Host manipulation by cancer cells: Expectations, facts, and therapeutic implications

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Similar to parasites, cancer cells depend on their hosts for sustenance, proliferation and reproduction, exploiting the hosts for energy and resources, and thereby impairing their health and fitness. Because of this lifestyle similarity, it is predicted that cancer cells could, like numerous parasitic organisms, evolve the capacity to manipulate the phenotype of their hosts to increase their own fitness. We claim that the extent of this phenomenon and its therapeutic implications are, however, underappreciated. Here, we review and discuss what can be regarded as cases of host manipulation in the context of cancer development and progression. We elaborate on how acknowledging the applicability of these principles can offer novel therapeutic and preventive strategies. The manipulation of host phenotype by cancer cells is one more reason to adopt a Darwinian approach in cancer research.

Keywords:
cancer cell; cancer progression; clinical oncology; host manipulation; parasitic ecology

Introduction

It is now well established that cancer development and progression represent an evolutionary process as Darwinian selection drives cancer cells along evolutionary landscapes, culminating in resistance to immune attack, malignant progression, metastasis [1], and even sometimes contagion (Box 1). For this reason, insights into the evolutionary and adaptation dynamics of cancers can be gained by studying the evolutionary strategies of organisms, especially of those which follow a parasitic lifestyle [2–6]. In non-transmissible cancers, malignant cells are, at best, under selective pressures for this parasitic lifestyle for only a few decades, i.e. according to the somatic mutation theory each cancer must "reinvent the wheel" because their evolutionary products die with the host [7] (but see [8, 9]). Conversely, in the cases of contagious cancers, fitness is not restricted by host death, allowing for a longer evolutionary history involving coevolutionary processes with the host species [10]. Given this ecological and evolutionary context, theory postulates that lineages able, like classic parasitic organisms (see Box 2), to manipulate phenotypic traits in their host in ways that favor their

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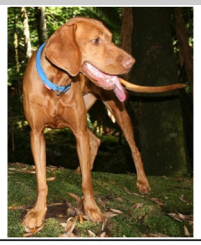
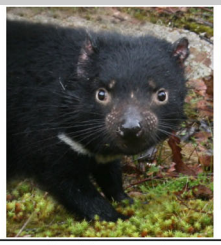
Abbreviations:
CTVT, canine transmissible venereal tumor; **DFTD,** Devil facial tumor disease.

Box 1

There are four examples of transmissible cancers: three mammalian (Devil facial tumor disease (DFTD), canine transmissible venereal tumor (CTVT), hamster-induced transmissible sarcoma) and one invertebrate (clam leukemia, CL) transmissible cancer cell lines have so far been identified. In these cases, cancer cells are true infectious agents (i.e. they are contagious) and hence escape the demise of the host organism. Image of Syrian hamster taken by cdrussorusso (https://www.flickr.com/photos/23516192@N08/), and used under Creative Commons – Attribution 2.0 Generic License.

	Canine Venereal Tumour Disease (CTVT)	Devil Facial Tumour Disease (DFTD)	Contagious reticulum cell sarcoma (CRCS)	Clam leukaemia (CL)
Species affected	Dogs, wolves, coyotes and jackals	Tasmanian devil (*Sarcophilus harrisii*)	Syrian hamster (*Mesocricetus auratus*)	Soft-shell clams (Mya arenaria)
Appeared	>10,000 years ago	>20 years ago	1960s	>40 years ago
Distribution	Worldwide	Tasmania	Laboratory colony	North Atlantic cost
Cell of origin	Myeloid cells	Schwann cells or precursors	Neoplastic histiocytes	Haemocytes
Emerged due to	Low genetic diversity of host species	Low genetic diversity of host species	Not known	Pollution, temperature, and overcrowding
Spreads via	Direct contact during sexual intercourse and licking of affected areas	Direct contact during social interaction (mating and fighting for food)	Subcutaneous implantation, feeding on the ulcerated tumours, cage contact, via mosquito bites	Filtration of seawater contaminated with neoplastic cells
Primary tumours	Genitalia	Face	Upper lip, subcutaneous	Haemolymph
Metastasis	Rare	70%	100%	100% (invade all tissues)
Mortality	Rare	Close to 100%	Animals were euthanized	Close to 100%
Manipulation of the hosts' microenvironment	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis	Potential paracrine signalling and chemotaxis
Manipulation for transmission	Upregulates oestrogen receptors and increases the hosts' sexual receptiveness and attractiveness	Potentially influencing boldness/shyness	Not known	Not known

proliferation and/or transmission to novel hosts (for contagious cancers) should achieve higher fitness, and consequently be favored by selection. However, the existence of host manipulation by cancer cells has not been extensively studied until now, and/or has been envisaged in isolation from parasitological research.

