The importance of cancer cells for animal evolutionary ecology

Reciprocal interactions between hosts, their symbionts and their oncobiota (cancer cell communities) are yet to be studied in detail. Considering malignant cells in addition to the holobiont perspective allows greater understanding of the processes governing both host phenotypes and cancer dynamics.

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It is now widely established that multicellular organisms are not autonomous entities, but rather 'holobionts' composed of the host plus all of its commensal and mutualistic microorganisms, as well as a diversity of parasite taxa (viruses, bacteria, fungi, protozoans and metazoans)[1]. Extensive research has demonstrated the considerable importance of parasites in influencing the phenotype of their hosts[2]. These studies have also demonstrated that the eco-evolutionary dynamics of animals (hosts) and symbionts (encompassing all types of symbioses) are inextricably linked with reciprocal interactions[3]. For instance, almost every aspect of an animal's behaviour — be it when feeding, breeding, or interacting with conspecifics — potentially contributes to increasing or decreasing the individual's probability of exposure to infection as well as altering the consequences of being infected[4]. In turn, behaviour may be affected by infection, and indeed parasite-induced changes in host phenotype (for example, activity, morphology, behaviour) are well documented for a wide range of host and parasite interactions[2]. In many of the best-known examples, these changes appear advantageous for the parasites' transmission and/or survival, or conversely are host adaptations aimed at eliminating the infection or reducing its cost.

More recently, it has been demonstrated that microbes, especially intestinal microbiota, affect and interact with the host akin to parasites. Host lifestyle factors and social behaviours, for instance, are capable of altering the microbiota[5–7]. Reciprocally, there are now several examples of intestinal microbiota affecting phenotypic traits such as their hosts' physiology, mood and behaviour[8–11], sometimes to increase their own fitness at the expense of host fitness[12].

Apart from microbiota and parasites, multicellular organisms also have a long evolutionary history with a third category of living entity inside their bodies: the community of malignant cells, here termed oncobiota. Malignant cells have been influencing host life-history traits and strategies since the transition from unicellular to metazoan life, approximately 1 billion years ago[13]. These cells originate from normal cells that have lost their typical cooperative behaviour during the host's lifetime, become malignant, and hence proliferated at greater rates than would normal cells. Even if they do not necessarily lead to invasive cancers, it is increasingly demonstrated that oncogenic phenomena (from precancerous lesions to final stages called metastatic cancers) are extremely prevalent in host populations, and not just in post-reproductive individuals as previously believed (for examples in humans and domestic animals see refs [14,15] and references therein; see ref. [16] for a recent review on wildlife species). On the timescale of an organism's lifetime, the duration of the interactions between a host and its oncogenic manifestations can vary from months to years, sometimes decades. Unlike microbiota and parasites, malignant cells are not transmitted between host individuals in most cases; although there are exceptions[17]. However, as for microbiota and parasites: (1) particular host phenotypic traits can influence malignant cell dynamics; (2) malignant cells can also be responsible for phenotypic alterations in the host; and (3) certain host phenotypic traits can both be underlying causative factors of cancer and in turn be fuelled by malignant progressions, opening the door for potential 'vicious circles' similar to those observed in certain host–parasite interactions[18]. In addition, there is increasing evidence that malignant cells are involved in reciprocal interactions with symbiotic microbes and parasites, thereby indirectly influencing interactions between host phenotype and symbionts. To our knowledge, the possibility for triple reciprocal interactions involving malignant cells, symbionts and hosts has been largely underappreciated, mainly because evolutionary biologists have typically ignored, or considered as 'noise', host phenotypic variations arising from oncogenic processes.

