Published: December 2017

www.chem-tox-ecotox.org/scientificreviews

SCIENTIFIC **REVIEWS**

Cancer as a Microcosm of Evolution? Cancer risk is inherent to the evolutionary 'design' of genome mutability

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ABSTRACT

The seminal publication of evolutionary biologists John Maynard Smith and Eörs Szathmáry in 1995 advanced the theory of major evolutionary transitions in the process of evolution of biological entities on Earth. They argued that these transitions went for millions of years through several major changes in the way genetic information was organized and transmitted from one generation to the next. Also, in their theory it was suggested that cancer is a disease that emerged out of the transition from single-celled organisms to multicellular organisms (animals, plants, fungi), half a billion years ago. Ever since then, evolution at the organismal level has been developing defenses to keep in check the potential for evolution at the cellular level.

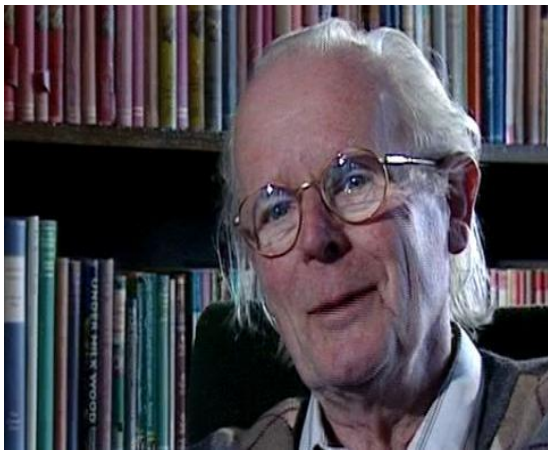
Cancer cells can be considered as microcosms of evolution. When tumors develop there is a mosaic of mutant cells competing for space and resources, while trying to evade predation by the immune system and can even cooperate to disperse and colonize new organs. The evolution of neoplastic cells explains both why we get cancer and why it has been so difficult to cure cancer tumors.

Professor Mel Greaves advanced in 2000 his evolutionary ideas on cancer with the book: Cancer: and Evolutionary Legacy" In which he proposed that "….Cancer is an evolutionary problem. First, and foremost, the process of progression from neoplastic to malignant tissue is a process of natural selection by which mutant clones evolve to escape cell cycle checkpoints, apoptosis, and other host defenses. This is the basis for the emergence of resistance and relapse after treatment. Second, cancer is a disease that emerged out of the transition from single-celled organisms to multicellular organisms, half a billion years ago. Third, and most difficult to assess, evolution has spent most of human history tuning our bodies for a set of experiences that most of us, happily, no longer share. Our modern lifestyles may relieve us from some of that suffering while also imposing new hazards for which our bodies are singularly unprepared. This review examines a series of recent research papers on the subject of evolution and cancer development. Explaining the basic theories based on scientific research, cancer can be placed within the broad framework of evolution. Cancer makes more sense in the light of evolution, and most cancer investigators would agree that taking into account the evolutionary dimension can promote more effective therapeutic trends.

Introduction

In 1995 the famous British biologist John Maynard Smith (theoretical evolutionary biologist and geneticist, University of Sussex, UK) and the Hungarian evolutionary biologist and ecologist Eörs Szathmáry (Eotvos University, Budapest, Hungary), wrote jointly an influential review in *Nature* (374:227-232, 1995) on the major evolutionary transitions of biological species on Earth. Also, in 1995 the authors advanced their ideas with the interesting book "*The Major Transitions in Evolution*". This book was a seminal publication that continues to contribute to ongoing issues in evolutionary biology. The authors identified several properties common to the evolutionary transitions, such as, smaller biological entities have often come about together to form larger entities. e.g. chromosomes, eukaryotes, sex multicellular colonies. They proposed that smaller entities often become differentiated as part of a larger entity, e.g. DNA and protein, organelles, anisogamy, tissues, castes. The smaller biochemical entities are often unable to replicate in the absence of the larger entity. e.g. DNA, chromosomes, organelles, tissues, castes. The smaller entities can sometimes disrupt the development of the larger entity, e.g. meiotic drive (selfish non-Mendelian genes), parthenogenesis, cancers, coup d'état. They proposed also that during these evolutionary transitions new ways of transmitting information have arisen. e.g. DNA-protein, cell heredity, epigenesis, universal grammar.[1-3]

The main line of their biological theory of evolutionary transitions was that life on Earth advanced through several major changes in the way genetic information was organized and transmitted from one generation to the next. These transitions include the origin of life itself, the first eukaryotic cells, reproduction by sexual means, the appearance of multicellular plants and animals, the emergence of cooperation and of animal societies, and the unique language ability of humans. In their book they proposed a unified discussion of the full range of these transitions highlighting the similarities between different transitions--between the union of replicating molecules to form chromosomes and of cells to form multicellular organisms. The authors trace a common theme throughout the history of evolution: after a major transition some entities lose the ability to replicate independently, becoming able to reproduce only as part of a larger whole. Also, they investigated this pattern and why selection between entities at a lower level does not disrupt selection at more complex levels. Their explanation encompasses a compelling theory of the evolution of cooperation at all levels of complexity.



