Opinion

Evolutionary Ecology of Organs: A Missing Link in Cancer Development?

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There is striking variation in the incidence of cancer in human organs. Malignant tumors are common in the colon and breast but rare in the heart and small bowel. The uterus frequently develops benign fibroid tumors but uterine cancers are relatively rare. The organ-specific difference in cancer prevalence has been explained primarily by the relative roles of intrinsic and extrinsic risk factors. In this opinion article, we propose also considering organs as distinct but connected ecosystems whose different vulnerabilities to malignant transformation may be partially explained by how essential each organ is for survival through the age of reproduction. We present and discuss some of the basic concepts and assumptions of this perspective on evolutionary medicine.

Intrinsic versus Extrinsic Cancer Risks: An Incomplete Debate

There is clearly variation in the incidence of cancer in human organs (Figure 1). Malignancies occur with a relatively high frequency in the colon, breast, skin, and prostate, but rarely develop in organs such as the heart and small bowel. The uterus frequently develops fibroids that can become very large but are rarely malignant, while the adrenal gland rarely develops primary cancer, but is the most common site of extrathoracic lung cancer metastases.

Most investigations into this phenomenon have focused on a distinction between intrinsic and extrinsic causes. Tomasetti and Vogelstein [1] recently sparked a debate by suggesting that the total number of stem cell divisions per tissue type could explain two-thirds of the variation in cancer risks (see, for instance [2–4]). Organs with high rates of cellular division are simply more likely to carry cancer-causing mutations, and thus subject to ‘bad luck’. In contrast, Wu and colleagues [5] proposed that cancer risk is primarily influenced by extrinsic factors, and that intrinsic risk factors only contribute modestly. For instance, primary lung cancers are common in cigarette smokers and rare in nonsmokers. Similarly, primary liver cancers are common in scarred, cirrhotic livers due to infection, alcoholism, or chronic iron overload and rare in otherwise normal livers.

In this opinion article, we propose an additional factor: vulnerability to cancer differs among organs in part because of their differing contributions to the host’s survival and Darwinian fitness. Selection for mechanisms to suppress cancer will be greatest in organs that are relatively small (and can, therefore, be compromised by even small tumors) or are critical for survival and reproduction, such as the heart, brain, and uterus (i.e., keystone organs). Organs that are large or paired, and thus can maintain function even when a relatively large tumor is present, will be less subject to anticancer selection forces. Although specific cancer-suppressing mechanisms

Trends

Despite extensive research, we lack a full explanation for why certain tissues exhibit more susceptibility to cancer than others. An approach focusing on the evolutionary ecology of organs could provide intriguing insights that transcend the dichotomist search for intrinsic versus extrinsic risk factors.

Organs in which malignant cells emerge, survive, and proliferate can be viewed as specialized islands in a living landscape, each with its own distinct ecologies.

All organs serve the organism as a whole, but they differ in how crucial they are to survival and reproduction.

Selection for cancer suppression should be stronger for organs that are more essential for the host’s survival and Darwinian fitness.

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can vary, in general they result in reduced vulnerability to tumor formation and/or metastatic invasion by mutant clones arising among cell populations under physiological conditions or following perturbations of the tissue adaptive landscape by infection, trauma, or toxins [6,7].

**The Multicellular Body: A Myriad of Distinct Ecosystems**

In complex multicellular organisms, cells combine to form tissues, then organs, and, ultimately, arrange in **organ systems** (see Glossary). Entities like tissues and organs have distinct structures and functions, as well as abiotic and biotic ecologies. For instance, abiotic factors (glucose, oxygen gradients, or water; or environmental conditions, such as temperature, pH, or UV light) vary significantly among locations and organs in the body. This is also the case with biotic factors, such as organ-specific microbial communities [8,9].