Host manipulation: What could we learn from classic parasites?

Not all phenotypic changes in parasitized hosts are parasitic manipulations: they may, variously, benefit the host (e.g. fever); benefit neither the host nor the parasite ("side-effects"); or benefit both the host and the parasite [11] (Box 3). As far as manipulation is concerned, parasitologists have identified three main evolutionary routes that can lead to this behavior: (i) manipulation sensu stricto; (ii) a mafia-like strategy; and (iii) exploitation of compensatory responses [12]. Route 1 is a decidedly manipulator-oriented view, while Routes 2 and 3 are scenarios in which the host genotype is also involved in the evolution of manipulation [13] (Box 3).

Manipulation sensu stricto, which is classically considered as the main manipulative process, proposes that host alterations that benefit the parasite are illustrations of the extended phenotype concept [14]: the altered host phenotype results from the expression of the parasite's genes. In this view, manipulator genes are selected for their effects on host phenotype. Parasites target at least four physiological systems that shape behavior in both invertebrates and vertebrates: neural, endocrine, neuromodulatory, and immunomodulatory [15–18].

Alternatively, "making the host do something" can sometimes be achieved when something is better than nothing for the host. In these situations, phenotypic changes in hosts can be the direct products of natural selection acting on the host genome, even when they result in significant fitness benefits for the parasite. In the context of mafia-like strategies (Route 2), parasites can select for collaborative behavior in their hosts by imposing extra fitness costs in the absence of compliance. By cooperating with manipulative parasites rather than resisting them, hosts might mitigate fitness costs associated with parasitism. The mafia-like strategy works from a theoretical point of view, but reports from natural settings are still scarce [19]: one such example is brood parasitism by cuckoos, in

Box 2

The outstanding diversity of host manipulation by parasites

Following the pioneer work of Bethel and Holmes [81], it is now well established that many parasitic organisms (e.g. virus, bacteria, fungi, protozoans, nematodes, nematomorphs, acanthocephalans, trematodes, cestodes, and insect parasitoids) have evolved the capacity to manipulate the phenotype of their hosts to increase their own probability of transmission and/or survival in a given host, or insure that their propagules will be released in an appropriate location or habitat (see reviews [13, 82–84]). Host manipulations are extremely diverse, ranging from small changes in the time allocated to some activities to the display of novel, sometimes multidimensional, phenotypic alterations that can impact behavior, physiology, and/or morphology [85].

