Cancer: a disease at the crossroads of trade-offs

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ABSTRACT

Central to evolutionary theory is the idea that living organisms face phenotypic and/or genetic trade-offs when allocating resources to competing life-history demands, such as growth, survival and reproduction. These trade-offs are increasingly considered to be crucial to further our understanding of cancer. First, evidence suggests that neoplastic cells, as any living entities subject to natural selection, are governed by trade-offs such as between survival and proliferation. Second, selection might also have shaped trade-offs at the

organismal level, especially regarding protective mechanisms against cancer. Cancer can also emerge as a consequence of additional trade-offs in organisms (e.g., eco-immunological trade-offs). Here, we review the wide range of trade-offs that occurs at different scales and their relevance for understanding cancer dynamics. We also discuss how acknowledging these phenomena, in the light of human evolutionary history, may suggest new guidelines for preventive and therapeutic strategies.

Introduction

Although medical and evolutionary sciences have traditionally developed in relative isolation (Williams and Nesse 1991), it is widely acknowledged that cancer is a process that is shaped by Darwinian evolution (Aktipis and Nesse 2013; Thomas et al. 2013a). Specifically, cancer is driven by both the somatic evolution of cell lineages that have escaped controls on replication, and the evolution of genes that influence cancer risk in populations (Aktipis and Nesse 2013; Thomas et al. 2013a). Therefore, applying evolutionary theories to cancer is relevant for understanding many aspects of this pathology, from its origin *per se,* to possible ways to control its progression, and how to prevent therapeutic failures (Aktipis and Nesse, 2013; Rozhok and DeGregori, 2015). Although these ideas first originated in the mid-seventies (*e.g.*, Cairns 1975; Nowell 1976), many promising opportunities for the application of evolutionary biology to carcinogenesis and oncology remain unexplored (Thomas et al. 2013a).

Central to evolutionary theory is the assumption that living organisms are, at some level, resource limited, and thus must face trade-offs among competing energy demands and life-history traits, such as development, survival and reproduction (Stearns 1992; Roff 1993). Life-history theory proposes that these trade-offs help to determine the evolution of phenotypes and could explain the diversity of life-history patterns found in biological populations (Hawkins 2004). This concept has lead to the idea that mammalian populations can be placed along a fast-slow continuum and has been confirmed by some empirical evidence (see Oli 2004 for review). Species selected to mature early, have high reproductive rates and short generation times and are considered to have a "fast" strategy, while species that have the opposite suite of traits are thought to represent the "slow" end of the continuum (Read and Harvey 1989; Promislow and Harvey 1990).

The main reason why trade-offs have played a prominent role in evolutionary thinking is their direct link with processes limiting the adaptive potential of organisms. Trade-offs lead to antagonistic relationships between phenotypic traits, and are thought to be determined both genetically and environmentally (Box 1). A large diversity of trade-offs have so far been identified, for example, the classical trade-offs between reproduction and survival, offspring number and quality, and current versus future reproduction (Stearns 1989; Agrawal et al. 2010); or in the context of host-pathogen interactions, between immune defenses versus reproduction or between resistance versus tolerance to pathogens (Sorci et al. 2008; Råberg et al. 2009).

Similar to other pathologies, the concept of trade-offs is increasingly being considered to be central in both fundamental and applied research on cancer (e.g., Aktipis et al. 2013; Roche and Thomas 2016). For instance, the emergence of malignant cell lines may be both cause and consequence of evolutionary trade-offs. In addition, most protective

mechanisms shaped by selection against cancer are costly and come with trade-offs (Hochberg et al. 2013), thus cancer can emerge as a consequence of trade-offs with life-history traits such as reproduction (Aktipis and Nesse 2013).

Here, we review how taking into account these trades-offs, from the perspective of the cancerous cells and from the perspective of the host, can help us to understand cancer dynamics. With such evolutionary approach, we suggest that it may be possible to identify aspects of anti-cancer adaptations that have been constrained by trade-offs and so may be effective targets for medical interventions.

