisms offers the possibility of extending the reach of Darwinian medicine—an approach that uses insights from evolutionary theory to throw light upon human health [21]. It is a truism to observe that ‘degenerative’ diseases of senescence are increasingly important in developed countries [22]. Endogenous parasitism opens the door to a different way of approaching and classifying such ‘diseases of civilisation’. It seems reasonable to speculate that the aetiology of disease processes such as atherosclerosis and the pathologies associated with Alzheimer-type dementia might be fruitfully analysed in terms of the development of endogenous parasites [9].

The message is bleak. The organism is disintegrating from the moment of its formation, due to the tendency for endogenous parasitism among replicating components. Senescence is apparently inevitable, either from neoplasia or from some other ‘selfish’ adaptation in some other sub-organismal component. If cancer does not kill us, it is likely that a different kind of endogenous parasite eventually will.

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