Importantly, tissues and organs provide specific microenvironments not only for microbes, but also for malignant cells that emerge, survive, and proliferate locally. Thus, organs in multicellular organisms can be viewed as specialized islands in a living landscape, with their own distinct
ecology characterized by structure, function, abiotic conditions, biotic community (microbes, malignant cells), carrying capacity, spatial distribution of resources, heterogeneity, network with other organs, and by exposure to acute and chronic external perturbations \[8,9\]. In this context, the fitness of the host depends on the function of each organ, and the survival and proliferation of each normal cell are fundamentally determined by the host. In contrast, the fitness of each cancer cell is not fully controlled by the host. Instead, tumor cell fitness depends on the rate of replication within a local tissue environment.

The Multicellular Body: Several Organs but One Evolutionary Function

All organs serve the organism as a whole, but their contributions to survival and reproduction are unequal and, as a result, they are subject to variations in the intensity of evolutionary forces. For instance, human fitness may be more affected by perturbations in the heart and brain than in the gallbladder or liver. Similarly, paired organs (lungs or kidney) can retain function even when one of the organs is damaged or rendered less functional by tumor growth. Reproductive organs are not essential for survival per se, but are crucial for reproduction and hence for fitness.

The assumption that evolutionary selection will optimize all organs to maximize health and longevity is common but has been questioned \[10\]. An alternative evolutionary perspective \[11\] emphasizes trade-offs and constraints when selection maximizes reproductive success at the expense of survivorship and longevity. As a result, organs that can undergo significant loss of function without altering the probability of reproduction may ironically be ‘more’ vulnerable to lethal pathologies such as cancer.

Evolutionary Ecology of Organs and Cancer Dynamics

Akin to microparasitic organisms, malignant cells depend on the tissue environment for sustenance, proliferation, and survival; and tumor development, progression, and metastasis are strongly dependent on the local conditions \[12\]. Several recent studies have clearly shown that ecological interactions such as competition, mutualism, and antagonism are likely to shape somatic evolution of cancer cells \[13,14\]. However, only few studies have placed these interactions within a spatial context, transposing landscape ecology to oncology \[15–17\].

Organ Ecology

Different organ ecologies can, at least partially, explain variations in cancer risks. For example, the relative rarity of heart and brain cancers can potentially be attributed to the low cellular turnover in these organs, and therefore to the low opportunities for oncogenic mutations \[1\]. We hypothesize that turnover rates may also be low in these organs because they are crucial to survival. For example, while the cell turnover rate of heart endothelial and mesenchymal cells is approximately 15% and 4% per year, respectively \[18\], and the annual striatal neuronal turnover is approximately 2.7% in the brain \[19\], the intestinal epithelium completely self-renews approximately every 5 days \[20\].

Interestingly, these traits might also render these crucial organs less capable of repair following injury, although traumatic damage to crucial organs would have been so consistently fatal in ancestral environments that selection for repair would be weak in any case \[20\].

Mutation rates may also be greatly affected by exposure to mutagens. This is common, for instance, in tissues such as the skin, or the respiratory and digestive epithelia, which are in direct contact with the external environment \[21\]. Therefore, melanoma can result from exposure to UV radiation, lung cancer from exposure to external carcinogens (e.g., pollution), and colon cancer from food-borne carcinogens such as polycyclic hydrocarbons. Organs that are regularly exposed to oncogenic infectious agents are also expected to be vulnerable to cancers; and hepatocellular carcinomas (the most common primary liver cancer), stomach cancers, and
cervical cancers are substantially attributable to hepatitis B and C viruses, *Helicobacter pylori* bacteria, and human papillomavirus, respectively [22]. Within this theoretical framework, and in accordance with observations [18], organs subject to injury and infection have a higher cellular turnover to allow repair of tissue damage. While this may increase the probability of cancer, it may also allow rapid elimination of mutant cells. Furthermore, these organs are relatively large, and fatal dysfunction would require the growth of large tumors over a long period.