I. **Life-history trade-offs at the malignant cell level**

Cells become malignant by acquiring genetic mutations that lead to increased survival and reproduction. However, cancer cells are not Darwinian demons able to maximize all fitness components simultaneously; instead recent evidence suggests that their functioning is constrained by a number of underlying trades-offs which are summarized in Figure 1.

A. Proliferation/survival

Because malignancies develop in environments that are expected to have limited resources (e.g. space and nutrients) (Alfarouk et al. 2013), a first trade-off in malignant cells may be between cell proliferation and survival. It has been predicted that, in a "rich" environment with high cell density, malignant cells will adopt a 'fast' life-history with rapid proliferation but low resistance to apoptosis, whereas in adverse environments cells will have a 'slow' life-history, with low proliferation but increased survival (Aktipis et al. 2013; Alfarouk et al. 2013). Cancer cells can indeed be categorized as proliferation-promoting or survival-promoting phenotypes, suggesting that they can display phenotypes "adapted" to

their environment (Aktipis et al. 2013). Selection for different life-history strategies in malignant cells could also fluctuate over time because tumorigenesis and/or therapies will generate distinct selective landscapes. Aktipis et al. (2013) hypothesized that these trade-offs may only happen in later stages of tumorigenesis, favoring extreme phenotypes such as rapidly proliferating cells with poor survival abilities or apparently dormant cells that can survive extremely well.

B. Dispersal and cell plasticity

Many animals disperse to reduce intraspecific competition (Fahrig 2007). Models in evolutionary ecology have also shown that organisms should move only when the costs of "staying at home" outweigh the potential costs of leaving the natal habitat (North et al. 2011). Cancer cells within organs face the same trade-off (Marusyk and Polyak 2010; Lee et al. 2011), and they can switch between migratory and proliferative phenotypes (e.g., squamous cell carcinoma; Biddle et al. 2011). A theoretical study has proposed that neoplastic cells, with deregulated metabolism, may be selected to have higher motility because their survival depends on their ability to move from a resource-restricted region to a new environment that can sustain their high metabolic needs (Aktipis et al. 2012). Moreover, numerous evidences suggested that when malignant cells are exposed to poor "environmental conditions" (hypoxia, toxins…) or when resources are spatially or temporally heterogeneous (oxygen, nutrients…), selection might favor metastatic cancer phenotypes (Anderson et al. 2006; Chen et al. 2011; Daoust et al. 2013; but see Arnal et al. 2016). In addition to these theoretical studies, it has been observed in a murine lung cancer model that toxicity mediated by the chemotherapy may induce metastasis (Daenen et al. 2011).

Cell plasticity is pervasive in cancer stem cells which can be proliferative or quiescent according to factors describing the tumor microenvironment, with the potential to influence cellular metabolism (DeBerardinis et al. 2008). Because phenotypic plasticity in organisms has been shown to be costly (DeWitt et al. 1998), exploring the costs for malignant cells of expressing conditional life-history strategies (e.g. cell plasticity) in different environments is also a promising direction for management of tumorigenesis (Aktipis et al. 2013).

C. Defenses against therapy and proliferation

As infectious agents do, cancer cells are able to develop adaptations to resist to therapeutic drugs. Most of them relay on pumps that expulse and reduce intracellular concentrations of cytotoxic drugs such as ATP-binding cassette (ABC) drug transporters commonly implied in multidrug resistance (MDR) (Fletcher et al. 2010). It has been observed that even if MDR lines (i.e., MCF-7/Dox) do not show constrained proliferation or survival in glucose-rich environment, they show a significantly decreased proliferation in glucose-limited conditions because of their higher ATP demands (Kam et al. 2011). Strategies taking advantage of the trade-off between proliferation and resistance have given raise to adaptive therapies. Such evolutionary approaches aim to combine the immediate cytotoxic effects of treatments with the ultimate goal of exploiting the adaptive responses of tumor cells (Gatenby et al. 2009a,b). For example, a theoretical approach has confirmed that selection of chemosensitive cells has the potential to destroy malignant cells through competition (Maley et al. 2004). Sensitive cells may be selected using a combination of cytotoxic drugs with drugs decreasing energy production which may accentuate the cost of resistance and suppress the proliferation of drug-resistant clones (Silva et al. 2012). Indeed, a new

treatment strategy, designed in murine breast cancer model, has allowed a continuous decline in tumor size even with long intervals between treatments through exploitation of the fitness cost of resistance (Enriquez-navas et al. 2016).

