Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors

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Cancer tumors as Metazoa 1.0: tapping genes of ancient ancestors

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Abstract

The genes of cellular cooperation that evolved with multicellularity about a billion years ago are the same genes that malfunction to cause cancer. We hypothesize that cancer is an atavistic condition that occurs when genetic or epigenetic malfunction unlocks an ancient 'toolkit' of pre-existing adaptations, re-establishing the dominance of an earlier layer of genes that controlled loose-knit colonies of only partially differentiated cells, similar to tumors. The existence of such a toolkit implies that the progress of the neoplasm in the host organism differs distinctively from normal Darwinian evolution. Comparative genomics and the phylogeny of basal metazoans, opisthokonta and basal multicellular eukaryotes should help identify the relevant genes and yield the order in which they evolved. This order will be a rough guide to the reverse order in which cancer develops, as mutations disrupt the genes of cellular cooperation. Our proposal is consistent with current understanding of cancer and explains the paradoxical rapidity with which cancer acquires a suite of mutually-supportive complex abilities. Finally we make several predictions and suggest ways to test this model.

1. Cancer as a product of evolution

Conceptualizing cancer in an evolutionary context promises to transform our understanding of the condition and offer new therapeutic possibilities (Merlo *et al* 2006). Conversely, a proper understanding of cancer will inform evolutionary biology and astrobiology by casting important light on the nature and evolution of complex life and the origin of multicellularity. A longstanding criticism of cancer biology and oncology research is that it has so far taken little account of evolutionary biology (e.g. Nesse and Williams 1996). Cancer is the result of the proliferation of misregulated cells belonging to the host organism, and while the onset of some cancers may be triggered by viral infection, or chemical carcinogens, cancer itself is not an infection. Cancer cells are the cells of our own bodies, not foreign viruses or bacteria. With the possible exception of the naked mole-rat (Suluanov *et al* 2009) it is likely that cancer occurs in almost all metazoans in which adult cells proliferate. This quasi-ubiquity suggests that the mechanisms of cancer are deep-rooted in evolutionary history, a conjecture that receives support from both paleontology and genetics. Dinosaur tumors, for example, have been documented many times (e.g. Rothschild *et al* 2003), and some oncogenes (genes thought to be responsible for causing cancer) are extremely ancient. '[T]heir precursors were already present in similar form in the primitive metazoans that served as common ancestors to chordates and arthropods', according to Weinberg (1983). Recent genetic studies of a freshwater *Hydra* indicate that the human oncogene *myc* dates back at least 600 million years (Hartl *et al* 2010) and more comprehensive studies are revealing even older dates (Srivastava *et al* 2010). Weinberg (1983) speculated on the implications of the fact that the genes that cause cancer are ancient and highly conserved: 'Such conservation indicates that these genes have served vital, indispensable functions in normal cellular and organismic physiology, and that their role in carcinogenesis represents only an unusual and aberrant diversion from their usual functions'. It has become clear that the genes responsible for the cellular cooperation necessary for multicellularity are also the genes that malfunction in cancer cells (Weinberg 2007).

In this paper we take further the idea that cancer has deep evolutionary roots and make specific predictions based on the connection between cancer and the evolution of multicellularity. Our central hypothesis is that cancer is an atavistic state of multicellular life. Atavisms occur because genes for previously existing traits are often preserved in a genome but are switched off, or relegated to non-coding ('junk') segments of DNA. For example, humans are sometimes born with tails, webbed feet, gills, hypertrichosis and supernumerary nipples (Le Page 2007). Mutant chickens can be induced to form teeth (Gould 1980, Chen *et al* 2000, Harris *et al* 2006). Atavisms result from the malfunction of the more-recently-evolved genes that suppress such ancestral developments (Hall 1984, Harris *et al* 2006). Hen's teeth, or cetacean's hind legs are atavisms expressing ancestral genes that became inhibited ∼60 million years ago (Gould 1980, Chen *et al* 2000). Traditionally, atavisms are associated with the morphological features of the developing zygote. Here we propose that cancer is an atavism associated with ancestral cellular functions regulated by genes that have been largely suppressed for more than 600 million years.