**Evolution of Organ-Specific Resistance to Cancer Growth**

Recently, Noble et al. [2], using the Tomasetti and Vogelstein dataset, suggested that variation in cancer risk across human organs is analogous to ‘Peto’s paradox’: an observed lack of correlation between cancer risk and body mass (and life span) across the animal kingdom. They conclude that variation in risk of human cancer types is analogous to the paradoxical lack of variation in cancer incidence among animal species and may likewise be understood as a result of evolution by natural selection. Tissues with high levels of turnover (e.g., the lining of the small intestine) may have evolved especially powerful anticancer mechanisms. In parallel, Davies et al. [23] suggested that organ-specific cancer rates correlate negatively with an organ’s evolutionary antiquity (estimated indirectly by considering the organs’ presence in extant vertebrate groups and the time at which those groups first appeared in the fossil record). Although this relationship may just be coincidental, it suggests the possibility that recently evolved differentiation states may be intrinsically more vulnerable to neoplastic change because selection has had less time to reduce neoplastic tendencies. These interesting proposals can be extended to the analysis of how different oncogenic manifestations (from precancerous lesions to metastatic cancers) interact with how vital the organ is to survival and fitness. Indeed, the malignant transformation of normal cells following mutations is probably not lethal in most cases unless it occurs in a small vital organ. Solid tumors become threatening when the angiogenic switch allows tumor growth, and/or when metastases spread to other more vital organs. In this context, one would expect that cells in small vital organs are especially resistant to malignant transformation, and/or especially vulnerable to apoptosis when they become malignant. In contrast, larger less essential organs are likely to be relatively less able to prevent malignant transformation, but should have been shaped to resist invasion by metastatic cancer cells. In evolutionary terms, noninvasive tumors in nonessential organs may persist because natural selection is too weak to eliminate them (i.e., the fitness costs of eliminating them could be too high and/or the fitness benefits too small). For instance, certain cancers, such as prostate cancer, grow too slowly to impact fitness (i.e., detrimental health effects appear only at ages when natural selection is weak). Thus, there could be little selection to inhibit the early stages of late-life cancers that do not significantly decrease fitness. Further, mechanisms that suppress small neoplastic growth may have costly trade-offs by inhibiting wound healing, immune function, or developmental processes that require active cell proliferation [24]. Finally, the energetic costs of adaptations that could eliminate a tumor might exceed the benefits, especially because the costs are imposed at ages when natural selection is most intense [25]. Autopsy-based studies in humans or other animals that died of causes other than cancer indicate that most individuals develop in situ tumors in many organs with aging (see [12,26]). Further studies are needed that correlate age-specific rate of precancerous tumor lesions in each organ with the number of cells in that specific organ, number of stem cells, rate of new cell formation, importance of the organ to survival, and the importance of the organ to reproduction.

If fatal malignancies derive mainly from in situ malignancies that progress, preventing the formation or persistence of these ‘seeds’ should decrease cancer mortality rates. Several studies have demonstrated that eliminating precancerous cells/lesions can prevent cancer. For example, ablating Barrett’s esophagus (a change in the lining of the esophagus tissue) may lower the risk of later developing esophageal adenocarcinoma [27], as does administration of agents that decrease inflammation [28]. Similarly, removing polyps decreases future colorectal
cancer occurrence by 75–90% [29], and eliminating precancerous cells on the cervix reduces subsequent risks of developing cervical cancer [30]. Applying such preventive strategies as early as possible, even before birth, would theoretically reduce levels of in situ tumors and thus reduce cancers in elderly individuals (see [31,32]). However, the costs of evolutionary trade-offs render envisioning the body of multicellular organisms free of precancerous cells unrealistic. Nevertheless, technological advancements could potentially fill certain loopholes of multicellular control to prevent cancer. For example, engaging the immune system in the systematic elimination of precancerous lesions via prophylactic cancer vaccination is among the most promising research directions to date (e.g. [33,34]). Yet, even this approach comes with compromises: it is well established that inflammation, a key element of active immune response, contributes significantly to neoplasm growth. It is also possible that the energy required by the frequent, if not permanent, activation of immune system would be too costly and detrimental to health. High inflammation itself increases risks of cancer (e.g. [35]). Even augmenting the body’s own tumor-suppressor mechanisms could unbalance system homeostasis and result in unintended consequences, such as collateral tissue damage, autoimmune inflammatory complications, and other nonspecific side effects.