D. Defenses against multiple aggressors

Decades of research in applied ecology have illustrated that the evolution of defenses against one natural enemy affects the individual's ability to defend against other enemies, and/or to optimally express other fitness-related traits (Sheldon and Verhulst 1996; Moret and Schmid-hempel 2000). The presence of multiple enemies can modify the resistance against one specific enemy, with the direction of evolutionary change depending on enemy encounter rates, defense costs and mechanistic interactions among defense mechanisms (Poitrineau et al. 2003). Cancer cells, like organisms, have to face attack from many different biotic and abiotic aggressors, e.g. immune system, oncolytic viruses and therapies. It is now well recognized that cancer cells can evolve resistance mechanisms to both chemotherapy (Gottesman 2002) and immunotherapy (Restifo et al. 2016). As investment in one defense could influence the level of investment in another, it has been suggested that biological and chemical therapies could be coupled in a strategic multistep approach (De Pillis et al. 2006). In agreement with this view, evidence shows that tumor cells able to successfully adapt to an immune attack are more sensitive to the cytotoxic effects of chemotherapy (Antonia et al. 2006).

II.   Life-history trade-offs at the organism level

A. Host protective mechanisms

Regarding fitness-reducing diseases, evolutionary theory postulates that organisms should be under selective pressures to (a) avoid the source of the pathology in the first instance, (b) then prevent its progression once sick, and (c) finally alleviate the fitness costs if further development is unavoidable (Thomas et al. 2009). This conceptual framework applies also to cancer and relies on trade-offs (Ujvari et al. 2016).

Cancer prevention

Environmental factors favoring cancer emergence and/or progression are potentially numerous, their origins being both anthropogenic (e.g., radioactivity; Møller and Mousseau 2015) and natural (e.g., natural radiation levels, oncogenic pathogens, transmissible cancers and secondary compounds of plants) (Ducasse et al. 2015). In this context, it is predicted that traits allowing individuals to reduce the frequency or the duration of exposure to those factors could be favored by selection as they decrease cancer risk, but will likely also entail costs (Vittecoq et al. 2015). Being choosy to avoid cancer risks (with respect to habitat, food or partners with a contagious cancer) may entail a cost that is higher when competition is more intense. In addition, adopting a lifestyle reducing exposure to mutagenic factors may result in a small selective advantage if most cancers are due to intrinsic factors (Tomasetti and Vogelstein 2014,Thomas et al. 2016b). Thus, considering that the probability of developing an aggressive cancer before or during the reproductive period is low (Ujvari et al. 2016), and that the perception of cancer risk may be unreliable, the benefit of prevention may be offset by its cost.

Even when a given trait (e.g. behavior) strongly contributes to protect an individual from a fitness-impacting cancer, it may not necessarily increase in frequency in the population. Indeed, when a trait is both essential to the host's survival and reproduction, but also enhances cancer risks, it will be subject to an evolutionary trade-off. Natural selection will most likely favor individuals whose trait expression ensures the optimal compromise between satisfying a need (e.g. reproduction) and minimizing the risk of detrimental consequences on health (Vittecoq et al. 2015). For instance, in the case of Tasmanian Devil (*Sarcophilus harrisii*) and their contagious cancer (Murchison 2009; Pye et al. 2016), natural selection cannot strongly favor individuals avoiding conspecifics, because at the same time sexual selection favors individuals displaying aggressive biting behavior that increases mating and breeding success (Ujvari et al. 2016).

Thus, despite the abundance of ecological contexts that are associated with cancer risks, there are only a few demonstrated examples of behavioral adjustments in wildlife species related to cancer prevention (e.g., antioxidant consumption; Senar et al. 2010). Acknowledging that most, if not all, ecosystems on our planet are now polluted by mutagenic substances to a greater extent than ever before (Ducasse et al. 2015), it is predicted that natural selection will favor cancer prevention to avoid fitness loss. Thus, for numerous species the benefits of behavioral adjustments will surpass their costs and examples of prevention could substantially increase in the future.