Phenotype and cancer

Most phenotypic changes in tumour-bearing individuals are only studied once cancer is diagnosed (that is, when tumours are large enough to be detected) and/or after treatment has started, which is often years, sometimes decades, after the cancer initiation[19]. Even though a larger effort should be made to explore when malignant cell-induced phenotypic changes occur in early stages of tumourigenesis (tumour production), it is likely that tumourigenesis induces host phenotypic alterations. To the extent that malignant cells are involved in (micro) parasitic-like interactions with their hosts, we can therefore expect that they too can alter the host phenotype through side effects of their presence (that is, non-functional by-products). In addition to these side effects, it is also predicted that malignant cells may be involved in host manipulation[20]. Alterations in host phenotype could also result from adaptive responses by the host aimed at eradicating the malignant cells (self-medication[21]). Phenotypic changes aimed at fighting malignant cells, similar to protective mechanisms in general, are likely to come

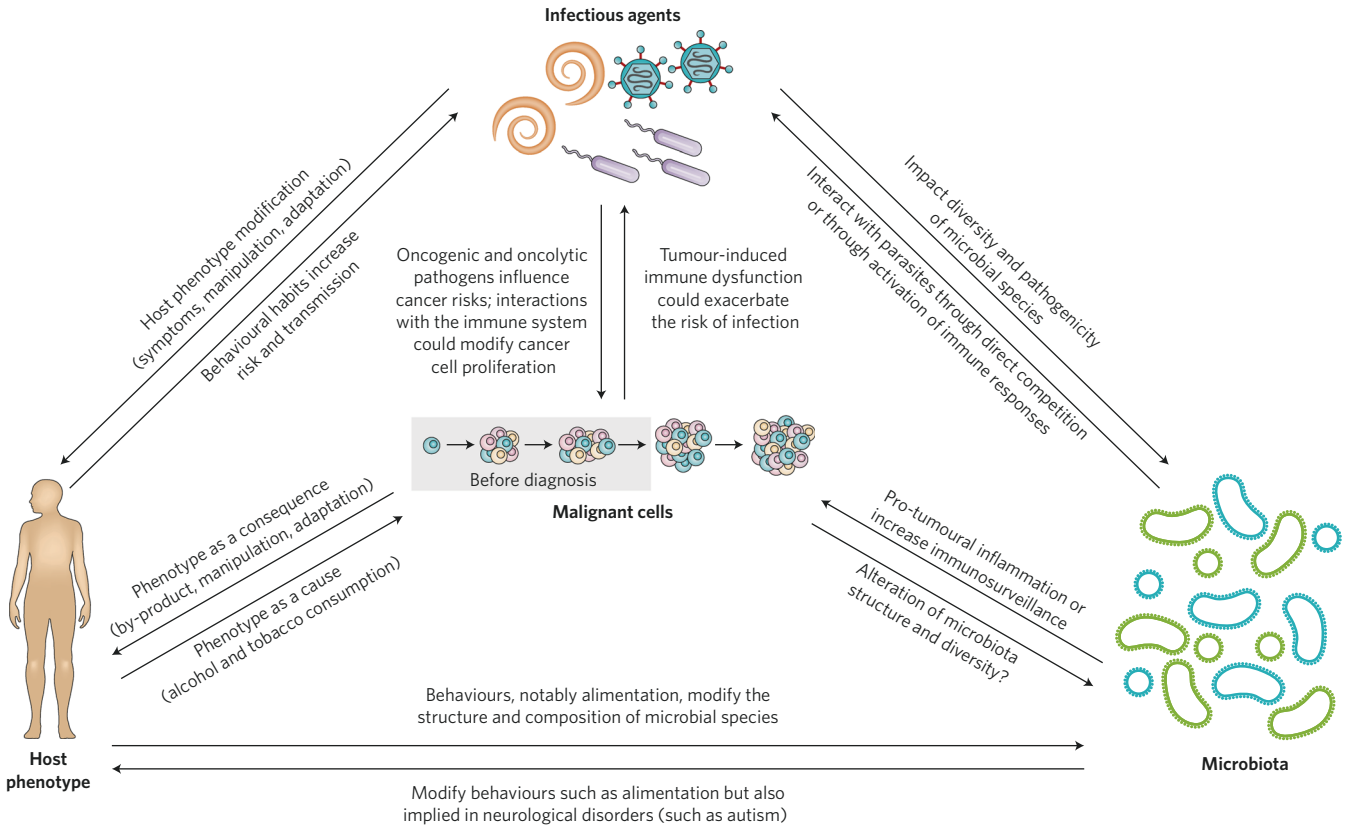

Fig. 1 | Interactions between oncobiota, host, infectious agents and microbiota.

