

Introduction: Five Evolutionary Principles for Understanding Cancer

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Evolutionary perspectives are transforming our understanding of cancer. The plural is appropriate because evolution offers five somewhat separate principles useful for understanding cancer. Each is a landmark on a map of a new scientific territory. Descriptions of each principle and their relationships can help maintain orientation in an exponentially growing new field.

Three of the perspectives focus on how malignancies grow within the body. The greatest excitement is coming from recognition that cancers evolve within the body by somatic selection, by which the fastest reproducing malignant cells increase their prevalence. In retrospect, it is amazing that this was not always obvious. The second perspective uses ecological principles to analyze how cancers create and interact with microenvironments that speed or slow tumor growth. The third uses principles from behavioral ecology to analyze how cancer clones compete and cooperate with each other. The final two perspectives focus on natural selection at the organismal level. The fourth uses principles of phylogeny and natural selection to understand why cancer is so rare. The ultimate perspective uses principles from evolutionary medicine to understand

Five evolutionary principles for understanding cancer

1. Somatic selection shapes malignancies.
2. Ecological principles explain how cancers interact with microenvironments.
3. Behavioral ecological principles explain competition and cooperation among cancer clones.
4. Natural selection explains why cancer is rare.
5. Evolutionary medicine explains why cancer is common.

All of these principles have been well described in recent articles and books (Aktipis and Nesse, 2013;

Greaves, 2000, 2007, 2015; Hochberg et al., 2012; Merlo et al., 2006; Nunney, 2013). Each of the chapters in this book elaborates details of one or another aspect. The bird's eye overview of the landscape in this chapter can not begin to summarize those details, it can only provide a rough map of this new exciting scientific territory.

SOMATIC SELECTION AND HOW CANCERS EVOLVE

An older view envisioned cancer as resulting from a defective cell that replicated identical copies of itself out of control. Remnants of this preevolutionary view of cancer persist, but recognition that cancer is an evolutionary process (Nowell, 1976) is growing fast, thanks in large part to new data showing massive heterogeneity among the cells in a single malignancy, a theme in many chapters in this book. That heterogeneity turns out to be important not only theoretically, but also as a predictor of the future trajectory of premalignant and malignant cell lines (Andor et al., 2016; Maley et al., 2006). As would be expected by Fisher's fundamental theorem, the rate of fitness change is proportional to the amount of variation, in this case, massive variation among individual cells in a tumor promotes rapid changes by somatic selection.

This revised view transforms our view of cancer (Aktipis and Nesse, 2013; Crespi and Summers, 2005; Greaves, 2015; Nunney, 2013; and many chapters in this book). The "war on cancer" encouraged thinking of it as one disease with one cause, but every decade of subsequent research has revealed new layers of complexity among related disorders that turn out to be diverse (Aktipis et al., 2011). Early studies looked for abnormalities in cancer cell lines, with little attention to selection that had taken place over the course of generations of replication in vitro. People still tend to think of cancers from each tissue as specific diseases: lung cancer, breast

cancer, prostate cancer and so on. It's now clear, however, that all cancers share deep similarities in the ways cell cycle control is disrupted, and that apparently similar cancers from the same tissue can be very different. There is continuing hope that distinct genotypes will define specific subtypes of cancer. Identifying such variations is certainly useful, especially for making decisions about chemotherapy, but an evolutionary perspective suggests it is unrealistic to expect to find a few genetically uniform specific subtypes. Instead, we should expect that almost all cancer clones, even those from different locations in the same malignancy, will be to some extent distinct. Heterogeneity is intrinsic to cancer (see especially Chapters 5, 10, and 17).

This new perspective has, in combination with new sequencing technologies and phylogenetic methods, encouraged investigations into the sequence by which individual cancers develop. The order in which various driver and passenger mutations arise is important in changing the selection forces that shape subsequent tumor development. Mutations that disrupt DNA replication and repair have special significance because they vastly increase the variation on which somatic selection can act. Variation among cells in different parts of a tumor is the norm, and that variation is an important variable that predicts progression (Andor et al., 2016). For instance, the heterogeneity of cells in Barrett's esophagus is a strong predictor of progression to cancer independent of information about individual cells (Maley et al., 2006).