The transition from unicellular to complex multicellular organisms took place over an extended period starting at least 1 billion years ago (Hedges and Kumar 2009). Importantly, 'advanced' metazoan life of the form we now know, i.e. organisms with cell specialization and organ differentiation, was preceded by colonies of eukaryotic cells in which cellular cooperation was fairly rudimentary, consisting of networks of adhering cells exchanging information chemically, and forming self-organized assemblages with only a moderate division of labor. These proto-metazoans were effectively small, loosely-knit ecosystems that fell short of the complex organization and regulation we associate with most modern metazoans. In short, proto-metazoans, which we dub Metazoans 1.0, were tumor-like neoplasms.

By 600 million years ago, Metazoa 2.0 had emerged. These organisms have a richer repertoire of biological processes needed to coordinate a larger number of highly differentiated cell types. They are characterized by sophisticated genetic and epigenetic command and control systems familiar from modern complex organisms such as humans. It is, however, in the nature of Darwinian evolution that life builds opportunistically on what has gone before. The genetic apparatus of the new Metazoa 2.0 was overlain on the old genetic apparatus of Metazoa 1.0. The genes of Metazoa 1.0 were tinkered with where possible, and suppressed where necessary. But many are still there, constituting a robust toolkit for the survival, maintenance and propagation of non-differentiated or weakly-differentiated cells—'tumors'—and when things go wrong (often in senescence of the organism) with the nuanced overlay that characterizes Metazoa 2.0, the system may revert to the ancient, more robust way of building multicellular assemblages—Metazoa 1.0. The result is cancer. In evading one layer of genetic regulation—turning proto-oncogenes into oncogenes—cancer mutations uncover a deeper, older layer of genes that code for behaviors that are often able to outsmart our best efforts to fight them. The idea of a pre-existing cancer toolkit is not new, but its adoption

has been tentative: 'Maybe the information for inducing cancer was already in the normal cell genome, waiting to be unmasked' (Weinberg 2007, p 79).

We thus argue that cancer cells are not newly evolved types of cells, but heirs to an ancient toolkit and a basic mode of survival that is deeply embedded in multicellular life. Cancer, like a lazy poet, when called upon to produce new poems, reaches into its trunk of old poems and pulls one out at random, often finding a good poem, popular a billion years ago. These poems are not shoddy, inefficient, preliminary doggerel, but elaborate compositions with pathways that took millions of years to evolve. Some of these pathways are still in active use in healthy organisms today, for example, during embryogenesis and wound-healing. Others have fallen into disuse, but remain, latent in the genome, awaiting reactivation. One might say that the appearance of tumors in the body is a manifestation of the inner Metazoan 1.0 in all of us.

Regarding cancer as the 'default option' for multicellularity is reminiscent of a computer that may start up in Safe Mode if it has suffered either a hardware or a software insult. Organisms may suffer mechanical damage such as wounding or inflammation (hardware insult), or genetic damage such as DNA base pair mis-copying (software insult), and as a result, they flip to Safe Mode, unlocking the ancient toolkit of Metazoa 1.0. Just as a computer deals with this crisis by performing system checks and corrections, so too will modern organisms run through a collection of reviews and strategies to repair the damage. If DNA cannot be repaired, there are secondary DNA repair mechanisms. If these fail and the cell begins to proliferate, cell signaling and growth inhibitors try their luck. If these fail to stop proliferation, there is another line of defense—apoptosis (programmed cell death). There is also the immune system. If all these fail, the outcome is malignant uncontrolled growth. It is because cancer is the Metazoan 1.0 default option that it is relatively easy to start and hard to stop. Cancer can be triggered in a wide variety of ways, but once it becomes established it is extremely hard to reverse. That is, we can treat cancer, for example by destroying tumors, but turning cancer cells back into healthy cells remains a major challenge (Wang *et al* 2010). The source of this asymmetry is not hard to find. It took more than a billion years to evolve the eukaryotic genes present in Metazoa 1.0 and a further approximately billion years to evolve the sophisticated genetic and epigenetic overlay that led to Metazoa 2.0. It is much easier to inactivate a gene or destroy a complex negative feedback loop than it is to evolve one. This asymmetry makes healthy cells vulnerable to mutations that wreck the delicate machinery of cellular cooperation, thereby reactivating pre-existing ancestral genes. But—and we wish to stress this point—such mutations are ineffective, over *somatic* time scales, at evolving any truly new adaptive features.