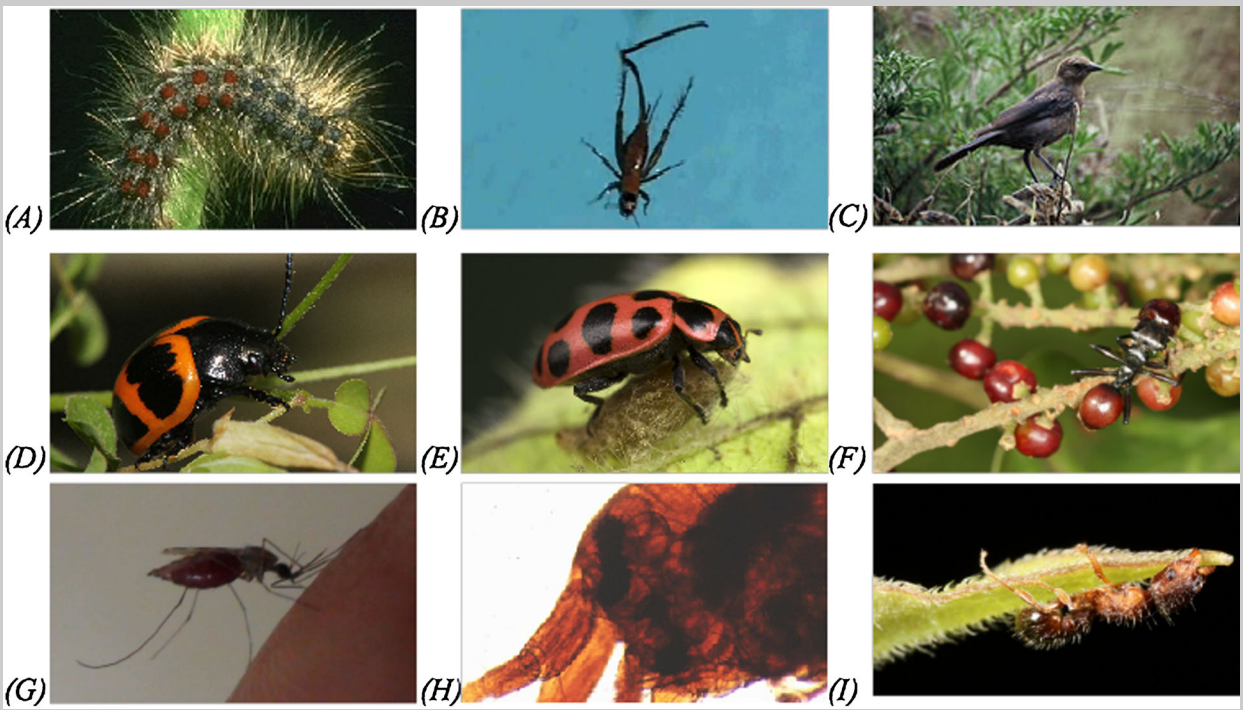
A: A gypsy moth caterpillar (*Lymantria dispar*) killed by a baculovirus (left), along with a "not yet dead – zombie" caterpillar (right) (photo Forest Service of the United States Department of Agriculture). Infected caterpillars climb to treetops where they are liquefied shortly before they die and release a shower of infectious viral particles. This elevated mortuary position allows optimum dispersion for the parasite: infectious particles fall onto lower-level leaves and healthy caterpillars become infected when ingesting contaminated leaves. This is a striking example of manipulation sensu stricto: there is a single viral gene encoding a protein (EGT) which inhibits a hormone in the host inducing the tendency to climb up [86].

B: The Gordian worm (*Paragordius tricuspidatus*) exiting the body of a cricket (*Nemobius sylvestris*) (photo F. Thomas). Infected crickets commit suicide by jumping into water, allowing the aquatic parasite to exit the host and find a mating partner [87]. This is another likely example of manipulation sensu stricto: proteomic analyses have revealed parasite production of molecules that may act directly on the cricket's central nervous system [88].

C: The brown-headed cowbird (*Molothrus ater*, photo L. Karney, USFWS), a brood parasite, is a classic example of manipulation based on mafia-like strategies. By manipulating ejection of cowbird eggs and cowbird access to nests of their warbler host, Hoover and Robinson [89] showed that 56% of ejector-nests compared with only 6% of accepter-nests were destroyed by cowbirds. In addition, the study found that warbler hosts produced significantly more offspring by accepting cowbird eggs. This mafia behavior therefore selects for collaborative hosts.

D: The leaf beetle host *Labidomera clivicollis* (photo Smidon33). In response to infection with the lifespan-reducing ectoparasite *Chrysomelobia labidomerae*, male beetles compensate for decreased longevity by engaging in more intense sexual behaviors which enhance both inter- and intra-sexual contacts (copulation and competition) [22]. This favors both the host, which maintains its fitness by increasing its mating rate, and the parasite, which achieves transmission to a greater number of hosts.

E: A manipulated beetle *Coleomegilla maculata* protecting the cocoon of the braconid wasp *Dinocampus*



coccinellae (photo with courtesy of P. Goetgheluck). Female wasps deposit a single egg in the hemocoel of the host, and during larval development the parasitoid feeds on host tissues. The larva keeps the host alive such that after emergence it becomes a bodyguard against natural enemies. Maure et al. [90] showed that protected parasitoid cocoons suffer less predation than unprotected cocoons. In addition, the length of the manipulation period is negatively correlated with parasitoid fecundity, providing evidence for a cost of manipulation.

F: The nematode parasite *Myrmeconema tropicum* turns the abdomen of its ant intermediate host *Cephalotes atratus* bright red, and drives the ant to go perch, with its abdomen raised, among patches of small red berries, to await the frugivorous birds that serve as definitive hosts for the nematode ([91], photo courtesy of S. Yanoviak). This is a typical example of simultaneous multidimensional manipulation: both the ant color and behaviors are manipulated.