Cancer suppression

Cancer appeared at the dawn of multicellularity (i.e. more than half a billion years ago (Merlo et al. 2006; Nunney 2013)), and a major aspect of this transition from unicellular ancestors has been the suppression of cell-level fitness in order to promote organism level fitness (Maynard-Smith and Szathmary 1997; Michod 2000). Effective multicellularity, therefore, required both cell cooperation and mechanisms for eliminating conflicts arising from mutations that can enhance cell-level fitness at the expense of the individual organism (Michod and Roze 2001; Aktipis et al. 2015). This situation resulted in selective pressures favoring the evolution of many cancer suppression mechanisms, from cell-intrinsic checks that prevent cellular proliferation and invasion of other tissues and organs, to integral controls that suppress cancer by operating at the level of tissue organization. These mechanisms include, but are not limited to, apoptosis, effective DNA repair, epigenetic modifications, cell cycle checkpoints, telomere shortening, tissue architecture, and immune surveillance (DeGregori 2011).

As evolution shaped larger and longer lived multicellular organisms, the problem of cancer suppression became even more challenging (Peto et al. 1975; Nunney 2013). To counteract the increased risk of developing a cancer, large and long-lived species may have optimized their tumor suppression mechanisms and adopted lower somatic mutation rates, redundancy of tumor suppressor genes etc (Caulin and Maley 2011; Abegglen et al. 2015). However solutions for suppressing cancer are not perfect, even if they are remarkably effective. For example, tumor suppressor genes and their resulting products sometimes fail to repair double strand DNA breaks without introducing errors (Khanna and Jackson 2001). Multicellular organisms could theoretically have better mechanisms to suppress cancer, but

the costs of such mechanisms might exceed the benefits when individuals reach a post-reproductive age (Hochberg et al. 2013). Thus, natural selection has mainly favored the evolution of anti-cancer adaptations that act before or during reproductive age (Crespi and Summers 2005; DeGregori 2011). Another way to manage the cost of cancer suppression mechanisms could be to select protective "low-cost" mechanisms that do not involve complete tumor elimination. For instance, auto-immunity is costly for organisms and immune tolerance occurs in response both to infections (Read et al. 2008) and cancer (Mapara and Sykes 2004). Even if it precludes the development of an adequate antitumor response, tolerance might be a better strategy than a costly over-activation of the immune system. Interestingly, strategies for breaking this tolerance have been studied as therapeutic approaches and led to promising results (Makkouk and Weiner 2015). For instance, the use of immune checkpoint blockades, that abrogate negative signals diminishing T-cell activation during the priming process, has been approved for the treatment of advanced melanoma (Ipilimumab) (Page et al. 2012).

A recent study argues that adopting a more organ centered approach is desirable for a full understanding of organ-specific trade-offs associated with cancer suppression mechanisms (Thomas et al. 2016b). Organs are the products of adaptation to natural and sexual selection (Nesse and Williams 1996). The importance and/role of various organs in keeping the organism functional and ultimately to maximize fitness vary substantially. For instance, organs like heart, brain or pancreas are absolutely essential for survival, while others like gall-bladder, are disposable. Organ-specific trade-offs have already been suggested in association with the energy allocated to their development. As some organs are considered to be metabolically expensive such as brain, gut and sexual organs, the expensive-tissue hypothesis suggests that the allocation of energy to develop large brains results in a

relatively smaller gut (Aiello et al. 1995). Other studies have proposed an expensive sexual tissue hypothesis that relies on negative relationship between investment in testes and investment in brain (Pitnick et al. 2006). In the context of cancer suppression, organ protection may not be maximal but rather suboptimal and unequal due to trade-offs with the other organs and mechanisms preventing malignant transformation *per se* should be more prominent in vital organs in order to preserve their functionality (Thomas et al. 2016a).