2. Problems with the 'rogue cell' hypothesis

It is sometimes remarked that cancer is a collection of rogue cells, or selfish cells, that recapitulate the world of *single* cellularity (Merlo *et al* 2006). This is superficially plausible. Single-celled eukaryotes obey a simple imperative—replicate,

replicate, replicate. By contrast, multicellularity demands that individual cells subordinate their selfish agenda to the requirements of the organism as a whole. In modern complex organisms, this is accomplished via the aforesaid command and control systems. It is the job of these systems to regulate cell differentiation and proliferation, so as an embryo develops, distinctive tissues and architectures emerge in an organized way and become compartmentalized. The organism functions with a high degree of cooperation between these components. Some organs, such as the gut, require rapid cell replication to replenish cells sloughed off by wear and tear, while others, such as the brain, have a slow rate of turnover. So long as individual cells respect which organ they belong to, and both receive and obey the replication commands from the genetic and epigenetic systems, all is well. But it is a hallmark of cancer that malignant cells ignore the normal signals that control replication and apoptosis and can thrive outside their organ of origin. They may invade the extra-cellular matrix, work their way through vessel walls into the blood or lymphatic systems, become mobile, and then colonize other organs in the body (a process known as metastasis). In short, they behave as a gang of selfish rogue cells.

This simplistic account, however, ignores more than a billion years of transitional forms between single-celled eukaryotes and Metazoa 2.0. It ignores Metazoa 1.0. It also fails to hold up to scrutiny. Two problems are immediately apparent. The first is the failure to account for the rather high degree of cooperative organization among cancer cells. The most striking example of this is angiogenesis, in which an entire tumor builds its own blood supply for the common good of all the tumor cells. A more contentious example concerns evidence that a small population of highly malignant cancer cells can be held in check by less malignant cells. Following chemotherapy that targets the dominant population of cancer cells, the restraint is removed, and the more malignant sub-population is unleashed (see, for example, Eikenberry *et al* (2010)). Similarly, surgically removing a primary tumor can result in the sudden flourishing of metastic tumors. Cancer cells are known to exchange chemical signals with each other and with the surrounding tissues, so some degree of cooperation is not unexpected. In this respect, neoplasms resemble ecosystems, consisting of a heterogeneous population of types, rather than a collection of fiercely competitive individuals. To be sure, there is competition, but there is also a certain degree of cooperation and division of labor—exactly what one might expect from Metazoa 1.0.

The second major problem with the rogue cell hypothesis comes when trying to explain cancer's remarkable ability to deploy a formidable array of survival tricks, sometimes all at once. Hallmarks of cancer include the silencing of tumor suppressor genes, switching off apoptosis and anoikis (programmed death when cells detach from the extracellular matrix), switching off senescence by manufacturing enzymes to repair eroding telomeres (Hanahan and Weinberg 2000), evading the immune system by removing surface receptors, dramatically changing the viscoelastic properties of cells to facilitate motility, invasion and colonization (Butcher *et al*

2009), secreting corrosive enzymes to dissolve through organ membranes, thus permitting the cells to enter the blood and lymphatic circulatory systems and spread around the body, thriving in hypoxic conditions by switching off the normal oxidation–phosphorylation metabolism of healthy cells and using the glycolytic cycle instead (the so-called Warburg effect; see Warburg (1956)), tolerating the resulting low pH conditions far better than healthy cells, shielding themselves from the 'alien cell' alarm signals from organs they invade, manufacturing their own mitogenic signals and growth factors to make them independent of chemical replication signals (Hanahan and Weinberg 2000), altering the physical and chemical properties of the extracellular matrix and other host tissues to optimize tumor growth and survival, and accelerating genetic instability to evolve immunity in changing conditions, while rapidly adapting the cytoskeleton dynamics to enable mitosis to operate across a range of karyotypes, including full-blown aneuploidy.