G: The tsetse fly *Glossina morsitans morsitans*, a vector of several *Trypanosoma* species responsible for human sleeping sickness (photo T. Lefevre). Host manipulation by parasites may have profound significance for human health. Many manipulative parasites are responsible for devastating vector-borne diseases such as dengue fever, malaria, leishmaniasis, or sleeping sickness [92]. These parasites induce changes in the behaviors of their insect vectors that affect the frequency of interactions between hosts and vectors. The onset of behavioral changes are synchronized with the parasite development. When the parasite is not fully mature, the contact rate with vertebrate hosts is reduced. Since biting is risky (e.g. host defensive behaviors can kill the vector and its parasite), reduced biting rate is beneficial to the parasite. In contrast, when the parasite is mature and ready to be transmitted, it modifies the behavior of its vector in a way that increases contact with the vertebrate host and hence transmission.

H: A cystacanth of the trophically transmitted acanthocephalan parasite *Polymorphus minutus* encysted in the body cavity of its intermediate crustacean host *Gammarus pulex* (photo F. Thomas). This parasite induces both simultaneous and sequential multidimensional manipulation. It modifies the crustacean geotactic and escape behaviors and thereby enhances the likelihood that the intermediate host is consumed by water bird definitive hosts. These changes do not occur before the parasite is mature and ready for transmission. Because premature predation would be fatal, parasites have evolved the ability to suppress predation on the intermediate host when uninfective to bird hosts.

I: An ant infected with the trematode *Dicrocoelium dendriticum* clamping down with its jaws on a grass tip (photo C. Eiseman). The parasite makes the ant leave its colony, cling to grass blades when dusk falls and wait for a herbivorous mammal (the definitive host). Photo D was taken by David Hill, and used under the Creative Commons – Attribution 2.0 Generic Licence. The photo was downloaded from https://www.flickr.com/photos/dehill/9254286400/.

which magpies that eject cuckoo eggs from the nest incur higher nest predation by cuckoos than those that accept parasite eggs [20].

Route 3 proposes that parasitic organisms affect fitness-related traits in the host to induce host compensatory responses that, at least partially, match the parasite's needs [21]. Parasites can themselves be the causal agents of the compensatory responses displayed by the host, and/or directly exploit compensatory responses that have been selected in other contexts by mimicking the causes that

Box 3

The three main types of manipulation among parasites (from [12])

1. Manipulation sensu stricto

Host behavioral alteration may be regarded as a compelling illustration of the extended phenotype [14], that is, the expression of the parasite's genes in the host phenotype. The extended phenotype perspective thus postulates that in some host–parasite interactions, the parasite genes are responsible for the aberrant behavior. In this view, genes of the parasite are selected for altering host phenotype.

2. Mafia-like manipulation

Host behavioral alteration may be regarded as a forced collaboration. Parasites may select for collaborative behavior in their hosts by imposing extra fitness costs in the absence of compliance. The parasite would be able to adopt a plastic strategy (i.e. facultative virulence) depending on the level of collaboration displayed by the host. According to this theory, genes of the parasite are selected for their ability to detect non-collaborative behaviors and their ability to produce retaliatory behavior.

3. Exploitation of host compensatory responses

Host behavioral alteration may be regarded as a host response to parasite-induced fitness costs. Parasites may affect fitness-related traits in their hosts such as fecundity and survival in order to stimulate host compensatory responses because these responses can increase parasitic transmission. Accordingly, genes of the parasite are selected for their pathological effects that induce a host compensatory response. Since behavioral changes both mitigate the costs of infection for the host and meet the objectives of the parasite in terms of transmission, natural selection is likely to favor all the genes involved in this interaction.

induce them. A potential example is the sexually transmitted ectoparasite *Chrysomelobia labidomerae* which parasitizes the beetle *Labidomera clivicollis*: infected males have lower survival than uninfected ones, but to compensate they exhibit increased sexual behaviors, which enhance opportunities for parasite transmission [22].

Host manipulation by cancer cells: What are the facts and expectations?