The process of somatic selection acting on cells is, however, somewhat different from natural selection shaping species. The generic principle of selection explains changes in a group that inevitably result when variations between individuals influence their future prevalence in a group. For instance, the collection of items in a cottage cupboard will tend to shift over the years toward robust items because fragile glassware is more likely to break and be discarded. Natural selection is the same process, with the addition of reproduction and heritability. When variations in heritable factors influence the number of offspring who make it to maturity, the average characteristics of a group will change over time to be more like those of the individuals who had more offspring than average.

This process of natural selection shapes mechanisms that maintain and transmit the information code with extraordinary fidelity. Almost all new mutations are harmful, so selection shapes mechanisms that minimize them, repair them, and compensate for them. The process is different in somatic selection. Cancers arise from driver mutations that give a cell line a selective advantage. Some of them initiate mutations that cause genome chaos beyond the mutation rate that would maximize tumor growth. Somatic selection can be for or against

cancer, and the direction of selection can shift as a malignancy develops in different loci (Michor et al., 2003).

Natural selection shapes phenotypes that maximize transmission of genes to future generations. For selection within the body, there is no surviving generation (with the informative exception of transmissible cancers (see Chapter 12). Whether somatic selection shapes traits that benefit the tumor as a whole at the expense of individual cells is a fascinating question, considered later.

Convergent evolution is prevalent in somatic selection, as it is in natural selection (see also Chapter 17). All cancers face the same set of constraints, and mutations that allow a tumor to escape from those constraints get a selective advantage and become more common. Thus, somatic selection increases the prevalence of mutations that disrupt apoptosis, preserve telomeres, stimulate angiogenesis, interfere with recognition by the immune system, and foster plasticity that enables coping with rapidly changing microenvironments (see Chapter 8). These ecological challenges faced by every cancer provide an evolutionary framework for understanding cancer that complements the well-known hallmarks of cancer (Hanahan and Weinberg, 2011).

Somatic selection and natural selection also differ in the role of epigenetics. In naturally selected species, epigenetic marks that inhibit, or stimulate gene expression can transmit information between one or a few subsequent generations; the extent to which this reflects adaptations or epiphenomena is an area of active study. Epigenetic changes that arise in the course of normal phenotype development influence gene expression patterns that tend to persist across the lifespan. They account for the differences between normal cell types in an individual, including the differences between germ cells and somatic cells, so it should not be surprising that they also account for many aspects of malignant transformation. Epigenetic changes are increasingly recognized as important and perhaps essential mediators that can prevent or speed transformation to cancer (see also Chapters 5 and 6).

ECOLOGICAL ENVIRONMENTS INFLUENCE CANCER GROWTH

There is no such thing as fitness for a gene or individual except in relation to a specific ecological environment. Fitness is a characteristic not of genotypes, but of phenotypes interacting with environments. The microenvironments inhabited by cancers influence their growth, as much as their genotypes. Furthermore, the growth of a tumor creates microenvironments that can speed or slow subsequent growth.

Of particular interest, and emphasized by several chapters in this book, is the hypoxia that results when

a tumor has an inadequate blood supply (see especially Chapters 8 and 19). Even in tumors that stimulate angiogenesis, unregulated growth is likely to block arterial routes providing oxygen and nutrients to small or large parts of the tumor. This can severely restrain growth or even eliminate a tumor. More often, however, the resulting hypoxia creates a microenvironment that compromises the efficiency of the usual immunologic tumor control mechanisms. This may have major implications for treatment strategies (see also pseudohypoxia in Chapter 4).