The conventional explanation for this multi-faceted armory is to appeal to straightforward Darwinian evolution, not among species, but inside the host organism, among competing sub-populations of cells within the neoplasm (Merlo *et al* 2006). We call this the 'internal' Darwinism hypothesis. In essence, the foregoing list of traits is attributed to mostly independent random mutations and the trial and error of normal Darwinian evolution. The evolution of these survival traits is facilitated by the rapid rate of mutation of cancer cells, combined with strong selective pressure as the organism 'fights back' (or a patient undergoes chemotherapy). As a result, an initially small sub-population of cancer cells that might by chance have evolved a trick or two to stymie the next threat (e.g. hypoxia, the immune system, membrane confinement, chemotherapy) are able to exploit their selective advantage and multiply. Then a sub-population of this new population by chance evolves the next trick, and so on step by step, so that by the time the cancer reaches full malignancy it possesses a large gamut of survival traits and is virtually indestructible.

3. Problems with 'internal' Darwinism

The appeal to 'internal' Darwinism to account for the multiplicity of cancer traits as merely 'lucky accidents' of evolution (unlucky for the patient of course) falls short of a full explanation, however. It is a fundamental tenet of evolution that random mutations are almost always deleterious, yet cancer seems to 'get lucky' on a suspiciously large number of occasions. Why don't the vast majority of mutations in tumor cells lead to mal-adaptation and death, as is the case for healthy cells? Especially striking are the large-scale mutations that create jumbled chromosomes and aneuploid cells—well-known features of advanced-stage cancer. These cells typically display gross structural changes, such as highly deformed nuclei accompanied by major chromatin reorganization (Zink *et al* 2004). Nevertheless, such cells seem not only to survive with their chaotic karyotypes, but also to be remarkably robust (Ao *et al* 2008). It appears that, rather than fatally disrupting the elaborate central machinery of cells, these drastic mutations have the opposite effect, of conferring

enhanced survivability. '[T]he acquisition of extra copies of one chromosome and the loss of another can create a genetic configuration that somehow benefits the cancer cell' (Weinberg 2007, p 11). This paradox has a ready explanation, however, in light of our atavism hypothesis. The reason that the gross random mutations are far less damaging than one might at first expect is because they have the effect of short-circuiting the cell's delicate regulatory mechanisms, causing the cell to default to the powerfully adaptive and robust ancient toolkit. Some of the tools are regulatory transcription factors and homeobox genes. Once triggered, they can set in train the orderly deployment of a succession of survival tricks, including those things that propagating colonies of non-differentiated (or very weakly differentiated) cells needed to do a billion years ago. The reason that old ancestral talents—newly reacquired—are able to benefit cancer cells dwelling within multicellular organisms is that much of the basic biochemistry has remained unchanged over the last billion years of evolution, and the ancestral talents are still useful to cells that do not obediently conform to the organism's newer agenda. Of course, there is a limit to the degree of genetic scrambling that can be tolerated. Our model predicts a Goldilocks zone: too few mutations and the cell functions normally, too many and it dies. At some moderate level, normal functional cooperation is lost but the older genes and more *laissez-faire* regulatory regime take over to ensure the cell's survival. It seems very likely that the large majority of severe mutations kill the cells, but there is clearly a selection effect at work: cells that die here and there are cleaned away and are not noticed. Similarly, mild genetic damage that does not seriously compromise the cell's normal functionality, even when widespread across the genome, goes unnoticed, unless discovered through sequencing studies. In between are genetically altered cells with reactivated metazoan 1.0 genes, and deactivated metazoan 2.0 cooperation genes. These are cancer cells, and after proliferating to an $\sim 10^9$-cell tumor, they attract attention.

Our explanation of cancer as an atavism that short-circuits the Metazoa 2.0 regulatory system and unleashes the suppressed Metazoa 1.0 system receives support from the amazing pleiotropy of some enzymes, and, as has been realized recently, some micro-RNAs (miRNAs). Thus the enzyme COX-2 and the miRNA known as miR-31 have been found to control not just one, but a collection of tumorigenic factors. Such remarkable efficiency and economy would be deeply puzzling if it arose from a few decades of internal Darwinism, but makes perfect sense if it had been honed by evolution over an extended period of time to form an optimized package that constitutes a type of on–off switch for a set of previously adaptive traits.