In the case of transmissible cancers, it is theoretically expected that manipulative strategies similar to those of parasites could have evolved, provided that enough evolutionary time and variation in cancer cell lineages have been available for selection to favor such adaptations. In addition, manipulative strategies leading to fitness benefits inside the host will also be favored when they facilitate crucial steps in tumorigenesis (e.g. malignancies must establish, receive nutrients, evade destruction from the immune system, and disseminate to distant sites), especially because it would cost less to cancer cells to delegate these functions through manipulation. For non-transmissible cancers, only the latter situation is relevant. However, we expect some manipulative strategies to emerge during the course of cancer progression. Notably, prior to cancerous cells switching to carcinogenesis, they nurture mutualistic relationships with other healthy cells and ultimately with the host. These interactions involve coordination between cells and organs via signaling and communication pathways. Cancer cells could thus quickly reroute these pathways to respond to their own microenvironmental constraints [23]. These hijacked traits would therefore evolve as exaptations (sensu [24]) for cancer cells, i.e. they would serve functions for which they were not designed.

Cancer cells manipulate their microenvironment

Tumor development (carcinogenesis, progression, and metastasis) strongly depends on the microenvironmental conditions met by cancer cells [25]. When considering effects of microenvironmental changes on cell selection during oncogenesis, the extended phenotype provides a conceptual framework; alterations of the microenvironment are viewed as parts of the extended phenotype of cancer cells that influence the success of cancerous and precancerous cells during oncogenesis [26].

Interestingly, there is mounting evidence that many non-neoplastic host cells collaborate with the tumor, contributing to its development [27] by promoting and facilitating: (i) establishment and proliferation, (ii) immune response modulation, and (iii) metastases.

Cancer cells manipulate their microenvironment to facilitate establishment and proliferation

For instance, most enzymes involved in extra-cellular matrix breakdown are secreted by normal cells adjacent to the tumor site (i.e. cancer cells induce these changes and/or just "free-ride" off normal cell physiology [28]). By producing growth factors and pro-inflammatory cytokines, normal cells are also involved in neoplastic transformation of cells and tumor clonal expansion [29]. Cancer cells send signals to induce epigenetic changes in surrounding stromal cells and recruit them to create a community of highly specialized cells able to sustain the needs of the tumor [2, 4, 30]. For example, the expression of the extracellular matrix metalloproteinase inducer (EMMPRIN) by cancer cells recruits fibroblast cells into the production of matrix metalloproteinases [31, 32]. In addition, stromal cells also release their own diffusible signals that themselves contribute to tumorigenic activities, participating in the recruitment of other stromal cells. For example, EMMPRIN promotes its own secretion in fibroblast cells [31]. Interestingly, growing evidence suggests that polyclonality in intestinal tumors may originate from the recruitment of normal cells into carcinogenesis by a single cell-of-origin [33, 34]. The benefits of polyclonality for cancer cells remain unclear, but could be associated with extensive cooperativity between cancer cells [35, 36].

Cancer cells manipulate their microenvironment to evade immune recognition

Tumor-infiltrating immune cells even reverse their normal function: instead of eliminating cancer cells, they protect them and have immunosuppressive effects in tumor environment [37, 38]. Indeed, cancer cells can actively manipulate immune cell function via secretion of tumor-specific miRNAs [39]. Additionally, innate immune cells promote angiogenesis by the production of growth factors and chemokines [38, 40], and in many cancers, the release of CXC chemokines recruits endothelial cells into angiogenesis [41, 42].

Cancer cells manipulate their microenvironment to facilitate metastasis

During the metastatic process, paracrine signaling and chemotaxis between the soil (novel tissue) and the seed (malignant cell) lead to tissue tropism of metastatic cells and the invasion of specific organs [43]. Stromal environments accommodating novel tumors can arise by manipulation at each site of tumor metastasis [10, 44, 45]. However, an interesting question concerning both metastatic processes and transmissible cancers is whether the evolved (clonally selected) abnormal stromal cells ("fellow-travellers"), which provide an optimal niche for primary tumor cells, accompany the invasive malignant cells during invasion of new organs and/or other host organisms [10]. Further studies are needed to answer whether intra- and/or inter-individual metastatic cells have evolved to be self-sufficient (i.e. grow and spread without supporting stromal cells), or rather rely on manipulation to successfully establish in a novel habitat.

All these manipulations apparently rely on molecular cross-talk between cancerous and healthy cells to induce collaborative responses from healthy cells. Collaborative behavior may result because healthy cells are directly victim of manipulative molecules produced by cancer cells, or because they respond to fake signals produced by cancer cells in a way that favors tumor development. Thus, manipulation

sensu stricto and compensatory responses (Routes 1 and 3) seem to be the major ways by which cancer cells manipulate healthy cells in their microenvironment.