Metastatic Cascade
In animal ecology, the local availability of resources not only impacts population size, but also drives local and long-distance population dispersal [36]. For instance, many animals disperse to avoid intraspecific competition, especially from kin [37]. Evolutionary models also suggest that organisms should move only when the costs of remaining in place outweigh the potential costs of leaving the habitat [36]. Cancer cells within organs face a similar trade-off [14,38,39]. When local conditions are harsh or when resources are spatially or temporally heterogeneous, somatic selection favors metastatic cancer phenotypes, that is, the so-called mesenchymal transition (40), but see [41].

As recently highlighted by Cunningham et al. [42], the metastatic process is highly inefficient, with less than 1% of circulating tumor cells (of millions shed per day) progressing into macroscopic tumors. It is now widely recognized that metastasis depends on the interaction between malignant cells and the microenvironment of the distant organ site (i.e., its ecology). Thus, only tumor cells that already are sufficiently adapted or that can evolve adaptations to the local growth constraints of the ‘foreign’ landscape of distant organs can form metastases. Cunningham et al. [42] therefore argued that treatment strategies against metastatic cells should consider not only the primary site, but also the newly colonized site, because the predicted convergence of phenotypes within organ-adaptive landscapes could propose organ-specific therapies.

Concluding Remarks
Organ-specific evolutionary ecological variations are likely to influence cancer cell population dynamics, including emergence, proliferation, movement, or interactions, among others. Clearly, more empirical research is needed to identify and to decipher the range of variables that define organ ecology (see Outstanding Questions).

Our theoretical concept proposes that natural selection has shaped increased protection against cancer for small, essential, unpaired organs compared with larger, less essential, and often paired organs. This should provide a crucial ecological framework for preventing tumor initiation, growth, and metastasis. We predict that after the effects of stem cell numbers, rates of cell division, and exposure to toxins and infection are taken into consideration, the ecology of different organs will account for considerable differences in vulnerability to cancer. A formal test of our hypothesis will require assembling all of these data for a variety of organs. This kind of evolutionary ecological analysis of variations in different organs may prove of great value in cancer prevention and treatment.
However, an alternative explanation could be that large organs (e.g., the liver) have an intrinsic high cancer risk and therefore had to evolve to be large and redundant enough to cope with primary tumors. Independent of the direction of causality, the correlation between organ size and cancer prevalence remains relevant. Further mathematical models, focusing on the evolution of organs and incorporating autonomous and nonautonomous factors controlling organ size (e.g., cell size, type and number, competition for limiting growth or survival factors, tissue/organ environment, and the propensity of oncogenesis) may be able to pinpoint the direction of selective forces.

Furthermore, our primary aim is to provide a simple concept (focusing on single organ evolution and ecology) that will initiate scientific debates and the development of theoretical and empirical approaches. Clearly, the topic would greatly benefit from a more holistic approach, for example, a systems ecology approach that applies systems theory to the correlation between the ecosystems of organs (i.e., the individual) and oncogenesis. For example, different organs are exposed to a mix of extrinsic and intrinsic exposures (e.g., possible influences of viruses and hormone fluctuations), as well as having intricate interconnected relationships. Emergent properties of simple entities (organs) may form a more complex behavior as a collective entity that can influence the functioning of the entire system. For example, a primary tumor may not have a significant effect in the organ of origin (e.g., breast cancer), but may have a fitness reducing effect when it metastasizes to a different organ (e.g., bones, lung, liver [43]). Metastasis to distant vital organs is determined by several factors, including the cellular origin, intrinsic tumor properties, circulation patterns, and tissue affinities [44]. Therefore, selection influencing tumor resistance may not only be driven by the potential emergence of selfish malignant cells, but also by the metastatic propensity of cells in a given organ, as well as by the interconnectivity of the different organs. Further studies will be necessary to investigate how the synergistic effects and complex behavior of properties (e.g., organs) within the ecosystem of an organism could lead to selection acting on the organ level in response to oncogenesis.

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Resources
1. http://see.cancer.gov/

References