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The interface between ecology, evolution, and cancer: More than ever a relevant research direction for both oncologists and ecologists

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Forty years ago, scientists started to describe the genetic cascade of events leading to cancer as “somatic evolution” (Cairns, 1975; Nowell, 1976). Even if the full relevance of these pioneer papers was not immediately perceived by the scientific community, they paved the way for one of the most stimulating and challenging research directions in the effort to predict cancer emergence, progression, and therapy outcomes. Evolutionary biology has indeed deeply transformed our understanding of cancer, gaining unprecedented international recognition among oncologists in the last decade (Ujvari, Roche & Thomas, 2017a). Nowadays, cancer is widely considered as a pathology that emerges due to clonal evolution and cell competition, Darwinian selection being the driver of cancer cells along selective landscapes, culminating in resistance to immune attack, malignant progression, resistance to therapies, metastasis, and even sometimes contagion between individuals and/or species (Ujvari et al., 2017b; Ujvari, Roche & Thomas, 2017a). Thus, as recently proposed by Mel Greaves through paraphrasing Dobzhansky’s famous dictum, “nothing in cancer makes sense except in the light of evolution” (Greaves, 2018). This interdisciplinary field of research remains at the moment extremely promising, but it is still in its infancy, and fundamental studies (both theoretical and experimental) are still needed to pursue our understanding of the evolutionary ecology of tumors and of host–tumor interactions. By assembling some of

the latest, most exciting results, syntheses, and perspectives relating to the topic Ecology, Evolution and Cancer, our objective with this special issue is to reinforce the construction of a solid base for a balanced approach to cancer research, for oncologists and for ecologists.

Despite the great advancements in cancer research and treatment over the last 50 years, understanding cancer susceptibility, emergence, progression, resistance to therapies, and ultimately predicting treatment outcomes still largely remain challenging. Here, Brown and Gatenby (in press, This volume) put forward an alternative model of somatic evolution. They propose that mutations accumulated during the host lifetime become carcinogenic only when the cells which carry them have a real opportunity to evolve. Most of the time, this is not the case because cells in multicellular organisms are involved in the cooperative functioning that governs the host as the unit of natural selection. As a result, they remain under control by local tissue constraints. However, when for different reasons, these mutated cells become free from these host constraints, they have their own Darwinian dynamics. Mutations previously accumulated over the lifetime of the host serve as their “genetic heritage” in their malignant trajectory. Still on this topic, Solary and Laplane (2020, This volume) described the dynamics of somatic mutation accumulations in healthy tissues during the life and discussed the role of the

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host environment in tumor emergence and progression. They also explored how tumors in return remodel their close and distant environments. It appears that promising strategies against cancer consist in preserving, as long as possible, the tumor suppressive properties of healthy tissue landscapes.

Cancer cells are also under selection to evolve traits that generate heritable variation. The diversity of mechanisms yielding this evolvability is far from being fully understood at the moment. Pienta, Hammarlund, Axelrod, Brown, and Amend (2020, This volume) proposed that we have until now underestimated the role of polyan euploid cancer cells. These cells would be an important source of heritable variation, allowing cancer cells to evolve rapidly, leading to therapy resistance and metastasis. On a related topic, Noble, Burley, Le Sueur, and Hochberg (2020, This volume) questioned the classical prediction that intratumor heterogeneity is a reliable prognostic biomarker for several cancer types. Employing a spatial computational model of tumor evolution, they highlight the need for considering both clonal diversity and genomic instability than each factor alone.

Birtwell, Luebeck, Carlo, and Maley (in press, This volume) also proposed that to understand the dynamics of cancer initiation and progression, it is crucial to acknowledge that epithelia are divided into subpopulations of tissue stem cells along with the transient amplifying cells and differentiated cells that they produce. Therefore, a fundamental question in cancers like those affecting the intestinal tract is to determine how the crypt-level metapopulation dynamics affect the accumulation of somatic mutations during carcinogenesis. In addition to these malignant processes occurring during the host lifetime, Schenk, López, Kschischo, and McGranham (n.d., This volume) also highlighted that, until now, little attention has been devoted to considering the potential influence of germline ancestry on cancer development and cancer evolution. This is unfortunate because emerging data suggest that germline ancestry can profoundly influence cancer disparities in cancer care and the subsequent disease course (e.g., Zhang, Edwards, Flemington, & Zhang, 2017, Akinyemiju, Sakhujia, Waterbor, Pisu, & Altekruise, 2018). Here, by comparing European Americans and African Americans, Schenk et al. (n.d., This volume) show that germline ancestry profoundly influences the somatic evolution of lung adenocarcinoma but not lung squamous cell carcinomas.