Can cancer cells manipulate beyond the microenvironment?

Cancer cells could manipulate beyond their immediate environment, targeting other host traits to satisfy different needs, a phenomenon that could greatly favor malignant progression and metastasis. Such multidimensional manipulations, either sequential or simultaneous, could be achieved by different cells in the tumor because tumorigenesis typically leads to tumor compartments each having distinct functions that cooperate to establish tumors [46]. These multidimensional manipulations would not simply be a summation of multiple smaller effects, but instead a novel collective phenotype may arise. Below we discuss eating behaviors and sleep as possible research directions on this topic.

Can cancer cells manipulate eating behaviors?

Cancer progression is often influenced by diet parameters (e.g. calorie intake, energy balance, diet composition [47, 48]). For instance, high-fat and carbohydrate diets significantly exacerbate cancer proliferation [49, 50]. Reciprocally, calorie restriction is being heralded as the most potent broadly acting dietary regimen for suppressing carcinogenesis [50, 51]. Therefore, cancerous individuals potentially have (at certain periods during carcinogenesis) some control over tumor progression by adjusting their diet in ways that limit cell proliferation (i.e. self-medication). Alternatively, just as gut microbes have been hypothesized to manipulate host eating behavior to promote their fitness at the expense of host fitness (e.g. [52]), cancer cells could also potentially modify host appetite to benefit the tumor. Since the metabolism of cancer cells is very different from normal cells, different nutritional requirements could arise at different stages of cancer development and progression compared with healthy cells. To satisfy their needs, cancer cells could then induce cravings for foods that they specialize on or that give them fitness advantages in the competition with healthy cells; furthermore, cancer cells might be able to induce dysphoria until foods that enhance their fitness are consumed. As a possible research direction, related to the higher metabolic demand of cancer cells, tumor-bearing individuals might be motivated to consume high energy substances, e.g. sugar, as a compensatory response. Interestingly, alterations of eating behaviors (e.g. taste changes, increased satiety with delayed gastric emptying [53]) are frequently reported by cancer patients, but it is unknown whether they correspond to host adaptations aimed at limiting cancer progression, cancer cell manipulation, or pathological consequences without adaptive value. While an increasing number of studies suggest that our bodies are composed of diverse organisms (microbiota) competing for nutritional resources, we believe that cancer cells should be considered as full players in these interactions.

As with gut microbes (see [52]), eating manipulations by cancer cells could theoretically be achieved through various, more or less direct, mechanisms. For instance, it could be done by influencing reward and satiety pathways, producing mood-altering toxins, modifying taste receptors, and hijacking the vagus nerve, i.e. the neural axis between the gut and the brain. From an evolutionary point of view, Routes 1 and 3 could be invoked for both gut microbes and cancer cells.

Can cancer cells manipulate sleep?

The biological functions of sleep are not fully understood, but several studies support the hypothesis that sleep duration is strongly associated with immune defense [54, 55]. For example, mammalian species that sleep longer also have lower levels of parasitic infections [56]. Given that one of the functions of the immune system is to recognize and eliminate altered cells including malignant ones [40], cancer resistance may have played a significant role in the evolution of sleep. Furthermore, variation in duration of the sleep/wakefulness cycle strongly influences the production of various hormones including melatonin, which are important anti-tumor agents [57]. Sleep disturbances are very common in people affected by cancer [58, 59]. Cancer patients (especially breast and ovarian cancer patients [60, 61]) show a reduced distinction between daytime and nighttime activities, suggesting circadian rhythm disruption. High rates of insomnia among patients with breast, gynecological and lung cancers are also frequently reported [62]. In parallel, it has been shown that fragmented sleep in mice speeds cancer growth, increases tumor aggressiveness, and reduces the immune system's ability to control cancer [63]. Similarly, severity of sleep apnea predicts aggressiveness of melanoma [64]. Although these sleep disorders may have a variety of causes, one possibility is a direct tumor effect on sleep cycles [62], mediated, for instance, via an influence of tumors on the secretion of the cytokines that modulate the sleep/wake cycle (i.e. Route 1). Because the symptoms are non-specific, it is unclear, at the moment, whether cancerous cells are more or less directly favored by selection through disrupting sleep, and/or if this is only a side-effect of being sick having coincidentally positive effects on carcinogenesis.