John Maynard Smith, 1920-2004

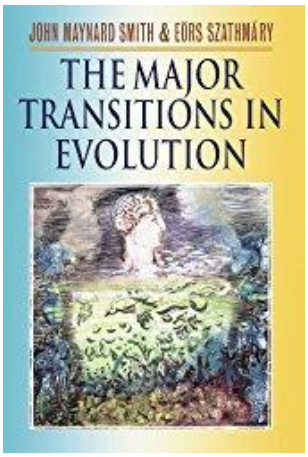


***Figure 1**. John Maynard Smith was one of the most influential evolutionary biologists of his generation that succeeded the "founding fathers" of population genetics, as he was fond of calling Fisher, Wright, and Haldane.*

They proposed that "…There is no theoretical reason to expect evolutionary lineages to increase in complexity with time, and no empirical evidence that they do so. Nevertheless, eukaryotic cells are more complex than prokaryotic ones, animals and plants are more complex than protists. This increase in complexity may have been achieved as a result of a series of major evolutionary transitions involving changes in the way information is stored and transmitted…". Also, in their theory it was suggested that cancer is a disease that emerged out of the transition from single-celled organisms to multicellular organisms (animals, plants, fungi), half a billion years ago. Ever since then, evolution at the organismal level has been developing defenses to keep in check the potential for evolution at the cellular level.[3,4]

Cancer as an evolutionary process

Cancer cells (or neoplasms) can be considered as microcosms of evolution. If we look carefully into a neoplasm, there is a mosaic of mutant cells competing for space and resources, their main effort is to evade predation by the immune system and can even cooperate to disperse and colonize new organs. The evolution of neoplastic cells explains both why we get cancer and why it has been so difficult to cure cancer tumours. Scientists suggest that the tools of evolutionary biology and ecology can provide us with new insights into neoplastic progression and the clinical control of cancer.[5]

Carcinogenesis has been traditionally interpreted as the sequence of initiation (mutations in the cellular DNA) and promotion (clone expansion), which has an interesting similarity with the neo-Darwinian theory of evolution. This theory is also called the modern evolutionary synthesis, that integrates Darwin's theory of evolution by natural selection, the theory of genetics (Mendel) as the basis for biological inheritance, and mathematical population genetics. The theory introduced the discoveries of units of evolution (genes) with the mechanism of evolutionary natural selection. Cancer rates show great variation in different countries of the world, a variation which is only marginally explained by genetic differences. Professor Paolo Vineis *(Chair of Environmental Epidemiology at Imperial College, London*) in an important paper suggested that mutated cells adapt to environmental "niches" better than normal cells, in a gene-environment interaction that involves the history of genetic changes in the cell and the type of the surrounding environment. According to Vineis, cancer might represent an attempt by the cells of an individual to adapt to a changing environment. The origin of cancer is similar to the process that leads either to speciation of to the adaptation of involved cells to a certain environment. The best example of a selection of clones at the cellular level is represented by immunity. These immunity cells are selected in order to produce large amounts of the specific antibody. This idea led to the attribution to lymphocytes of the same evolutionary potential that Darwin attributed to a population of organisms that have to adapt to changing environmental conditions. In the past a debate was going among scientists about whether cancer is mono- or polyclonal. The latest conclusion is that the pre-neoplastic events are polyclonal, i.e. cell proliferation that precedes cancer tends to involve several cell clones. However, the crucial event leading to cancer seems to be the selection and further expansion of a single clone, characterized by a `carcinogenic advantage'.[6-8]

It is argued that although the theory of cancer initiation and progression is deeply rooted in evolutionary and ecological concepts, many promising opportunities for the application of evolutionary biology to oncology remain unexplored.[9,10]