The rapid changes in microenvironments also may select for plasticity in tumors. Clones gain an advantage if they have the capacity to adapt their metabolism to sudden changes in oxygen tension or nutrient availability without changes in their genomes (see also Chapter 6). When nutrient supply is limited, cells that can enter a dormant state get an advantage, with major implications for how best to use chemotherapy agents that preferentially attack rapidly dividing cells (see also Chapter 20). An ecological approach offers the foundation for adaptive therapy that adjusts chemotherapy doses to minimize tumor growth, instead of to attempt to kill every malignant cell (see Chapter 14).

Many other ecological principles are useful for understanding the ecological setting in which tumors grow (Daoust et al., 2013; Ducasse et al., 2015; Thomas et al., 2013). The limitations of blood supply and its availability only along widely separated routes creates riparian environments with selection forces that differ depending on the distance of a cell from the blood supply. Principles of island ecology are relevant to understanding isolated tumors and metastasis. Thinking of islands of cancer cells as if they were an endangered species provides suggestions for how to speed their extinction (Korolev et al., 2014). Chapters 8 and 11 provide more about ecological applications in cancer, as do several articles in a special issue of *Evolutionary Applications* on cancer (Thomas et al., 2013). Of particular interest is the possibility that tumors can create their own niches, perhaps even with different clones cooperating to construct and expand the niche (Barcellos-Hoff et al., 2013).

BEHAVIORAL ECOLOGY AND COOPERATION AMONG CANCER CLONES

Heterogeneity in cancer is now well recognized, along with increasing understanding of its several possible origins. On the cutting edge is consideration of the possibility that different clones can provide resources that promote the survival and replication of other clones in a process that is something like cooperation (Aktipis et al., 2015, see also Chapter 17). There is no higher-level enforcement of cooperation in a tumor, and selection

cannot shape persisting sophisticated coordinated systems like those that account for termite societies or the cooperation among cells in metazoan bodies. Nonetheless, it is important to consider how different clones may cooperate and compete with each other, and studies of such systems may yield new therapeutic strategies.

A simple example is when some malignant cells secrete substances that disrupt host cells and expand the ecological space while other cells manufacture angiogenesis factors that vascularize the space. Such interactions bring the principles from behavioral ecology into play. Somewhat separate groups of cells may well both benefit from mutualistic interactions. All clones are inevitably shaped, however, to maximize growth in whatever environment they exist in.

Hypoxia induces the transition of malignant cells from attached epithelial cells into mesenchymal forms that are free to circulate and initiate metastases. Many higher organisms have evolved behavior regulation mechanisms that monitor the environment and initiate movement elsewhere when conditions deteriorate. The analogy is attractive despite the major differences. It is also of special importance because of the possibility that treatments causing hypoxia might stimulate this transition in ways that influence metastasis.

EVOLUTIONARY EXPLANATIONS FOR WHY CANCER IS RARE

From an evolutionary perspective, cancer is astoundingly rare. Controlling unrestrained cell growth is the original giant problem that multicellular life had to overcome before large complex organisms could evolve (Smith and Szathmary, 1995). Attachment between cells is easy to explain; individuals with tendencies to attach to each other can increase their nutrition and safety in ways that increase their own replication. Shaping mechanisms that reduce the fitness of individual cells in ways that benefit a completely larger organism is a challenge more difficult by orders of magnitude. The process took billions of years for good reasons, a main one being the challenge of controlling the unregulated cell divisions that are the hallmark of cancer (see Chapter 1).

The earth is about 4.5 billion years old. Life emerged, in the form of bacteria that leave their traces in stone about 3.7 billion years ago, about within the first 20% of time from earth's origin. Multicellular organisms didn't appear until over 3 billion years later. Complex multicellular organisms have existed for only the most recent 10% of the history of the planet. The fast emergence of life, and the extended delay until the emergence of complex multicellular organisms, suggests that simple life forms may exist on many other planets, but complex multicellular organisms are likely to be rare.