Can contagious cancers manipulate for transmission?

Canine transmissible venereal tumor (CTVT) and Devil facial tumor disease (DFTD) are considered the two oldest naturally occurring cancer cell lines, having appeared approximately 11,000 and 20 years ago, respectively [65, 66]. Evidence suggests that the evolutionary history of these cancers has promoted the development and implementation of highly elaborate adaptive strategies that maintain reproductive potential in the hostile micro- (stroma) and macro- (host genotype) environment of their canine and Tasmanian devil hosts [67]. Interestingly, the coexistence of CTVT with its hosts for millennia also resulted in its apparent ability to manipulate host sexual receptiveness to enhance its chances of transmission. By increasing estrogen receptor expression, CTVT enhances neoplastic growth factor production in the progestational vagina, which maintains high vascularization

and nutrient flow, and facilitates neoplastic development [68]. Via modulating the local vaginal tissue environment and increasing estrogen receptor expression, CTVT may also manipulate the host's sexual attractiveness and receptiveness, by potentially regulating receptiveness signaling odors and altering estrus cycle timing. An interesting hypothesis to investigate is whether, by altering odor cues, CTVT actively encourages matings and hence transmission. Laboratory experiments have shown that upregulation of estrogen receptor activity in sexually receptive female mice mediates male risk-taking behavior, and reduces the males' aversive response to predators [69]. Additionally, estrogenic signaling is involved in social interactions and avoidance of conspecifics carrying pathogens or malignant cells [7, 70]. Therefore, activation of estrogen expression by CTVT may not only "create" bolder males ready to fight for mating success, but also to mate with cancer-carrying females. Interestingly, bite patterns and behavior of Tasmanian devils revealed that primary tumors occur predominantly inside the oral cavity, and submissive animals are less likely to develop DFTD. Transmission seems to occur via dominant individuals biting the tumors of other devils [71]. Whether DFTD manipulates devil behavior by altering the hormones responsible for boldness/shyness remains unknown.

What are the therapeutic implications?

Knowing why, when, and how cancer cells manipulate their host could be very valuable in combating cancer. For infectious diseases, determining whether a manifestation benefits the host, the parasite, neither or both has important therapeutic implications [11]. The same logic applies to cancer. Clinicians and researchers have in fact for decades been implementing anti-manipulative strategies, e.g. in combating angiogenesis and immunosuppresion, but more effort could be done in this direction. There is currently a pressing need to understand the selective pressures and proximate factors shaping the evolution of manipulative abilities in cancer cells, in order to successfully deal with their consequences. In addition to its direct impact on health, host manipulation by cancer cells can influence the rate of expansion of invasive cancers within and/or between hosts.

Targeting and dismantling the cancer supportive microenvironment

By improving our knowledge of the proximate factors involved, certain therapies could target the effect of manipulative cancer cells on healthy cells. Dismantling the network of supportive-manipulated cells could also be achieved by directly or indirectly (via bacteria or viruses) eliminating the "traitor" normal cells. Thus, therapy could target the information flow between cancer and manipulated cells, to either disrupt communication or induce signals that switch these cells (e.g. immune cells) back to the war against cancer [72]. This would have the double desirable effect of impairing cancer progression and forcing cancer cells into developing costly adaptations [73]: either by increasing the effort toward manipulation, or by selecting self-sufficient clones. If self-sufficiency could emerge for some functions, such as vasculogenic mimicry replacing or complementing angiogenesis [74, 75], for other (e.g. immune) functions cancer cells may be forced to manipulate host cells, and targeting these particular functions may serve to avoid recurrence. Further theoretical and experimental investigations are necessary to explore tumor responses, because we cannot presently reject the hypothesis that a given therapy could instead favor the selection of more aggressive clones and/or rapid metastasis (i.e. just as vaccination can select for virulence in pathogens [76]). Thus, identifying and targeting cancer cells primarily contributing to host manipulation, as well as non-neoplastic cells that are manipulated by, and collaborate with the tumor, could be crucial for treating malignant diseases.

Targeting manipulative mechanisms

Another promising research direction is to explore the proximate mechanisms used by parasites that manipulate their hosts in a similar way to cancer cells. For instance, like developing tumors, the nematode *Trichinella spiralis* (an intra-multicellular parasite) needs to recruit new blood vessels toward the developing nurse cells to meet its ever-growing demand for nutrients. Phylogenetically unrelated parasites often increase the chances of their transmission by inducing similar phenotypic changes in their hosts (e.g. [77]). Because these convergent strategies rely more or less on the same biochemical precursors, it could be expected that such convergence also exists with cancer cells. Thus, therapies that target manipulative activities in parasites could be equally effective against manipulation by cancer cells (see [78]).