The scientific literature of the last decades, showed limited examples on the applications of evolutionary biology in areas of understanding carcinogenetic mechanisms and controlling neoplastic initiation and progression. Advances of knowledge in this field can throw enough

light for the processes of mechanisms and prevent therapeutic failures in cancer treatments. This situation has changed now. Scientists in the last decade started to show a growing interest in the interface between cancer and evolutionary and ecological biology. Despite the useful understandings of evolutionary changes in cancer progression many basic parts of the puzzle are missing. Scientists need to know how variation is created and selected for, and the adaptive consequences of interactions between environments and genes. They also need to understand the relative roles of stem cells and differentiated cells in cancer dynamics.[11]

Perhaps, the greatest challenge is to understand the relevance of carcinogenic processes occurring at one scale for patterns at another.[12] It is increasingly recognized by cancer experts that many neoplasms are associated with chronic inflammation, aging, and changes in local microenvironments, and as well as in tissue structure and architecture. So, the questions, are these phenomena causes or consequences of genetic instability and progression, or less interestingly, correlations without demonstrable causation?[13-15] Applying evolutionary theories to cancer initiation and progression can bring better understanding but the road is very long and includes difficult scientific challenges. Scientists propose that the drivers of carcinogenesis lie more in the adaptive changes that are enabled by local or systemic alterations of tissue architecture than in the genetic changes observed in cancer cells. A full understanding of cancer biology and therapy through a cataloguing of the cancer genome is unlikely unless it is integrated into an evolutionary and ecological context.[16]

Cancer as a Darwinian struggle. The evolutionary legacy

Cancer is often portrayed as a Darwinian struggle in which a progenitor cell evolves or progresses over a series of hurdles. However, evolution is a concept much easier to recognize than to define or apply. All living things evolve. The puzzle is which one of a number of plausible or seemingly improbable pathways is taken. The usual question that somebody hears nowadays, but why so many people develop the cancer disease at some point in their lives? To get to the answer, we must understand that cancer is an unfortunate by-product of the way evolution works. Large and complicated animals like humans are vulnerable to cancer precisely because they are large and complicated. But even though it is evolutionary processes that have made cancer such a problem, it is also evolutionary thinking that is now leading to pioneering treatments that could stack the odds against cancer and in favour of our health.

In 2000 Mel Greaves (Professor of Cell Biology, Institute of Cancer Research, London) published a thought provoking perspective on cancer based on the evolutionary perspective, under the title, *Cancer: The Evolutionary Legacy* (Oxford University Press). Although there were some scientific articles and reviews on the subject, this was the first book to put the story of cancer in an evolutionary perspective. It emphasized the fact that cancer is a particular type of disease that emerged out of the evolutionary transition from single-celled organisms to multicellular organisms, half a billion years ago on Earth. Explains why different cultures have different cancers. Also, in the book, Greaves provide the historical context of the issues relating to cancer. [17]

The book was reviewed in medical publications. Dr. CC Maley (Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, WA, USA) wrote: "….Cancer is an evolutionary problem in three ways. First, and foremost, the process of progression from neoplastic to malignant tissue is a process of natural selection by which mutant clones evolve to escape cell cycle checkpoints, apoptosis, and other host defenses. This is also the basis for the emergence of resistance and relapse after treatment. Second, cancer is a disease that emerged out of the transition from single-celled organisms to multicellular organisms, half a

billion years ago. Ever since then, evolution at the organismal level has been developing defenses to keep in check the potential for evolution at the cellular level. Third, and most difficult to assess, evolution has spent most of human history tuning our bodies for a set of experiences that most of us, happily, no longer share. Our modern lifestyles may relieve us from some of that suffering while also imposing new hazards for which our bodies are singularly unprepared. Greaves hits upon all three of these aspects of cancer in his recent book, "*Cancer: The Evolutionary Legacy*". The reviewer states: " …*The Evolutionary Legacy* is intended for a popular audience…… Throughout the book, Greaves is careful to provide the historical context of the issues. He also connects the issues in cancer to other areas of medicine when they involve the same processes. The first part of the book, on progression, contains the most interesting discussions of the role of evolution in cancer. The evolutionary arguments are weaker in the epidemiological section, perhaps reflecting the difficulty of addressing stories in our inferences of human adaptations. The last section on treatment also contains interesting evolutionary ideas but is too short to really develop them.