with trade-offs with other functions (see ref. [22] for a recent review). Thus, even when organisms are apparently cancer-free, oncogenic processes should not be ignored when studying the host phenotype because of the probable costs of preventing microscopic — yet growing — colonies of cancer cells from becoming lethal tumours. When cancer growth is unpreventable, individuals may react adaptively to minimize impacts, for example through changing life-history decisions to reproduce early before the impacts of cancer become too great[23–25]. It has recently been argued[19] that phenotypic alterations (such as diet preferences) that are beneficial for tumour-bearing individuals (that is, those that maximize their fitness before death) can be beneficial to tumour progression as well, provided that cancer-induced death occurs sufficiently late in life (when natural selection is weak).

Interactions with symbiotic organisms

Infections are well recognized as a fundamental aspect of cancer causation, with a growing number of pathogens recognized as oncogenic[26]. Given that the immune system plays a key role in the control and suppression of malignant cells through immunosurveillance, any disequilibrium in immune system homeostasis (due to infections, for example) may enhance or constrain the proliferation of malignant cells[22]. However, the effect of tumour-induced immune dysfunction/suppression, which can be frequent[27,28] and often results in exacerbated risk of infection in cancer patients[29,30], has not been extensively studied or widely appreciated. One study suggested that oncogenic phenomena in wildlife could be involved in the initiation of vicious cycles[18]: hosts in poor condition due to malignancies are more susceptible to higher parasite occurrence and infection intensity, further weakening them as well as increasing their probability of subsequent infections and cancer progression. As parasites are ubiquitous[31] and co-infections, as well as malignant cell proliferation through life, remain the norm rather than the exception, a better understanding of how parasite communities may prevent or exacerbate carcinogenesis is urgently needed[22].

In addition to the potential interactions between malignancies and pathogens, there are interactions with the microbiota and its possible role on carcinogenesis[32]. It is now well established that changes in interactions among the microbiota, intestinal epithelium and host immune system are indeed associated with many diseases, including cancer[33]. A pro-tumoural role of microbiota has been linked to inflammation[34]. For example, disruption of the mucosal/epithelial barrier results in induction of pro-inflammatory cytokine secretion that ultimately induces tumour growth in colon adenoma mouse models[35]. In addition, colon carcinogenesis is also driven by microbiota through other mechanisms such as the alteration of retinoic acid metabolism[36]. Relationships between malignant cells and microbiota may also be more complex, involving the host immune system[37]. For instance, the presence of malignant cells and/or their products can modify the efficiency of adaptive immunity that controls both the richness and diversity of the microbiota[38]. Reciprocally, microbiota can also fundamentally influence the efficiency of the immune system[39] that promotes anti-tumoural surveillance, thereby preventing cancers, or at least limiting tumour growth. Microbial products shape T-cell repertoires[40] and could regulate anti-tumour responses through the priming of cross-reactive T cells specific to both bacterial and tumoural antigens[37]. Unravelling host–microbiota interactions

and assigning causal roles in cancer to specific microbiota are areas of intensive interest. While the presence of bacteria in tumours may be associated with the development of specific cancers, it may also reflect local infections of existing malignant tissue (that is, opportunistic infections of established tumours[41,42]).