Finally, suppression of neoplastic growths may lead to trade-offs in other essential functions that require cell proliferation (Aktipis and Nesse 2013b). First, the capacity to repair tissues while limiting uncontrolled cell division represents a key trade-off for any multicellular organism (Aktipis and Nesse 2013b). Second, cell capacities during embryogenesis and development (e.g. 'invasion' of cells into other developing tissues during gastrulation), which are essential for reproducing organisms, confer a risk for developing cancer (Ben-David and Benvenisty 2011). Finally, the p53 protein, with a well-known cancer-suppressive function, leads to reduced tissue renewal and repair, stem cell deletion, and organismal aging through an antagonistic pleiotropy effect (Campisi 2002, 2003; García-Cao et al. 2002). For instance, mice carrying a *p53* mutation (with a phenotypic effect analogous to the up-regulation of the gene) have a lower risk of cancer development but their lifespan is reduced and accompanied by early tissue atrophy (Donehower 2002; Tyner et al. 2002). However, a recent study contradicts this observation in mice and has demonstrated that elephants, that are long lived mammals, have a high number of extra p53 copies (Abegglen et al. 2015). Thus, studying how elephants have overstepped the trade-off that governs cancer suppression by p53 is of crucial interest to design therapies that reduce the cost of natural mechanisms and thus indirectly improve cancer suppression.

Alleviating the fitness consequences of cancer

There are several examples in the parasitological literature illustrating that hosts, unable to resist infection by other means (e.g. immunological resistance, inducible defenses or long-distance migration), present adaptive and flexible life-history traits that partly compensate parasite-induced fitness reduction (e.g., by reproducing earlier; Forbes, 1993; Hochberg et al. 1992; Michalakis and Hochberg 1994). Although further evidence would be welcome, similar life-history trait adjustments may also exist in hosts harboring tumors (Ujvari et al. 2016). From an epidemiological point of view, such responses could contribute to influence cancer risks through the evolution of differential cancer vulnerabilities. For instance, BRCA1 and BRCA2 mutations are inherited and predispose women to breast and ovarian cancer, but even though carriers of these mutations have reduced survival, they also have enhanced fertility (Easton et al. 1995; Smith et al. 2012). Similarly, the shorter CAG repeat region within the androgen receptor gene increases an individual's risk of developing prostate cancer, but it also increases fertility earlier in life (Summers and Crespi 2008). These findings may indicate an adaptive response to compensate the risk of fitness loss due to cancer predisposition. Such adaptive response is of considerable significance as it may allow the persistence of mutations with deleterious effects across generations (Vittecoq et al. 2015). Thus, we suggest that the existence of life-history trait adjustments could influence the persistence of oncogenic mutations over evolutionary time (Ujvari et al. 2016).

B. Costs of reproduction

Evolution produces biological entities that tend to increase reproductive success, sometimes at the cost of health and longevity. In fact, the presence of early-late life trade-offs has been supported and suggests that individuals have to trade somatic maintenance later in life for

high allocation to reproduction early in life because of resource-limited environments (Lemaitre et al. 2015). Costs of reproduction are therefore fundamental to understand diseases, including cancer. Mechanisms underlying the cost of reproduction are numerous from hormonal regulation to reduced immune functioning and lower defenses against stress and toxicity (Harshman and Zera 2007). This suggests that selection for increased reproduction could also result in increased cancer susceptibility.

Sexual competition

There is little evidence on the effect of intrasexual selection (e.g. male-male agonistic interactions) on cancer risk. In the case of a very specific type of cancer, the transmissible Tasmanian Devil Tumor Disease, it has been reported that Tasmanian devils have higher risk of contracting cancer when they compete with other males for mates (Pearse and Swift 2006; Hamede et al. 2009).

In the context of intersexual selection, secondary sexual traits (e.g., impressive ornaments) may also select for mechanisms that enable rapid cell proliferation that could, in turn, enhance tumor formation as suggested by a theoretical study (Boddy et al. 2015). In addition, enhanced allocation of energy to secondary sexual traits rather than to mechanisms of somatic maintenance (DNA repair or immune defenses) could also elevate cancer risk by increasing accumulation of somatic mutations (Boddy et al. 2015). Knowing that success in mating competition has greater reproductive payoffs for males than for females, investment in competitive abilities at the expense of cancer risks should be particularly prominent in males. Antagonistic pleiotropy might also favor the persistence of mutations that confer a reproductive benefit to the carrier even if they increase the cancer risk of an individual. For example, in *Xiphophorus* fish, melanoma-promoting oncogene

alleles are associated with larger body size and aggressiveness and confer early life advantages in male-male competition and female mate choice (Fernandez et al. 2008, 2010). One important limitation to studying the link between sexual competition and cancer risk is methodological constraints. Generally, investigations in organisms in the in wild do not test living individuals for the presence of tumors and the assessment of the cause of death is often impossible. Development of non-invasive methods to detect cancer as well as population monitoring is crucial to progress our understanding of the impact of trade-offs between reproduction and cancer risk.