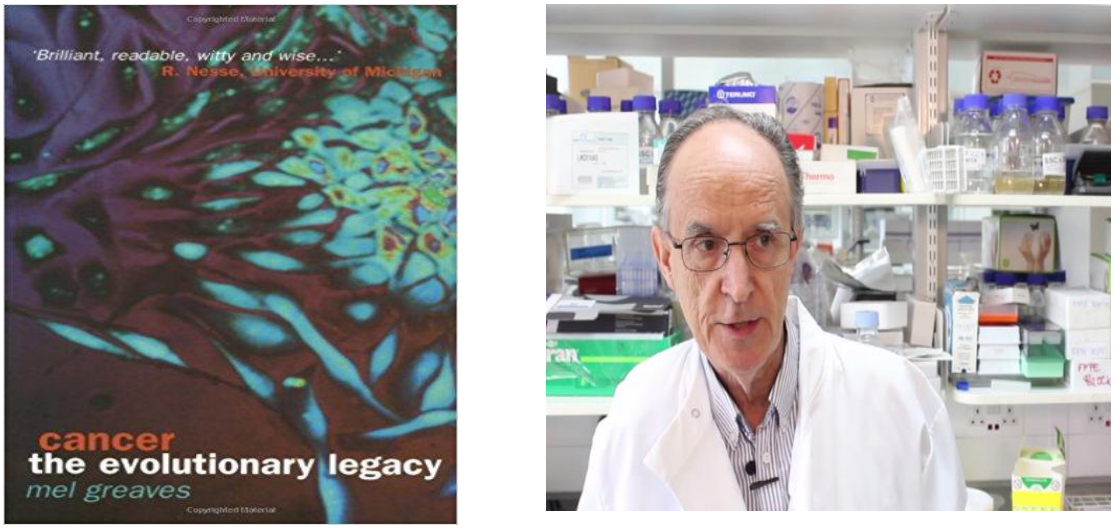


Figure 2*. Mel Greaves, Cancer: The Evolutionary Legacy (Oxford University Press, 2000). The book was a thought provoking perspective on cancer. Prof. M. Greaves contacted innovative research to unravel the causes of childhood leukaemia. He has received many awards, Prof. Greaves is Fellow of the Royal Society (F.R.S).*

"…. On the whole, the book is too short. Greaves raises a variety of fascinating topics, whetting our appetites. I only wish he had had more space to serve up the full smorgasbord. Perhaps this is too much to ask for a survey of the entire cuisine of cancer, and one accessible to the general public at that. ……. Greaves shows an appreciable mastery of the issues, and does not try to obscure their complexity. He also shows a refreshing willingness to express his personal opinions on these issues, and the intellectual honesty to clearly acknowledge them as such. If you are looking for a thoughtful overview of the issues of evolution in cancer, *The Evolutionary Legacy* is a good place to start whetting our appetites. I only wish he had had more space. Greaves shows an appreciable mastery of the issues, and does not try to obscure their complexity. He also shows a refreshing willingness to express his personal opinions on these issues, and the intellectual honesty to clearly acknowledge them as such. If you are looking for a thoughtful overview of the issues of evolution in cancer, *The Evolutionary Legacy* is a good place to start…".[18]

Another review of the M. Greaves' book appeared in *New England Journal of Medicine* by Shibata D, M.D. (*N Engl J Med* 342: 1762, 2000). In the review Dr. Shibata wrote: "….Recent advances allow increasingly fine dissections of the mechanisms underlying cancer. What causes a normal cell to become a killer? Although the final missteps are a natural focus, the development of cancer is contingent on remarkable chains of events. As in many disasters seen in retrospect, the final flaw is seldom the sole culprit. Greaves illuminates this deep evolutionary trail. *Cancer: The Evolutionary Legacy* is a thought-provoking perspective on cancer and evolution. It is a personal, high-spirited narrative by an experienced and knowledgeable cancer researcher and is written in a style similar to that of popular books on evolution. Because formal studies of evolution are often impenetrable, Greaves's unconventional approach succeeds remarkably. By clearing away the intellectual camouflage guarding evolution and cancer, Greaves makes the topic accessible to both general readers and specialists. The thesis of this book is logical, but it differs from that of most books on cancer. In essence, Greaves argues that cancers are the ends of long, unbroken evolutionary chains that extend back billions of years. The lineage of a cancer cell has existed since the dawn of life. A journey through time does much to explain cancer and the value of studies of organisms such as yeasts, flies, and mice in attempts to cure cancer. At both ends of a cancer lineage, single clones are selected for survival, expansion, invasion, and migration. In between is the harmony of metazoan life, where the behavior of individual cells is harnessed for the good of the whole. Millions of years of socialization are lost within a few decades of tumor progression. The chain that connects this past and the present is DNA. The standard principles of evolution apply. DNA replication is inherently prone to error, and these errors provide new substrates for evolution or progression. Selection acts as a filter that determines which mutations persist. The complete history of a cancer cell includes the making and then the breaking of the genetic controls needed for multicellular life. Chance pervades the entire process because of the randomness of mutation, the ambiguities of selection, and the blindfold nature of evolution. The author uses numerous persuasive examples to illustrate the concept of cancer within this framework of evolution. Germ-line mutations can prematurely start progression, whereas lifestyle alters the odds, highlighting nature–nurture mismatches. About a third of the book is devoted to epidemiology, with excellent expositions of prostate, breast, and cervical cancer. Tobacco and radiation are given their well-deserved roles as important environmental carcinogens. Overall, Greaves does an excellent job of explaining and placing cancer within the broad framework of evolution. Cancer makes more sense in the light of evolution, and most cancer investigators would agree with the author's views and conclusions. Books such as this shed light on cancer by elegantly incorporating the unifying theme of evolution, but inevitably, studies of cancer will, in turn, shed light on the mysteries of evolution…".[19]