Why did it take about 75% of the time of earth's existence for simple life to evolve into complex multicellular life (see also Chapter 1)? Among several obstacles overcome by major transitions, difficulty of evolving mechanisms to enforce cell cooperation was crucial. As cells united to begin to form early multicellular organisms, their generation times increased, so faster-evolving smaller organisms could overcome their defenses. However, being larger also offers protection against predators, and ecosystems had open niches for larger organisms (Bonner, 2011). The related challenge was the need to inhibit cell division, foster division of labor, and create ways to purge cells that nonetheless replicated at the expense of the whole organism (Smith and Szathmáry, 1995).

The Cambrian explosion, in which small simple organisms evolved into large complex ones, was but an eye blink in the history of life (Chapter 16). It started 542 million years ago, and gave rise to the main phyla of metazoans in as little as 25 million years. This speed has been attributed to the emergence of predators whose presence created strong selection for larger prey in a rapid process of coevolution that also rapidly made predators larger (Niklas, 2014). These larger bodies required new mechanisms to enforce cooperation. It is fascinating to consider that external threats may have been a crucial factor that shaped cells to sacrifice their own reproduction for the benefit of larger bodies, and that there is still much debate about this (Erwin and Valentine, 2013).

Multicellular species in which all cells are capable of reproduction cannot become complex with division of labor because there is no way to enforce cooperation. The differentiation of a sterile line of somatic cells was the key innovation that made the transition to complex multicellular life possible (Buss, 1987; Smith and Szathmáry, 1995). Sterile cell lines can advance their genetic interests only by advancing the interests of the whole organism, or rather, the organism's genes. Once a sequestered germ line is separated from a sterile somatic cell line, selection can shape specialized kinds of somatic cells with separate functions, including enforcing cooperation among other cells. The dynamics of this transition have been the focus of intense study (Queller, 2000).

Any cell potentially capable of independent reproduction poses a threat that must be carefully monitored and controlled. For organisms as complex as vertebrates, somatic cells cannot establish their own continuing separate lineages, with the dramatic exception of transmissible cancers (see Chapter 12). Even stem cells cannot get out of the body and reproduce on their own. However, because they lack the controls that strictly limit replication of all normal somatic cells, stem cells are capable of indefinite replication, and thus cancer.

This helps to explain many curious aspects of stem cells (Greaves and Maley, 2012). They are relatively rare,

for the good reason that they are vulnerable to malignant transformation. They tend to be sequestered in locations away from toxins and damage. The sequence with which they differentiate into descendant cells is strictly controlled. This means that mutations that immortalize cells are essential to malignant transformation.

This perspective distinguishes the several factors necessary to control aberrant cell division (Aktipis et al., 2015). First, there must be a restraint on division. Second, there must be policing to eliminate or dissociate cells that try to divide at a cost to the group. Third, there must be policing to prevent individual cells from taking advantage of group resources for their own benefit. Finally, there must be a mechanism to eliminate cells that go rogue. Chapter 7 provides comprehensive details in a comparative perspective.

These different factors have varied requirements and impacts in different species, making comparative studies valuable. The idea that cancer is only a disease of humans is contradicted by evidence for cancer in animals in the wild (see also Chapter 2) and an overview of cancer across the breadth of the living world (Aktipis et al., 2015). The similarity in rates of cancer in organisms with orders of magnitude different numbers of cells is Peto's paradox (Nunney et al., 2015; Peto, 1977). The solution to the paradox is that natural selection shaped mechanisms that provide protection against cancer that are adequate to however many cells a phenotype has; the effectiveness of these mechanisms is limited not by the number of cells, but mainly by tradeoffs with their costs. This perspective has inspired research that has predicted and confirmed increased number and expression of tumor suppression genes in large organisms (Caulin and Maley, 2011; Nagy et al., 2007; Sulak et al., 2016).