Sexual hormones

Estrogens are the principal hormones that regulate the female reproductive cycle and have been associated particularly with receptive behaviors (Lynch et al. 2005). Thus, females producing high levels of estrogens could be selected in a context of intra-sexual competition. Recent studies have highlighted the strong interactions between estrogens and immune system activation (see Khan and Ansar Ahmed 2016 for review). High levels of estrogens during pregnancies could increase cancer cell elimination and could explain the negative correlation between parity and risk for several cancers (Wu et al. 2015; Chen et al. 2016). Nevertheless, evidence suggests that circulating estrogens are associated with increased postmenopausal breast cancer risk (Key et al. 2002), suggesting antagonist pleiotropy even if mechanisms are not well identified. Finally, modification of modern reproductive patterns has been associated with an increase in estrogen positive receptor (ER+) breast cancer suggesting that women experience the cost of a modernity mismatch (Aktipis et al. 2014).

For males, testosterone has been reported to have an immunomodulatory role by reducing cytokine responses to infection (Trumble et al. 2016). Regarding cancer development,

Alvarado (2013) provided evidence that in human subpopulations where competition is intense (e.g. polygamous societies), males have higher testosterone levels and increased mating success, but at the cost of increased rates of prostate cancer. However, recent studies do not report significant association between testosterone concentrations and prostate cancer (Roddam et al. 2008). Nevertheless, considering hormones involved in reproductive behaviors could be of interest in social species with hierarchical dominance. In fact, subordinate individuals show a high level of stress associated with low levels of circulating testosterone, but also with a suppressed immune system through production of glucocorticoids (Sapolsky 2016). Social species, with differential cancer risk between dominant and subordinate individuals, could be a relevant biological model to study interactions between sexual hormones, immune system and cancer development.

C. Eco-immunological trade-offs

Infectious disease burdens

Throughout evolutionary history, humans have been exposed to a large number of diverse infectious agents (Wolfe et al. 2007). In wealthy countries, the decreased prevalence of infectious diseases, in particular of those caused by helminths, has been paralleled by an increased incidence of cancers (Zacharia et al. 2003). The helper T lymphocytes may have a central role for understanding the link between infections and cancer dynamics. In fact, several studies have shown that Th1 response is protective against several cancers (Haabeth et al. 2011; Ingels et al. 2014) and intracellular pathogens. In contrast, Th2 activation is linked to negative prognosis in some cancers (Lippitz 2013) and it confers protection against macroparasites. A trade-off may exist because the cytokines that instruct immune cells to differentiate into the Th1 pathway tend to inhibit Th2 effectors (Kidd 2003). As selection

may have favored one specific pathway at the expense of the other in our ancestral environment, the rapid and radical change of our infectious environment may create a mismatch with consequences for cancer risk (Oikonomopoulou et al. 2013). One example of such a genetic trade-off comes from the relative vulnerability of African Americans to malignant diseases compared with Caucasian Americans (Walker et al. 1995). Relocation of Africans from tropical countries, where inflammation following Th2 activation was beneficial, to North America, and the consequent decrease in infection risk, may have exposed them to a higher risk of cancer (O'Byrne and Dalgleish 2000). The use of immunoregulatory helminth-products has been suggested to reduce inappropriate pro-inflammatory responses and thereby cancer risk (Finlay et al. 2014).