It is well known that most cancer-related deaths are due to metastasis, but basic information is often missing concerning the evolutionary ecology of this dispersal process. An intriguing aspect concerns the fact that circulating malignant cells can be single or in clusters. Circulating tumor cells in clusters are generally associated with higher metastatic potential and worse prognosis. Campenni, May, Boddy, Harris, and Nedelcu (n.d., This Volume) proposed a mechanistic agent-based model to investigate how clusters, depending on their sizes and densities, respond to different challenges. They also made predictions on the potential combination of factors and parameter values that could decrease the fitness and metastatic potential of malignant cells in these clusters.

Ecological and evolutionary approaches have already made great advances in explaining the origins and recrudescence of cancer cells, as

well as elucidating the reasons of therapy failures, but would they be applicable to propose innovative novel directions in cancer treatment? The answer is yes. Following the theoretical advancement of the interface of *Ecology, Evolution and Cancer* a few years ago, the field is now moving into the experimental and clinical phases, and recent developments include the ability to predict which tumors will be harmful for patients (e.g., Campbell et al., 2020; Maley et al., 2017), as well as novel therapeutic approaches that are able to slow down tumor growth in invasive late-stage cancers. Currently, the most emblematic and advanced evolutionary-based cancer therapy is adaptive therapy, developed by Gatenby, Silva, Gillies, and Frieden (2009). A major conceptual breakthrough compared to traditional approaches has been the acceptance of when cancer eradication is no longer an option, treatment that focuses on containing the malignant progression is preferable. The latter approach aims to turn cancer into a chronic disease, by efficiently keeping the tumor burden below the level that threatens loss of life and/or quality. The majority of cancers are fatal due to the cancer cells' propensity of unlimited cell division, circumventing natural defenses, and ultimately resisting therapies. While the evolution of malignant cells represents a major hurdle in treatment development, it can actually be the Achilles heel of these fatal pathologies. Scientists could theoretically exploit the evolutionary pathways of cancer cells and strategically drive their evolution toward equilibria where they will no longer be detrimental to the host. To achieve this, evolutionary-based therapies need to be adaptive and dynamic, and to continuously anticipate the evolutionary response of cancers and adjust treatments accordingly, ultimately thwarting evolutionary resilience. Some of these approaches are very similar to (and emerged from) the evolutionary double-bind theories developed in pest management in applied ecology (Basanta, Gatenby, & Anderson, 2012). Similar to pest management, where the combination of chemical toxins, with introduction of predators, parasitoids, or pathogens, achieves more durable pest control, adaptive cancer therapy allows incurable tumors to persist but keeps them under control via various strategies (combination of chemo- and immune therapies, modulated dose schedule, competitive inhibitors (Enriquez-Navas & Gatenby, 2017)). These latest approaches are the most innovative and promising directions so far proposed by ecological and evolutionary sciences to transform cancer from a lethal disease, into a chronic, manageable pathology. Oncologists may, however, sometimes face a dilemma between choosing treatments that can sometimes cure the patient and regimens that can delay progression but not cure the patient. In this special issue, Hansen and Read (2020, This volume) investigated this crucial question, discussing which aspects of the evolutionary ecology of tumor dynamics should determine whether it is better to attempt cure or to manage resistance. The authors also highlight that before the advent of evolutionary strategies aimed at resistance management, there was often no choice. Because this is not the case anymore, it is now important to also adapt the ways we communicate treatment options to patients.