The application of biological theories of sociality to cancer is opening up whole new realms of cancer biology. Who could have anticipated that deep thinking about altruistic behavior in bees (Hamilton, 1964) would develop into an elaborated and still-developing body of theory crucial for understanding cancer (Aktipis et al., 2015; Frank, 2007; Nunney, 2013)?

WHY IS CANCER SO COMMON? EVOLUTIONARY MEDICINE

Even as we marvel at the ability of natural selection to shape mechanisms to prevent cancer, the reality is that about one half of us will have cancer at sometime during our lives. Explaining such vulnerabilities to disease is a primary focus for evolutionary medicine (Nesse and Williams, 1994). A list of possible kinds of evolutionary explanations for apparent maladaptations helps to avoid the tendency to overemphasize one explanation

(Crespi, 2000; Nesse, 2005). For instance, a kerfuffle was aroused by a recent publication showing that variation in vulnerability to cancer across species is directly proportional to the number of stem cells and the number of their divisions (Tomasetti and Vogelstein, 2015). Journalists took the implication that most cancer is a result of “just bad luck,” arousing rebuttals that emphasized the role of environmental factors, and the difference between explaining variations in cancer rates and causes of cancer (Couzin-Frankel, 2015).

Two kinds of questions need to be distinguished. First is the usual question about why some individuals get a disease and others do not. Such questions are answered by descriptions of individual differences in mechanisms at a reductionist level, and factors that influence those mechanisms. Evolutionary medicine asks a different question about why all members of a species are the same in ways that leave them vulnerable to disease. Such questions have six possible kinds of answers, each of which is summarized briefly later.

Constraints

The traditional explanation for traits that leave bodies vulnerable to disease is that natural selection has limits. Mutations happen. Natural selection tends to eliminate deleterious ones, but the process takes time and is subject to the vagaries of any stochastic process. Useful mutations tend to increase, but genetic drift makes the process uncertain. The limits of selection offer a powerful and correct explanation that is only part of the picture. It is often framed using an outmoded model of the body as a designed machine whose robustness depends only on redundancies, instead of the complex networks that make bodies stable (Nesse, 2016). Explanations that refer to mere chance are also unwelcome. People who have cancer want to know what caused it; understanding a specific cause gives hope of a specific cure, or at least better prevention. Few people are willing to accept the reality that natural selection is incapable of shaping mechanisms to prevent all cancers. However, there are five other good reasons why selection has not shaped better protections against cancer.

Tradeoffs

A second closely related explanation is that trade-offs limit the perfection of all traits shaped by natural selection. In the case of cancer, tradeoffs are present in abundance. Tighter controls on cell division would decrease risk of cancer but would also decrease the ability of wounds to heal, and of cells in organs, such as the liver to divide in order to replace losses. Shorter telomeres, and increased sensitivity of apoptosis regulation

mechanisms, would decrease rates of cancer, but they would increase rates of aging. More aggressive immune systems would likewise decrease cancer, at the cost of increased tissue damage and possible autoimmune disease. On a macro level, tall people get many advantages in life, especially in mating, but every 10 cm increase in height increases the cancer risk by at least 10% because of increased cell number and the associated extra growth factor stimulation (Green et al., 2011). Light skin increases Vitamin D synthesis, but at the cost of increased vulnerability to skin cancer (Greaves, 2014). There is no free lunch; trade-offs are intrinsic to all cancer prevention mechanisms (Aktipis et al., 2013; Boddy et al., 2015, see also Chapter 1).