Professor Mel Greaves is also a founding author of **The Darwin Cancer Blog** (keeping an evolutionary eye on cancer, https://thedarwincancerblog.com/), a forum for discussion of how an evolutionary perspective is changing thinking about cancer.

Interview: Greaves on cancer through the lens of evolution (2016)

(Mel Greaves: Cancer through the Lens of Evolution. Online: 26/10/2016. *Trends in Cancer*, Open Access, DOI: http://dx.doi.org/10.1016/j.trecan.2016.10.007).[20]

Q. You have always advocated that cancer should be studied from an evolutionary perspective. Why is that so?

AN. My answer is both pragmatic and philosophical. Cancer, like other complex problems in biomedicine and science generally, is more likely to be tackled successfully if we have a coherent and unifying view of its fundamental nature. In the 19th century, cancer was

widely regarded by surgeons and pathologists as a 'disease of civilization or stress'. Not much of an advance on the ancient Greek view that cancer was a manifestation of a melancholic predisposition. In the 20th century, inspired by Boveri [Theodor Heinrich Boveri (1862 – 1915) a German biologist who was notable for first hypothesising the cellular processes that cause cancer], it was confidently concluded that cancer was 'a genetic disease'. This has now been superseded in the 21st century with the notion of cancer as 'a disease of the genome'.

There is of course an element of truth in those latter descriptions, but in my view they do not cut it. They fall short and lack context. The problem here relates to how scientists of different disciplines handle the notion and meaning of 'cause'. It is not surprising that epidemiologists, cell and molecular biologists, geneticists, and oncologists, at least in the past, saw the issue of cause somewhat differently with respect to questions and answers. To my mind, any fundamental explanation of cancer as a disease has to accommodate three related challenges to be credible. One, what are the key ingredients of cancer risk? Two, what drives (or restrains) the emergence of a malignant tumour? And, three, what is the mechanistic basis of cancer cells' resilience or resistance to our best therapeutic tools? An evolutionary perspective fits the bill. It provides a framework or context that can make sense of the details. Dobzhansky [Theodosius Dobzhansky (1900 – 1975) a famous and prominent Russian-American geneticist and evolutionary biologist, his work shaped the unifying modern evolutionary synthesis] surely had it right in 1973 when he opined that 'Nothing in biology makes sense except in the light of evolution.' Although I doubt if he had pathology and medicine in mind as well.

In 1976, Peter Nowell [Peter Carey Nowell (1928 –2016) was an American cancer researcher, he discovered the Philadelphia chromosome in patients with chronic myelogenous leukemia, a critical step in showing that cancer has a genetic basis, contrary to a widespread belief at the time], in his landmark review in *Science ("*The clonal evolution of tumour cell populations", 1976), highlighted that cancer clones evolve or change over time, and that this has relevance to treatment. Embed that concept within a Darwinian ecosystem context, and empower it with genomic insights, and we have the essence of cancer clone development, as most practitioners of cancer research and oncology now recognize. I have argued that by focusing on proximate causal factors (important though they may be from the perspective of prevention) we miss a whole dimension of risk. **Cancer risk is inherent to the evolutionary 'design' of genome mutability, stem cells, multicellularity, and our prior (beneficial) adaptations**; for example with skin pigmentation and hormonal cycles. For me, causal exposures only make sense in that context.

And, finally, the resilience of advanced cancer to therapeutic assault is perhaps what you should expect of a semi-autonomous and robust cellular parasite. They can call on survival tactics for which there is a billion-year memory – playing by numbers with rare escapees fuelled by the lottery of random mutation, exploiting signal network plasticity or hunkering down in a dormant state. It's survival of the fittest. I started my scientific career in the 1960s learning evolutionary biology from John Maynard Smith and others, so I was primed, and may be biased, from that point on. But somehow the answer now just seems so dammed obvious.