Ecology and evolution

Phenotypic alterations in hosts harbouring oncogenic phenomena are likely to influence key ecological variables — competitive abilities, feeding strategies, metabolism, immune-competence, vulnerability to predators and ability to disperse — in just the same ways that we would expect microbiota and parasites to affect these processes[18]. Such indirect effects on ecosystem functioning, and their potential evolutionary feedbacks (host biology is shaped by oncogenic processes), are yet poorly understood, although they may be a major (so far missing) piece of the eco-evolutionary puzzle[43]. If malignant cell-induced changes in host phenotypes occur before the end of the reproductive period, they will influence the immediate and long-term action of natural selection on hosts. Indeed, strong environmental effects on phenotype can render selection 'myopic'; that is, capable of seeing and acting only on the phenotypes that are present in given conditions. Malignant cells, in a similar way to microbiota and parasites[44], could weaken the coupling between selection on phenotypes and selection on genotypes. Thus, one effect of malignant cells might be to slow down evolutionary changes as long as tumour-bearing individuals still pass on their genes to the next generation.

Medical implications

Knowing why, when and how cancer cells, alone or in interaction with symbiotic organisms, modify the phenotype of their host could be very relevant in the war against cancer. For infectious diseases, determining whether a manifestation benefits the host, the parasite, neither or both has important therapeutic implications[45]. The same logic applies to cancer. Understanding phenotypic changes in the host due to cancer cells, or reciprocally those that favour directly or indirectly (through microbiota alteration) malignant cell proliferation, is only the first step; the challenge will be to integrate this knowledge into the design of prophylactic or curative strategies, as parts in neoadjuvant and/or adjuvant therapies, for example. If oncogenic progression from precancerous lesions to metastasis relies on a more or less constant/obligatory sequence of phenotypic changes and/or microbiota alteration, adaptive therapies could indeed aim to alter these processes. However, more research is needed to distinguish phenotypic changes that are host adaptations aimed at favouring early reproductive investment[24] from those that are beneficial for survival. The latter is particularly relevant for human populations where long life expectancy is favoured over maximizing reproduction. Developing tools for monitoring the phenotypic changes induced by cancer cells on all relevant scales should also permit the identification of actual life periods when the risk of invasive cancer initiation is highest. Finally, it would also be crucial to identify anticancer treatments that fight malignant cells and at the same time support microbial communities in maintaining homeostasis and a cancer-restrictive environment. More generally, given that treatments (such as antibiotics and anti-inflammatory medications) against numerous pathologies may result in behavioural as well as microbiota alterations[46–48], it is imperative to determine their impact, either beneficial or detrimental, on long-term cancer risk.

Concluding remarks

Phenotypic differences between healthy and tumour-harbouring individuals are at least in part the tractable outcome of the intimate interaction between a tumour and its host. Studying these differences is therefore central to both cancerology and understanding of the pivotal role of oncogenic phenomena in host evolutionary ecology and ecosystem functioning[43]. Until relatively recently, the roles of parasites and microbiota in host biology and evolution were ignored by ecologists[1]. However, since we started to explore them with appropriate tools, we have discovered that it is impossible to omit them[49]. In fact, malignant cells — at least in our opinion — have the same importance in evolutionary biology and ecology as non-self parasites, and therefore should be considered as important as parasites and microbiota (Fig. 1). To explore this novel direction, research must first rely on tractable animal model systems such as mice or *Drosophila*, allowing (1) the manipulation of the microbiota (for example, inoculating axenic individuals with either single or different combinations of bacterial species[11]), (2) the controlled initiation of cancer (such as from genetically modified organisms[50]) and (3) the subsequent monitoring of host phenotypic changes from the point of cancer initiation to the end of life. Another major advantage of using animal models is that phenotypic traits can be monitored and studied without interfering with the psychology of cancer-bearing and control animals. Multidisciplinary science, specifically mathematical and computational modelling, will also play a crucial role in such a holistic view. We hope that our ideas presented here will pave the way for exploring the underestimated role of oncogenic processes in shaping the biology, ecology and evolution of their multicellular hosts. ❐

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Competing interests

The authors declare no competing financial interests.