On a related topic, it is also predicted that slowing down malignant progressions, rather than attempting to eradicate malignant cells, can be an efficient way to prevent tumor growth, prolong drug efficacy, and ultimately to prevent deaths. Using a strain of

Saccharomyces cerevisiae as a model system, Merlo et al. (in press, This volume) investigated how the application of simultaneous selective pressures can be an efficient option to slow adaptation. Parallels with cancer cell populations are discussed in a therapeutic perspective. Finally, a novel evolutionary-based strategy for cancer therapy is proposed by Girard et al. (2020, This volume). This innovative approach elegantly exploits the properties of the "smoke detector" principle (Nesse, 2001). By sending large amount of false alarms to malignant cells, the treatment induces a new "alarm down" state in the tumor cells which subsequently lower their ability to respond to high "danger" signal.

Cancer is not only a leading cause of human death worldwide but also a pathology that affects all multicellular organisms since the dawn of multicellularity more than 500 million years ago (Aktipis & Nesse, 2013). As a result, the field of comparative oncology has emerged and facilitated the comparison of cancer dynamics across taxa, leading to insights on how biological, genetic, and ecological factors drive individual and species variations in cancer diversity, incidence, and lethality. Disparities in natural history and life-history strategies across species can exacerbate cancer risk and concomitantly drive the evolution of cancer defenses in organisms. Comparative oncology studies have so far mostly focused on the processes and patterns associated with "Peto's paradox" (lack of statistical relationships between cancer incidence and body size and longevity) that remain key to our understanding of cancer epidemiology, prevention, and improved therapies both in animal and in human populations. In this special issue, Nunney (in press, This volume) attempted to resolve this paradox, testing five hypotheses with a modeling approach, one due to intrinsic metabolic rate/body size scaling and four arising from adaptive evolution. This work supports the hypothesis that the incidence of cancer is regulated primarily through the recruitment of additional layers of genetic control whenever a cancer significantly reduces average fitness. On a related topic, Erten and Kokko (2020 This volume) introduced the concept of 'ontogenetic management strategies' to explore the rules of dividing, differentiating, and killing somatic cells depending on the mature body size targeted by organisms. With this approach, they also explored how well a strategy evolved in small-bodied organisms performs if implemented in a large body and vice versa.

Rozhok and DeGregori (n.d., This volume) provided a complementary view, proposing that carcinogenesis is shaped by three major orthogonal processes: accumulation of somatic mutations over lifetimes, species-specific evolution of cellular genetic machinery, and physiological aging-induced shifts in selective microenvironments in tissues. Because these three processes are interconnected through the evolution of life-history traits, they also vastly differ across species.

While large and long-lived animals are often investigated for anti-cancer defenses, Thomas et al. (2020, This Volume) argued that more attention should also be devoted to studying domesticated animals. For different reasons associated with the domestication process, domesticated species often display high rates of cancer,

but artificial selection may have also favored the evolution of compensatory anti-cancer defenses. Therefore, domesticated animals would constitute a group where seemingly rare anti-cancer adaptations and novel cancer treatments could be found. Following the same idea that novel therapy strategies can emerge from the "secrets" used by wild and captive animals to fight this disease, Noble, Rohaj, Abegglen, and Schiffman (n.d., This volume) also provided a large synthesis on the most promising animal-derived cancer therapeutic agents, notably derived from insects, arachnids, amphibians, and marine organism. For each compound, they present the history of their discovery, their mechanism of action, and their extent of clinical development.

A large proportion of cancers (app. 15%–20% across the globe) is initiated and caused by infectious agents, such as viruses, bacteria, and parasites (Dheilly, Ewald, Brindley, Fichorova, & Thomas, 2019; Plummer et al., 2016). These pathogens can disrupt signaling pathways that control cell proliferation, weaken the immune system, and/or cause chronic inflammation that can increase the risk of developing cancer (Ewald & Swain Ewald, 2014). As the pathogens can be passed from one individual to other, these cancers present fascinating topics to study for both evolutionary biologists, disease epidemiologists, and oncologists. Undoubtedly one of the major innovative direction of this field to emerge recently is understanding the reciprocal interactions between parasites, host microbiota, and cancer dynamics (Dheilly et al., 2019). Ewald & Ewald (in press, This volume) discussed the idea that symbionts may improve the effectiveness of immunological defenses against cancer, through a diversity of interactions between parasitic and mutualistic microbes. An original situation occurs when the host's ability to muster escalated attacks on tumor cells is influenced by symbionts, through the relaxation of immunological checkpoints.