Q. How are new technologies enabling evolutionary studies?

AN. There is no substitute for creative ideas in science but, unquestionably, technological innovations greatly fuel and accelerate progress. Evolutionary studies in cancer to date, especially on cancer clone evolution, have benefited in particular from single-cell analytical methods: monoclonal antibody-based immune-phenotyping, gene expression signatures, genotypes and lineage-tracking *in vivo*. These tools have revealed remarkably complex and

dynamic phylogenetic architectures of cancer cell clones and their variegated genetics. Tracking clonal evolution in real time via sensitive serial screening of cell-free DNA in plasma now offers the prospect of monitoring the emergence of recurrent or resistant clones, enabling prompt intervention. This circumvents some of the problems linked to the complex topography of subclonal distribution in tissues and the inherent selectivity or bias of biopsies.

Q. Where do you feel cancer evolutionary biology will have the biggest impact?

AN. The only thing that we can reliably predict about the future is that it will happen. I certainly hope that an evolutionary perspective will strongly endorse the importance and potential impact of prevention and early intervention in cancer. The epidemiological evidence linking most common cancers to potentially avoidable or modifiable lifestyle factors is strong. Early tumours in most, although perhaps not all cases, will be less resilient to challenge. A caveat is that we need to be smarter at distinguishing or predicting bad from benign players. The biggest challenge is how best to thwart the evolutionary resilience of cancers that present late in the clinic, for example those of pancreas, lung, brain, and ovary. Evolutionary principles and methods are likely to be important, and there is much that could be learned or borrowed from other fields – antibiotic resistance in bacteria and drug resistance in malaria, tuberculosis, and HIV. Some promising ideas are currently being explored including therapeutic combinations, coopting the versatility of recognition of the immune system into an arms race in cancer. A new and exciting prospect is evolutionary steering. Studies in simpler microbial systems suggest that it may be possible to design scheduling of drug combinations to steer or push cancer clone evolution into a more benign cul-de-sac.

Q. What are the most exciting questions in cancer evolution?

AN. Once you embrace an evolutionary perspective, a host of exciting questions are opened up. For me, one of the most interesting is whether it is possible to both predict in advance and then modify cancer clone evolutionary trajectories. I subscribe to the view that cells with self-renewal, or stem cell-like potential, are the cellular drivers of cancer evolutionary progression, metastasis, and recurrence or relapse. The necessary caveat is that this is not an inherent or stable state. I am excited by the prospect of learning more about how the self-renewal option operates and is regulated. Personalised, genome-guided therapeutics are a real if challenging prospect, but isn't there an opportunity also for a more generic approach tackling cancer via the essential self-renewal bottleneck?

Q. What other issues or challenges remain unresolved in the drive to understand and exploit the evolutionary biology of cancer?

AN. A whiff here of Rumsfeld's unknown unknowns? We do have some important known unknowns. We still remain ignorant of some of the crucial biology of cancer cells and are probably underestimating complexity. I am somewhat wary of a very gene-centric approach. It would be interesting and potentially of practical value if we had more insight into the ecosystem pressures that select for improved fitness of cancer cells. But then to understand cellular fitness, we also need to have a better grasp of how inherited gene variants and acquired mutations operate collectively or epistatically in a network providing the phenotypic substrates for selection. Despite being a biologist rather than a clinician, I have always been a strong advocate of 'real' or patient-based studies. Nevertheless, I suspect that further validation and understanding of the ecology of cancer will require better models of the disease *in vivo* and in more realistic 3D culture systems.

Q. Are there other areas of medicine where evolutionary thinking has or can make a difference?

AN. Certainly, and most obviously with antibiotic resistance, which has recently been highlighted at the UN as an urgent, worldwide problem. Evolutionary or Darwinian medicine is a relatively new branch of biomedical sciences that seeks to apply evolutionary principles to all areas of medicine including chronic diseases of modern societies – diabetes, obesity, and neurodegenerative conditions. Perhaps the clearest example, other than cancer, of evolutionary ideas being highly pertinent to medicine is with infectious disease. Here we witness, not dissimilarly to cancer, an arms race between rapidly-evolving pathogenic species and the immune surveillance system. Vaccination can tip the balance in our favor, but high mutation rates and fast replication are winning cards for the bugs.