Another problem with the 'internal' Darwinian account of cancer was pointed out by Bernards and Weinberg (2002a), and concerns the spread of cancer through the body of the host organism. Merlo *et al* (2006) summarize the problem: 'Metastasis requires that cells leave the primary tumor, but few such cells successfully colonize a distant organ. This leads to a paradox: metastatic clones should have a fitness disadvantage relative to non-metastatic clones in the primary tumor owing to

the loss of the progeny that emigrate'. Bernards and Weinberg (2002b) offer a tentative explanation based on a 'pre-ordained' correlation between some earlier acquired advantageous genes and the genes that empower metastasis: '. . . the tendency of a tumor eventually to metastasize is already pre-ordained by the spectrum of mutations that progenitor cells acquire relatively early in tumorigenesis; that is some cancers start out "on the wrong foot". . . the mutant genes that are known to confer Darwinian selective advantages early on may be the same genes that, further down the line, empower metastasis'.

The metastatic paradox is immediately resolved, however, by the atavism hypothesis, because the metastatic phase is internally pre-programmed from the start, and does not emerge via a random 'internal' Darwinian process within the host organism. If the relevant genes are not acquired via random mutations but are already latent as a package in the genome, ready to be reactivated by a 'spectrum of mutations', then the 'pre-ordained' nature of metastasis is no longer a mystery. The issue of 'starting out on the wrong foot' then simply means that a relatively early genetic or epigenetic mutation opens up access to a pre-existing adaptation for colony formation which manifests itself as the colony-forming abilities of metastatic cancer. The genetic or epigenetic mutations that open up access to pre-existing adaptations can be caused by chronic inflammation, viral infections or other environmental causes.

Because of their pre-existing nature, cancer adaptations should more accurately be called exaptations (Gould and Vrba 1982). Here an analogy might be helpful. Cancer's acquisition of ancient traits could be compared to the memory card game in which all the cards are laid out in pre-arranged order face down, and then turned over one by one at random. Initially the distribution of face-up cards looks chaotic, but once a large subset of the cards is turned over the order becomes apparent. The emergence of pre-existing order by random uncovering is clearly vastly more efficient than the generation of the same order *ab initio* by a Darwinian process of blind trial and error. Of course, the pre-existing order represented by cancer genes (the toolkit) *was* the product of a Darwinian process, but one that took place, not in the host organism over a few years, but in its ancestors hundreds of millions of years ago. Thus we distinguish between acquiring genes from parents (Darwinian evolution, vertical gene transfer), acquiring genes from peers (Lamarckian evolution, horizontal gene transfer) and reactivating the genes of distant ancestors (the atavism known as cancer). We do not claim that internal Darwinism is irrelevant to the progression of neoplasms. Rather, we assert that atavistic transformations are a relatively rare part of normal Darwinian evolution but that they play the dominant role in the progression of cancer.

4. Phylogenetic tests of the atavism hypothesis

If tumors are a type of living fossil from the era of Metazoa 1.0, we might expect to find genetic and even fossil evidence. Extant organisms that branched off close to the transition zone between Metazoa 1.0 and Metazoa 2.0 may offer clues. Significantly, the polyp *Hydra*, the basal eukaryote referred to earlier in connection with the oncogene *myc*, has the power

to regenerate itself, cancer-like, from a tiny fragment, and can go on doing so seemingly indefinitely. This ability is reminiscent of the immortalization seen in cancer cells, where the regulated cell divisions of somatic cells undergo an atavistic transformation to their previous less-regulated, pre-multicellular, proto-colonial reproductive regime. Sponges are also recognized to represent a very ancient form of multicellular life (Brocks and Butterfield 2009), but lack certain features to qualify them for inclusion in the standard definition of eumetazoa (what we are calling Metazoa 2.0 here). The recent sequencing of the Great Barrier Reef demosponge *Amphimedon queenslandica* (Harcet *et al* 2010) supports the hypothesis presented in this paper. It was possible to identify parts of the genome responsible for rudimentary cell cooperation, including cell–cell adhesion and—crucially—the regulation of cell proliferation. In effect, the latter are ancient tumor suppressor genes, dating back as far as multicellularity itself. The cancer-as-atavism hypothesis predicts that future phylogenetic studies will find that many oncogenes (the genes that malfunction in the Metazoa 2.0 toolkit) will be found to have evolved during the Metazoa 1.0 to Metazoa 2.0 transition that occurred between 1.3 billion years ago and 600 million years ago.