Sleep

Another trade-off may exist between developing a powerful immunological memory to eradicate cancer by sleeping longer and short term survival by prospecting for food and limiting predation risk. In fact, by avoiding long periods of sleep, species reduce their risk of being predated (Lima et al. 2005). Humans are not an exception and it has been proposed that human sleep has been selected to be deeper but significantly shorter than for other primate species (Samson and Nunn 2015). However, it has been shown that sleep has a specific role in the formation of immunological memory (Besedovsky et al. 2012). A link between cancer risk and sleep has been identified in a cohort of women with breast cancer, where it has been reported that women who routinely sleep few hours may develop more aggressive breast cancers compared with women who sleep long hours (Thompson and Li 2013).

Growth

At the species level, immunity could trade-off against growth. Species with a long embryonic period have been hypothesized to invest more energy to develop an immune system that is able to resist to infections (Ricklefs 1992). Thus, because species with higher growth rates will be those with higher rates of cell division and weaker immune systems, they should also be those with higher incidence of tumors (van der Most et al. 2011).

Concluding remarks and perspectives

There are some compelling indications that cancer dynamics may rely on and perhaps originate from numerous trade-offs at the malignant cell and the organismal level (i.e., ontogenetic, physiological and anatomical scales summarized in Figure 2). Acknowledging it not only permits us to highlight fundamental processes governing cancer, but also allows us identifying tools that could be useful in the development of new therapeutics.

At the cellular level, future studies taking an evolutionary-ecological perspective into account are needed to uncover novel adaptations of malignant cells and elucidate the trade-offs under which they have evolved. Such knowledge could lead to therapies that favor cancer cells with slow life-history strategies (high survival, low dispersal and slow development), thereby allowing for long-term cancer control (Aktipis et al. 2013). Emerging disciplines such as evolutionary cell biology (Lynch et al. 2014) are promising for understanding the diversity of trade-offs governing the functioning of malignant cells, their consequences for tumor evolution and their implications for novel therapies. For example, certain malignant cells may behave as social parasitic clones within the tumor benefiting from the metabolic investment made by their neighbors (e.g., stimulating neo-angiogenesis and the release of growth factors) without experiencing costs themselves (Merlo et al.

2006). Interestingly, it has been proposed that these "cheaters" may create a hypertumor, which could in return damage or destroy the original neoplasm (Nagy et al. 2007). However, the existence of trade-offs at the cell level (and hence their potential use for therapies) implicitly suggests that resources are limited. At the moment, the extent to which this is the case must be clarified since, for instance, malignant cells could manipulate their host to obtain higher level of resources (Tissot et al. 2016).

By harnessing modern technology as a supplement to natural anticancer adaptations acquired through natural selection, medical intervention could modify trade-offs providing opportunities for prevention, detection and treatment that have not previously been available to humans (Table 1). For example, we already employ novel agents like non-steroidal anti-inflammatory drugs to prevent malignant cancer cell growth (Rothwell et al. 2012), acting through the reduction of an inflammatory response that is non-optimal in a modern environment. In addition, identification of trade-offs involving behavioral habits can lead to prevention, such as condom use (to prevent transmission of cancer causing viruses) and increased sleeping time, which can reduce cancer risk. In a cancer elimination context, engaging the immune system into the systematic elimination of precancerous lesions via prophylactic cancer vaccination is a promising research direction (e.g. Yaddanapudi et al. 2012). However, this intervention technique becomes detrimental to individual health if it results in overly frequent (if not constant) activation of the immune system. Intervening with the body's own tumor-suppressor mechanisms could unbalance system homeostasis and result in unintended consequences such as collateral tissue damage, autoimmune complications and non-specific side effects. Therefore, it is important to notice that modern technologies could also results in costs like over-diagnosis and overtreatment.

Modern humans live longer than our ancestors because of benign and infrequent exposure to infectious diseases, predation and violence. This situation results in increased cancer incidence because the largest risk factor for most cancers is simply aging (Frank 2007). By considering differences between what natural selection acts on (reproductive fitness) and our current goals in the modern world (improving health and well-being), it may be possible to identify aspects of anti-cancer adaptations that have been constrained by trade-offs and so may be effective targets for intervention. In fact, as evolution has not apparently strongly selected for late-life cancer prevention (Frank 2007), this may represent an opportunity to 'do better' than evolution's current prescription. For instance, ontogeny requires that cells have the capacity to move and proliferate, capacities which may be 'reactivated' in cancer. After development is completed, it may be possible to constrain somatic cell phenotypes so that they are less likely to call upon developmental programs reducing risk of cancer development.