Q. Overall, are you optimistic that evolutionary studies of cancer will be beneficial?

AN. One must be an optimist to survive and thrive in science. But there are real and tangible reasons for being optimistic that an evolutionary perspective on cancer will pay rich dividends; not least it's logical coherence, technological underpinning, and the superb cadre of young scientists now active in the field.[20]

How cancer shapes evolution and evolution shapes cancer

In the last decades many evolutionary theories of cancer appeared on the scientific literature. The analysis and understanding of evolutionary characteristics in cancer cells according to some scientists is critical for understanding cancer development at the level of species as well as at the level of cells and tissues, and for developing effective therapies. It is argued that animals have evolved potent tumour suppressive mechanisms to prevent cancer development and these mechanisms were initially necessary for the evolution of multi-cellular organisms, and became even more important as animals evolved large bodies and long lives. The biological studies for the development and architecture of animal tissues (including humans) indicate that evolutionarily constrains were advanced in order to limit the development of cancer. Cancer development within an individual is also an evolutionary process, which in many respects mirrors species evolution. Species evolve by mutation and selection acting on individuals in a population; tumours evolve by mutation and selection acting on cells in a tissue. The processes of mutation and selection are integral to the evolution of cancer at every step of multistage carcinogenesis, from tumour genesis to metastasis. Two very important factors which are associated with cancer development, such as aging and exposure to extrinsic carcinogens, have been shown to promote cancer evolution by impacting both mutation and selection processes. Experimental experience showed that there are therapies that can decimate a cancer cell population, but unfortunately, cancers can also evolve resistance to these therapies, leading to the resurgence of treatment-refractory disease.[21-23]

Understanding cancer from an evolutionary perspective can allow us to appreciate better why cancers predominantly occur in the old age people (elderly), and why other conditions, from radiation exposure to smoking, are associated with increased cancers. Importantly, the application of evolutionary theory to cancer should engender new treatment strategies that could do a better control or even cure of the disease. Old age in animals is associated with a general decline in tissue structure and function. This decline is thought to reflect the lack of selective pressure to maintain tissues beyond an age when the animal would be likely to contribute genetically to future generations.[24,25]

Similarly, there is little selective pressure to limit cancer development in old animals that are substantially beyond their reproductive years. For example, while mice can live 2-4 years in

the laboratory under normal conditions, and tend to develop cancer in their second and third years, it is rare to find a mouse greater than 1 year old in the wild. Wild mice do not last for so long, most are dead from other causes, such as cold, hunger, disease or predators, well before the age when cancer would be a likely cause of their death. It can be argued that evolution has favoured a "breed early, breed often" strategy for mice. Investment in better tissue maintenance in mice or cancer prevention well after 1 year of age would have required allocation of precious energy early in life, when this energy would be better spent on survival and reproduction during youth. Of course, for humans the situation is more complex, as even our hunter-gatherer ancestors may have had a reasonable chance of living past 50 once they survived to adulthood.[26,27]

Is there a link between evolution and cancer?

In the last decades, a broader knowledge on the biochemical mechanisms of carcinogenesis has formulated the predominant theory concerning the formation of cancer. Cancer is considered a genetic accident, with accumulation of damaging mutation on the nuclear DNA. It has been found that various intrinsic and extrinsic carcinogenic agents are thought to cause DNA damage which then in the progressive stage activate oncogenes and inactivate tumour suppressor genes.[28]

According to some scientists cancer is a natural consequence of human evolution and in other animals. Human genes have not developed to give us long and happy lives. They are optimized to copy themselves into the next generation - irrespective of our personal desires. These are some of the ideas of Professor Jarle Breivik (Department of Behavioral Sciences in Medicine, University of Oslo, Norway), who thinks that this evolutionary implication might be an obstacle to find a final solution to cancer. His research at the Institute of Basic Medical Sciences, explored the connection between cancer development and Darwinian evolution.[29]

The basic idea is that multicellular biological species and their bodies are not static systems. For example, the cells in the human body are in a constant state of development, and new genetic variants (through intrinsic mutations) arise continuously. Many of these mutants are removed by the immune system but, sooner or later, a cell will break through the defenses and develop into a tumour of wild-growing renegades. Cancer development is an evolutionary process within the multicellular organism, but it is also related to the general process of evolution through the generations. Life begins when our parent's genes are united in the zygote. These genes have been selected through millions of generations for their ability to create a functional organism, but few days after fertilization the genes split up in two different directions. Some end up in the germ cells (sperm and ova) that will bring them to the next generation, while the rest end up in the somatic cells that make up our body. The somatic cells are initially programmed to cooperate, but as we age and new mutations arise, the evolutionary process will favour cells that break ranks and propagate freely within the body. Thus, according to Breivik, the division between germ cells and somatic cells represents the Darwinian explanation to cancer.[29]