It is apparent that important new insights into the nature of cancer are increasingly coming from efforts of this sort which seek to correlate the details of the phylogenetic evolution that led to multicellularity, with oncogenes, tumor suppressor genes and specific mutations that lead to cancer. For example, Srivastava *et al* (2010) compared the genomes of organisms that diverged about a billion years ago from the lineage that led to bilaterians and chordates (see also Srivastava *et al* (2008), Putnam *et al* (2007, 2008)). By looking at the differences in the genomes of representative species at increasing depths in our phylogenetic tree, eumetazoa, metazoa, holozoa, opisthokonta and multicellular eukaryotes, they were able to establish a preliminary chronology for the order in which the genes associated with multicellularity evolved. These are the genes for cell cycling, growth signaling, apoptosis and cell differentiation—genes whose malfunctioning is implicated in cancer. Recent work by Domazet-Lozo and Tautz (2010) on the phylostratigraphic tracking of cancer genes also lends supports to our cancer-as-atavism hypothesis in that their work establishes a closer link between cancer and the emergence of multicellularity.

By identifying and ordering in time the evolution of cell differentiation and cooperation we may simplify our understanding of the currently forbiddingly complex toolkit of cancer. Since each organism possesses pathways toward cellular differentiation that are initially identical and then branch off (Sulston and Horvitz 1977), we postulate that the progression of cancer in each cell type will be correlated with the reverse order in which they differentiated. That is, the order in which the effects of mutations can be observed in cells during the progression of cancer should reflect reverse phylogenetic history, in loose analogy with Haekel's maxim that 'ontology recapitulates phylogeny'. Ontogeny recapitulates phylogeny largely because mutations inserted later in a developmental pathway do less harm than those

inserted earlier (Gould 1977). When genes are knocked out, the consequences vary. Ancient genes are more likely to play a fundamental role than more recently evolved genes, so the consequences of disabling the former tend to be more drastic and likely to lead to cell death.

Our prediction can be tested by genomic studies of cancer progression to discover any preferential ordering of traits; for example, is the switching off of apoptosis before or after the secretion of membrane-dissolving proteins or the activation of metastatic pathways? And if there is a preferential sequence, does it reflect the phylogenetic order of the evolution of the genes responsible for these transitions? (Mann 2010). Of course, the postulated correlation may be hidden amid noise, given the high degree of genetic instability in cancer cells, but may nevertheless be discernible in a broad systematic analysis.

One way to embark on such an analysis is to study the development of cancer in representative organisms with different numbers of cell types, that branched off from our lineage at increasing depths. Vertebrate blastula, for example, differentiate into ~225 cell types. Invertebrate bilaterian blastula (e.g. *Drosophila*, *Caenorhabditis elegans*) differentiate into 50–100 cell types, while *Nematostella* and *Amphimedon* have 10–15 cell types. The placozoan *Trichoplax* has only 5 cell types (Srivastav *et al* 2010). The complexity of cancer in a species should reflect the number of cell types in that species. We would expect, for example, that *Trichoplax*, *Nematostella* or *Amphimedon* might suffer, in old age, from much simpler cancers whose simplicity might make them easier to study and control. If we can find large numbers of individuals with cancer within these earlier diverged clades, then we may be able to study the genomic progression of simpler cancers, based on the malfunctioning of fewer, more basal oncogenes.

Plants and fungi are also multicellular eukaryotes, and have also evolved inter-cellular cooperation mechanisms. There should be an analog of cancer for plants and fungi but not a great deal is known about this (see, for example, Sachs (1991)). Our common ancestor with plants lived ~1.6 billion years ago (Hedges and Kumar 2009) and was probably a facultatively colony-forming protist. Some of the earliest genes of cooperation probably evolved around this time and can be identified by the comparative genomics of basal multicellular eukaryotes. Our common ancestor with fungi lived ~1.3 billion years ago. The deepest-rooted fungi (the chytrids such as *Neocallimastigomycota*, *Blastocladiomycota* and *Chytridiomycota*) have flagellated motile spores similar to choanoflagellates (basal Holozoans, see King *et al* (2008)). By comparing the genomes of many species of basal fungi with many species of basal holozoans, and obtaining their branching order in the phylogenetic tree, it should be possible to build a comprehensive account of the evolution of the genes of cellular cooperation between 1.3 and 1.0 billion years ago. This would extend the work of Srivastava *et al* (2010) by using more basal metazoan species to obtain a higher time resolution, more statistically robust phylogenetic branching order and therefore more robust conclusions about the order of evolution of the genes that enable multicellularity.