To conclude, we emphasize the benefits of playing by the evolutionary rules that regulate the risk of cancer, rather than adopting treatment of symptoms. This work calls for a more integrated approach to cancer research that will consider evolutionary trade-offs. In particular, treatment strategies that will shift these trades-offs away from cancer and favor the host may be a promising way to discover new methods of prevention and treatment.

Box 1: Levels of analysis

Trade-offs exist at different levels, namely phenotypic, genotypic, and in intermediate structures, which lies between the other two (Stearns 1989). The phenotypic level concerns whole-organism studies of traits directly connected with ontogeny, reproduction and survival. For instance organisms acquire limited resources and then differentially allocate them to competing functions like growth, survival and reproduction. The genotypic level refers to all types of evidence claimed to be genetic (using quantitative, Mendelian or molecular genetics approaches). This evolutionary level reflects the constraints (negative genetic correlations) operating on multiple traits that are linked in ways that prevent simultaneous optimization of all of them. By intermediate structure, we imply all mechanisms connecting the genotypic to the phenotypic levels, including physiological and developmental mechanisms under endocrinological control that result in the allocation of resources among the functions of maintenance, growth, storage, reproduction and survival (Stearns 1989). Finally, two kinds of trade-offs are recognized, those for which opposing selection across different environments result in a polymorphic trait and trade-offs which are the consequences of competition for shared limiting resources and that act on multiple traits (Agrawal et al. 2010).

Figure 1: Tumor dynamics rely on numerous trade-offs at the malignant cell level.
Neoplastic cells have to face numerous trade-offs to increase their fitness in the host.

Figure 2: Cancer susceptibility rely on numerous trade-offs at the individual level. Most of the protective mechanisms of the host are retained by selection against cancer and rely on underlying trade-offs. Host susceptibility to cancer can also emerge as a consequence of other trade-offs in organisms.

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Level	Trade-offs	Potential interventions suggested by trade-off framework	Theoretical references	Experimental references	Clinical references
Cellular	Proliferation / Survival	Resource limitation and normalizing therapy to favor survival	(Aktipis et al. 2013)	(Gatenby et al. 2009)	
	Dispersal / Proliferation	Blockage of Epithelial Mesenchymal transition (EMT)	(Anderson et al. 2006; Daoust et al. 2013)	(Aref et al. 2013) (Davis et al. 2014)	
	Resistance / Proliferation	Adaptive therapy	(Maley et al. 2004)	(Enriquez-navas et al. 2016)	
	Defenses against multiple aggressors	Combination of biological and chemical therapies	(De Pillis et al. 2006)	(Machiels et al. 2001; Wheeler et al. 2004)	(Huncharek et al. 2001)
	Cooperation / Egoism	Use hyper-tumor to destroy original neoplasm	(Nagy et al. 2007; Marusyk et al. 2014)	(Archetti et al. 2015)	
Individual	Reproduction / Cancer	Condom use, vaccines against oncogenic pathogens			(Söderlund-Strand et al. 2014)
		Preventive removal of the organ (e.g., Mastectomies for women BRCA1/2)			(Meijers-Heijboer et al. 2001)
		Hormonal treatments (e.g., post-menopausal women and breast cancer)	(Boddy et al. 2015)		(Goss et al. 2011)
	Immune tolerance / Auto-immunity	Immunotherapy (e.g., immune checkpoint inhibitors)		(Beatty et al. 2011)	(Page et al. 2012)
	Responses to infection / Cancer	Use of helminths regulatory products	(Harnett and Harnett 2010)	(León-Cabrera et al. 2014)	
		Anti-inflammatory drugs	(Oikonomopoulou et al. 2013)	(Valle et al. 2013)	(Rothwell et al. 2012)
	Sleep / Predation	[Speculative] Favor longer sleep (sleeping pills)			

Table 1: Different scales of trade-offs and their potential applications in public health: evidences from theoretical, experimental and clinical studies.

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