Apart from malignancies with underlying pathogen infections (Ewald & Swain Ewald, 2013), cancer is generally not contagious. However, there are nine noticeable exceptions in the wild, where clonal cancer cell lines are able to transmit between individuals: one in dogs, two in Tasmanian devils, and six in six bivalve species (Ujvari et al., 2017a; Yonemitsu et al., 2019). Research into transmissible cancers has rapidly been gaining momentum, as these cancers are one of the most intriguing and unexplored host–pathogen systems. Although transmissible cancers are a rare type of life form, their ecological consequences can be major, as illustrated by the dramatic quasi eradication of a top predator, Tasmania devils (*Sarcophilus harrisii*). Despite the increasing interest in these malignancies, major questions still remain to be unanswered: Why do transmissible cancers emerge? How do they evolve? What are their ecological and evolutionary impacts and how to manage/mitigate them? Dujon et al. (2020, This volume) provided an interesting global meta-analysis of over 50 years of multidisciplinary and international collaborations on transmissible cancers.

Oncogenic processes are inevitable phenomenon in metazoans. Despite their omnipresence in multicellular species, ecologists and evolutionary biologists have so far either neglected them, as well as their role in ecosystem functioning (Vittecoq et al., 2013), or considered them as "noise" on host phenotypic variations. Prior

to becoming the direct cause of host death, oncogenic processes are likely to alter various fitness-related traits in their hosts, like the vulnerability to predators or to pathogens, their competitive and dispersal abilities. There is also increasing evidence that malignant cells are involved in reciprocal interactions with symbiotic microbes and parasites, thereby indirectly leading to the possibility of triple reciprocal interactions (Thomas et al., 2017). Thus, the coming years bring exciting opportunities for ecologists and evolutionary biologists to finally consider and accept oncobiota as a key player of the holobiont, and thus initiate and conduct theoretical and empirical research that adopts a very innovative perspective on the ecological and evolutionary importance of malignant cells. Using Tasmania devils and DFTD as a model system, Hamede et al. (2020, This volume) discussed the relevance of cancer cells as selective agents and suggested a holistic framework to understand the interplay of ecological, epidemiological, and evolutionary dynamics of cancer in wildlife. Using a modeling approach, Perret, Gidoin, Ujvari, Thomas, and Roche (2020, This volume) explored, for the first time at the ecosystem level, the role of cancer in species interactions, notably host–predator interactions, and how in return, the outcome of altered interplay could affect the evolution of resistance mechanisms against cancer. A first conclusion is that cancer has a limited impact on prey populations compared to predator ones. Biotic interactions can also lead to a null or positive effect of cancer on host population densities and to vary resistance levels in predator populations. With anthropogenic impact (including pollution, climate change, urbanization) predicted to dramatically increase the coming decades, it is foreseeable that the risk of cancer, and the number of cancer incidences in the wild should also increase significantly in the near future (Giraudeau, Sepp, Ujvari, Ewald, & Thomas, 2018). There is thus a need to explore, especially in long-lived species, the evolution of protective mechanisms against neoplastic processes and natural cancer defense mechanisms in general. Meitern et al. (2020, This volume) proposed that seabirds are promising model given their longevity and their habitats that are currently often polluted. This study revealed that old gulls differ from young ones both from the aspect of cancer susceptibility and of tumor suppression at the genetic level.

More than ever the topic Ecology, Evolution and Cancer offer promising challenges not only to prevent and to cure cancer, but also to understand multiple aspects of the evolutionary ecology of multicellular organisms in our changing world. We hope that this special issue will present materials useful for a broad audience of scientists, from oncologists to ecologists and that it will stimulate novel discussions across the disciplines of evolutionary biology and oncology.

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CONFLICT OF INTEREST

None declared.

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