Preventing invasive cancer initiation

Acknowledging that host manipulations by cancer cells exist is only the first step. The challenge will be to assess their influence on malignant progression, and to integrate them as a factor in the design of preventive strategies and/or cures. Developing tools for monitoring manipulative activities by cancer cells at all relevant scales should permit the identification of actual life periods when the risk of invasive cancer initiation is highest. We need to determine whether oncogenic progression, from precancerous lesions to metastasis, relies on a more or less constant/obligatory sequence of manipulative events, which could potentially be altered by adapted therapies.

Conclusions and outlook

Is it possible to ignore host manipulation in cancer processes? The answer is clearly no: most, if not all cancers, strictly rely on host manipulation for their development. Because of this strong dependence on host manipulation, exploring the extent to which manipulation by cancer cells occurs during carcinogenesis is a legitimate question, and curative strategies could clearly be developed from this knowledge. As a scientific

field, host manipulation has, until recently, been addressed in relative isolation from other scientific disciplines. This probably explains why, despite the extensive efforts of parasitologists to study manipulative strategies, few studies have so far established parallels with cancer cell strategies. Another reason is that host manipulation by parasites has been usually considered in the context of transmission strategies, but transmissible cancers appear to be rare. As demonstrated above, cancerous cells should be further investigated from the viewpoint of how they manipulate their immediate microenvironment, and also how they influence host behavior. It also seems that the main modes used by parasites to achieve manipulation may all apply to cancer cells (except possibly mafia-like strategies, which are rare in true host-parasite systems). Manipulations by cancer cells rely on the exaptation of pre-existing signaling pathways. By this way, they recruit healthy cells, which then engage additional healthy cells to perform tasks requested by tumor cells [31, 38, 40]. Given that host manipulations by cancer cells are likely to be subtle, we strongly encourage researchers to systematically explore the myriad symptoms displayed by cancer patients in order to discover those that could be host manipulations versus those that are host defensive responses to the manipulation and/or non-adaptive pathological consequences (i.e. by-product of being unhealthy). Additionally, due to the huge number of non-genetic variables involved in tumorigenesis, the question arises as to whether evolution of host manipulation by cancer cells should be considered within the framework of phenotypic plasticity rather than in a purely genetic framework. Further studies would also be required to explore if different types of cancer have different manipulative abilities (e.g. if colon/gut cancer influences/manipulates host diet more than for instance lung cancer). Finally, to understand the evolution of host manipulation by cancer cells, one must consider the complete ecological context in which tumors evolve, notably the community of organisms that inhabit the host and that may have shared or conflicting interests regarding its exploitation [79]. Only such an approach will permit a true assessment of the selective pressures acting on cancerous cells to manipulate the host. For instance, cancer is fueled by deregulation of signaling pathways in control of cellular growth and proliferation, but these pathways are also targeted by infectious pathogens (e.g. [80]). Although throughout our paper, we made the assumption that oncogenic selection should be strong enough to result in convergent evolution in manipulative strategies, little or no evidence has been found to support our theory. Therefore, we must also question whether each and every cancer is able to re-invent this particular wheel (i.e. manipulation) in more or less the same way in every patient time after time, based on the Darwinian principle of random variation. Alternatively, we cannot exclude that there is an underlying program that cancer cells are able to access but which is normally repressed. Numerous authors have, for example, noted the similarities between placentation, wound-healing, and embryogenesis, on the one hand, and cancer on the other [8, 9], and conversely suggested that cancer is a tissue-based disease and proposed an alternative theory of carcinogenesis, i.e. the tissue organization field theory (TOFT [8]). Clearly under the TOFT theory, cancer manipulative strategies would follow different evolutionary pathways. Because one single method or model cannot thoroughly describe host manipulation by cancer cells, researchers interested in these responses must engage in greater exchanges and collaborations with scientists from different disciplines.

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The hamster and clam images in Box 1, and panels A,B,D,G,H in Box 2 were updated on February 23, 2016. The respective image attributions in the text of Boxes 1 and 2 were also updated.

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