"….Natural selection favours genes for their ability to replicate in their given environment. Through the course of evolution, they have thereby developed increasingly more complex mechanism for self-replication, first as single celled organisms and later as cells that cooperate in complex colonies. This is where humans belong. We are cell colonies developed for propagating our genes from one generation to the next. As soon as our children can take care of themselves, we are irrelevant to the genes. Caring grandparents may be good to have, but dozens of enduring ancestors will not increase a gene's chance for survival—on the contrary, they may represent a waste of valuable recourses. The entire human genome is therefore probably developed to give us a limited lifespan," says Breivik.

He believes that many of our genes are constructed in order to protect against cancer in the first part of our lives, but that they are programmed for destruction as we get older.

His main argument is that "… scientific discoveries indicate that cellular DNA contains repair genes. This has been one of the most important discoveries in the last decade. DNA repair genes code for proteins whose normal function is to correct errors that arise when cells duplicate their DNA prior to cell division. They are active throughout the cell cycle, particularly during G2 after DNA replication and before the chromosomes divide. Mutations in DNA repair genes can lead to a failure in repair, allowing subsequent mutations to accumulate. DNA repair mechanisms protect humans from cancer in early life, nut these genes also contain unstable DNA sequences that increase their probability for breakdown as time passes. These sequences are ticking time bombs in our genome and represent a paradox. If we take the perspective of the genes', on the other hand, the phenomenon is quite logical".[29]

Cellular DNA is the repository of genetic information in each living cell, its integrity and stability is essential to life. DNA, however, is not inert; rather, it is a chemical entity subject to assault from the environment, and any resulting damage, if not repaired, will lead to mutation and possibly disease. Beyond environmental agents, DNA is also subject to oxidative damage from byproducts of metabolism, such as free radicals. DNA repair processes exist in both prokaryotic and eukaryotic organisms, and many of the proteins (enzymes) involved have been highly conserved throughout evolution. In fact, cells have evolved a number of mechanisms to detect and repair the various types of damage that can occur to DNA, no matter whether this damage is caused by the environment or by errors in replication.[30]

Scientists mow know that every day, thousands of DNA damaging events take place in each cell of human body (and other biological systems), but efficient DNA repair systems have evolved to prevent that. However, DNA repair systems of most organisms are not perfect. As accumulation of DNA damage is progressing carcinogenic mechanisms can be initiated, and genetic deficiencies in specific DNA repair genes are associated with tumour-prone phenotypes. In addition to mutations, which can be either inherited or somatically acquired, epigenetic silencing of DNA repair genes may promote tumourigenesis.[31]

Jarle Breivik extends his theory further into the difficulties of medical treatment of neoplastic diseases. "…..Despite important advances in therapy, all statistics show that the cancer incidence will continue to rise. The better we get at treating cancer, the older we become and the more cancer there will be in the population. Additionally, better therapy for children and young people implies that more cancer genes are passed on to the next generation. From what we know about evolutionary dynamics, I believe it's impossible to find a therapeutic solution to cancer. The basic problem is that we are trapped in a body that the genes have made to be disposable. A solution will therefore be something much more radical than a new drug. Some thought provoking scientific papers on the subject appeared in the scientific literature.[32-35]

Conclusions

A guiding principle in cancer research is that tumour initiation and progression result from the sequential acquisition of genetic mutations that contribute to subsequent clonal expansions. This view is strongly supported by many studies where genetic mutations were analyzed across different stages of cancer development. These studies established that genetic changes *cause* phenotypic manifestations, a finding that added significant weight to the idea that cancer development follows the rules of Darwinian evolution. Over the last

decades, there has been a revolution in our understanding of cancer growth. Advances in sequencing technologies have paved the way to deciphering the tumour genome. It is becoming increasingly clear that a tumour does not have one single tumour genome, but instead comprises multiple genomes that belong to distinct subclones. In nature, evolution creates biodiversity and this in turn makes an entire ecosystem robust. In cancer, diversity within tumour cells at the genetic and functional level together with their coexistence with the microenvironment also increases tumour fitness, allowing tumour cells to offset survival pressures imposed by therapy. More effective therapies will require gaining insight into this diversity. So, treating cancer means controlling a diverse population of rapidly evolving cell lineages. This challenge helps explain why research has not yet provided us with a cure, but also points the way toward new solutions that take evolution into account.[36]

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