Extant organisms most similar to these ancestral forms may be found among colonial choanoflagellates, which

congregate in tumor-like colonies of undifferentiated or weakly-differentiated cells. One might also wonder whether there are fossils dating from the pre-Ediacara era that display the general type of morphology associated with some modern tumors (see, for example, Maloof *et al* (2010)). Because tumors are only loosely organized and highly heterogeneous, such a comparison would not be easy, but certain basic features may be discernible. Morphological classification using fractals offers a possible scheme (Baish and Jain 2000). It would also be interesting to discover whether Metazoa 1.0 evolved in hypoxic and low pH conditions—cancer's preferred habitat (Semenza 2007).

5. Implications for cancer therapy

In this paper we have argued that regarding cancer as a collection of rogue individual cells randomly evolving increasingly refractory survival traits within a few years inside the host organism ('internal' Darwinism) is incomplete and possibly misleading. We postulate that the principal mechanism causing cancer is the accumulation of mutations which destroy the genetic regulation that evolved during the evolution of metazoan multicellularity, thereby reactivating an ancient genetic toolkit of pre-programmed behaviors. In terms of therapeutic response, the distinction between rogue cells and cooperatively organized cells is crucial. Rather than attacking tumors indiscriminately ('the only good cancer cells are dead cancer cells'), understanding their origin, managing them and containing them might be a far smarter strategy.

Given cancer's formidable complexity and diversity, how might one make progress toward controlling it? If the atavism hypothesis is correct, there are new reasons for optimism. The postulated toolkit of Metazoa 2.0, although admittedly complex, is nevertheless a fixed and finite feature of multicellular life. The number of tools in the kit is not infinite. What one cancer learns cannot be passed on to the next generation of cancers in other patients. Cancer is not going anywhere evolutionarily; it just starts up all over again in the next patient (see however O'Neil (2010)). Although cancer may seem like a perpetually moving target, a given cancer has a strictly limited set of atavistic possibilities open to it. Thus, cancer is a limited and ultimately predictable adversary. This understanding of cancer as a limited atavism should engender optimism among oncologists. The anticipated precision of personalized drug therapies will not be infinite. This view contrasts sharply with the open-ended possibilities for cancer implied by the 'internal Darwinism' model.

If the key to controlling cancer lies with the elucidation of the hypothesized finite number of tools in an inherited toolkit, then advances in technology hold great promise. DNA microarrays, the current super-Moore's law progress in sequencing technology and the construction of the Cancer Genome Atlas (http://cancergenome.nih.gov) should soon uncover the limits of the essential genomic varieties of cancer and the limits on their temporal progression. When applied to organisms that branched off from our lineage at different depths, this technology should enable us to obtain the evolutionary sequence of the cooperative genes that led to

multicellularity—not just in metazoans but possibly in fungi and plants as well. With that new basis of understanding, the way to more effectively combat specific cancers will lie open.

Acknowledgments

References

Ao P, Galas D, Hood L and Zhu X 2008 Cancer as robust intrinsic state of endogenous molecular-cellular network shaped by evolution *Med. Hypotheses* **70** 678–84

Baish J W and Jain R K 2000 Fractals and cancer *Cancer Res.* **60** 3683

Bernards R and Weinberg R A 2002a A progression puzzle *Nature* **418** 823

Bernards R and Weinberg R A 2002b Bernards & Weinberg reply *Nature* **419** 560

Brocks J J and Butterfield N J 2009 Early animals out in the cold *Nature* **457** 672–3

Butcher D T, Alliston T and Weaver V M 2009 A tense situation: forcing tumor progression *Nat. Rev. Cancer* **9** 108–22

Chen Y *et al* 2000 Conservation of early odontogenic signaling pathways in Aves *Proc. Natl Acad. Sci.* **97** 10044–9

Domazet-Lozo T and Tautz D 2010 Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa *BMC Biol.* **8** 66