Mismatch

Natural selection can change a species only slowly, so many aspects of bodies become vulnerable to disease when environments change rapidly, as they have dramatically for humans in recent generations. The American Cancer Society estimates that more than half of all human cancers could be prevented by modifying environmental factors (Fontham et al., 2009). The big one is tobacco use, which accounts for a third of all cancers. Other environmental factors, including sun exposure, modern diets, and obesity also increase risks substantially. Much research looks at specific factors, such as the multiple aspects of modern environments that can increase rates of breast cancer. High levels of nutrition and leisure induce high levels of reproductive hormones that are correlated with breast cancer rates (Jasińska and Thune, 2001). They also lead to early menarche, which combines with delayed first pregnancy to create an interval in which breast cells are particularly vulnerable to metaplastic transformation (Russo et al., 2005). Furthermore, in ancestral environments the average woman had only about 100 menstrual cycles because of lactation induced amenorrhea while in modern societies the number is over 400 per lifetime (Strassmann, 1997), driving the system with endocrine stimulation unprecedented in the history of our species. Finally, exposure to light at night is also associated with higher rates of breast cancer (Stevens, 2009). Combinations of aspects of modern environments help to explain increased vulnerability to other kinds of cancer, and offer a potent prescription for prevention (Hochberg et al., 2013).

These environmental factors interact with genes to influence cancer risk. Common genetic variations found to strongly influence risk are likely to be those with few deleterious effects in ancestral environments, otherwise, they would have been selected out. Such variations associated with cancer should not be assumed to be deleterious; they may be “quirks” that were harmless in the environments in which we evolved.

Benefits to Genes at the Expense of Health

Natural selection shapes maximum health and longevity only to the extent that they contribute to increased reproduction. An allele that increases reproduction will tend to spread, even if it increases the risk of cancer. Such variations that have gone to fixation are very hard to identify, because they would need to be compared to some alternative that would be hard or impossible to recognize. However, some of the increased vulnerability of males to cancer may be explained, because they get a relatively greater reproductive payoff for investments in competition, while females get a relatively greater payoff for tissue maintenance and repair (Kruger and Nesse, 2006). Also, specific alleles have been suggested to perhaps increase reproduction at the cost of cancer; for instance, BRCA1, seems to be correlated with increased fecundity in some studies (Smith et al., 2012), although it is hard to control for confounding factors that could potentially explain this finding. Transmission of cancers between individuals is a dramatic example that is rare for good evolutionary reasons.

Coevolution

That infectious agents cause cancer has long been recognized, but the phenomenon is increasingly studied in evolutionary perspective. The role of papilloma virus in causing cervical cancer is well-established, as is the efficacy of vaccine prevention. An evolutionary view of why infection causes cancer begins with the general observation that tissues subject to chronic inflammation are also subject to genetic damage that can increase the risk of cancer. However, Ewald and others have suggested, and shown, that certain pathogens get reproductive advantages in the body by disrupting cell junctions and other manipulations that allow them to persist within hosts (Ewald, 2009; Ewald and Swain Ewald, 2012, see also Chapter 3). This is a classic example of coevolution, in which every improvement in the body's ability to resist infection is countered by the rapid evolution in pathogens of mechanisms to get around the defenses. The resulting arms races are extremely expensive, leaving hosts with defenses that decrease the risk of infection but increase the risk of cancer.

Defenses

Many defenses are facultative adaptations shaped by natural selection that are aroused when needed, such as fever, pain, vomiting, and inflammation. Defenses against cancer provide similar protection, but only some are aroused by specific threats, more are continuously preventing malignant transformation and eliminating rogue clades. The long-recognized special role of the im-

mune system in controlling cancer has led to dramatic new therapeutic options now under intense study (see also Chapter 9).

CONCLUSIONS

All five evolutionary perspectives offer useful insights about cancer. Keeping them separate encourages clear thinking. They are, however, intimately related. For instance, comparative studies looking at different rates of cancer among species need to be informed by both consideration of the role of chance mutations resulting from stem cell divisions, and also different life history patterns, and body designs with different compartments. Behavioral ecological approaches that analyze why cooperation sometimes breaks down among metazoan cells are closely connected with analyses of tradeoffs, and the costs and benefits of different strategies. These behavioral and ecological principles are also essential for understanding how cancers may shape their own ecological environments, and be shaped by those environments.

The transition to a fully evolutionary view of cancer offers huge promise, and many challenges (see Chapter 18). A description of five relevant principles provides useful landmarks as the territory continues to expand.

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