Eikenberry S E, Nagy J D and Kuang Y 2010 The evolutionary impact of androgen levels on prostate cancer in a multi-scale mathematical model *Biol. Direct* **5** 24–52

Gould S J 1977 *Ontogeny and Phylogeny* (Cambridge, MA: Harvard University Press)

Gould S J 1980 Hen's teeth and horse's toes *Nat. Hist. Mag.* **89** 24–6

Gould S J and Vrba E S 1982 Exaptation—a missing term in the science of form *Paleobiology* **8** 4–15

Hall B K 1984 Developmental mechanisms underlying the formation of atavisms *Biol. Rev.* **59** 89–122

Hanahan D and Weinberg R A 2000 The hallmarks of cancer *Cell* **100** 57–70

Harcet M, Roller M, Ćetković H, Perina D, Wiens M, Müller W E G and Vlahoviček K 2010 Demosponge EST sequencing reveals a complex genetic toolkit of the simplest metazoans *Mol. Biol. Evol.* doi:10.1093/molbev/msq174

Harris M P, Hasso S M, Ferguson M W J and Fallon J F 2006 The development of archosaurian first-generation teeth in a chicken mutant *Curr. Biol.* **16** 371–7

Hartl *et al* 2010 Stem cell-specific activation of an ancestral *myc* protooncogene with conserved basic functions in the early metazoan *Hydra Proc. Natl Acad. Sci.* **107** 4051–6

Hedges S B and Kumar S 2009 *The Timetree of Life* (Oxford: Oxford University Press)

King N *et al* 2008 The genome of the choanoflagellate *Monosiga brevicollis* and the origin of metazoans *Nature* **451** 783

Le Page M 2007 The ancestor within *New Sci.* **193** 28

Maloof A C *et al* 2010 Possible animal-body fossils in Marinoan limestones from South Australia *Nat. Geosci.* **3** 653–9

Mann A 2010 Sponge genome goes deep *Nature* **466** 673

Merlo L M F, Pepper J W, Reid B J and Maley C C 2006 Cancer as an evolutionary and ecological process *Nat. Rev. Cancer* **6** 924–35

Nesse R M and Williams G C 1996 *Why We Get Sick: The New Science of Darwinian Medicine* (New York: Vintage)

O'Neil I D 2010 Tasmanian devil facial tumor disease: insights into reduced tumor surveillance from an unusual malignancy *Int. J. Cancer* **127** 1637–42

Putnam N H *et al* 2007 Sea anemone genome reveals ancestral eumetazoan gene repertoire and genomic organization *Science* **317** 86–94

Putnam N H *et al* 2008 The amphioxus genome and the evolution for the chordate karyotype *Nature* **453** 1064–71

Rothschild B M, Tanke D H, Helbling M II and Martin L D 2003 Epidemiologic study of tumors in dinosaurs *Naturwissenschaften* **90** 495–500

Sachs T 1991 *Pattern Formation in Plant Tissues* (Cambridge: Cambridge University Press) p 38

Semenza G L 2007 Hypoxia and cancer *Cancer Metastasis Rev.* **26** 223–4

Srivastava M *et al* 2008 The *Trichoplax* genome and the nature of placozoans *Nature* **454** 955–60

Srivastava M *et al* 2010 The *Amphimedon queenslandica* genome and the evolution of animal complexity *Nature* **466** 720–7

Sulston J E and Horvitz H R 1977 Post-embryonic cell lineages of the nematode *Devl Biol.* **56** 110–56

Suluanov A *et al* 2009 Hypersensitivity to contact inhibition provides a clue to cancer resistance of naked mole-rat *Proc. Natl Acad. Sci. USA* **106** 19352–7

Wang J, Xu L, Wang E and Huang S 2010 The potential landscape of genetic circuits imposes the arrow of time in stem cell differentiation *Biophys. J.* **99** 29–39

Warburg O 1956 On the origin of cancer cells *Science* **123** 309–14

Weinberg R A 1983 Oncogenes and the molecular biology of cancer *J. Cell Biol.* **97** 1661–2

Weinberg R A 2007 *The Biology of Cancer* (New York: Garland Science)

Zink D, Fischer A H and Nickerson J A 2004 Nuclear structure in cancer cells *Nat. Rev. Cancer* **4** 677–87