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Abstract

1. Evidence for actuarial senescence (i.e. the decrease in survival with increasing age) are now widespread across the tree of life. However, demographic senescence patterns are highly variable both between and within species. To understand these variations, there is an urgent need to go beyond aggregated mortality rates and to investigate how age-specific causes of mortality in animals interact with age-specific physiological performance. We address this question in the context of cancers.
2. Cancer is a leading cause of death in human populations and has recently been shown to be more prevalent across species than previously thought. Since anthropogenic perturbations drastically increase cancer rates in wild populations of animals, deciphering the complex interactions between senescence and cancer now constitute a key challenge in evolutionary ecology.
3. Based on classical evolutionary theories of aging, we first demonstrate that the occurrence of cancers might constitute an underestimated piece of the life-history jigsaw. We propose that the selection for an increased allocation of resources towards growth and reproduction during early-life might potentially favor cancer development, a life-history pathway that might be functionally mediated by the process of immunosenescence. While we discuss the relevance of other proximate mechanisms suggesting that cancer arises as a direct consequence of senescence, we also argue that cancer itself can promote senescence by notably increasing the amount of resources required for somatic maintenance.
4. Contrary to theoretical predictions, recent empirical evidence suggests that senescence is an asynchronous process among physiological functions. At the same time, the timing of occurrence varies widely between the different types of cancers. We suggest that similar evolutionary forces might shape the synchronicity of senescence and cancer patterns, which emphasize the tight and complex relationships linking these processes.
5. We propose a conceptual background to lay down the foundations and the directions of future research projects aiming to disentangle the dynamic relationship between the evolution of cancer and senescence. We argue that studies embracing these research directions will markedly improve our understanding of both cancer prevalence and timing at the individual, population and species level.

1. THE PROBLEMATICS OF SENESCENCE AND CANCER

The last decades have seen a burst in the number of studies providing evidence for a decrease in survival and reproductive success with increasing age (processes coined actuarial and reproductive senescence, respectively) in both wild and captive populations of animals (Jones et al., 2014; Nussey, Froy, Lemaître, Gaillard, & Austad, 2013). Such declines in age-specific life history traits are supposed to be underlined by a progressive deterioration of organism along the life course (henceforth coined 'senescence'), generally described in free-ranging populations through a loss of body mass (e.g. Douhard, Gaillard, Pellerin, Jacob, & Lemaître, 2017) or physiological performance (e.g. immune performance, Ujvari & Madsen, 2011). While the demographic senescence process appears pervasive across species, the complex interplay between the deterioration of physiological functions and body condition and the concomitant increase in susceptibility to diseases culminating in death, is yet to be deciphered. The 'emperor of all maladies', cancer, illustrates this complexity.

Cancer is a leading cause of death worldwide in humans (Bray et al., 2018) and, albeit the extensive investment into molecular and cellular research focusing on the mechanisms of carcinogenesis, whether senescence and cancer development share similar evolutionary pathways remains to be determined (De Magalhães, 2013). Currently, the lack of congruence between mechanistic and eco-evolutionary models linking age-specific deterioration of physiological functions and cancer hinders our understanding of the role of cancer in actuarial and reproductive senescence. In addition, the limited information available on cancer incidence in relation to age in wild populations (Albuquerque, Drummond do Val, Doherty, & de Magalhães, 2018; Madsen et al., 2017) hinders any empirical assessment of the functional relationship linking demographic senescence and carcinogenesis. While cancer is ubiquitous in multicellular organisms (Aktipis et al., 2015), we are not yet able to predict a species'

cancer prevalence with respect to its phylogenetic history, ecology, physiology, lifestyle and biodemographic strategy (Thomas, Kareva, et al., 2018). In fact, based on limited data, cancer prevalence and age-specific incidence appear not to lie in any of the known ecological continua structuring the diversity of life-history strategies (e.g. slow-fast continuum, Gaillard et al., 2016), nor fitting the dominant mechanistic molecular and cellular model of carcinogenesis (see Box 1).

Cancer originates from the (epi)genetic alterations of a given cell. The dominant theory (also referred to as the 'Doll-Armitage multistage model', Armitage & Doll, 1954) is that carcinogenesis is a multistage process of accumulation of (epi)mutations in a mitotic cell lineage that liberates a cell from homeostatic mechanisms of cell division; often due to inhibited attrition of telomeres. Although it has recently been argued that lifetime risk of cancer correlates with the total number of cell divisions in a given tissue (Tomasetti, Li, & Vogelstein, 2017; Tomasetti & Vogelstein, 2015), the kinetics of damage accumulation with age and its consequences on the age-specific patterns of cancer prevalence and incidence remain largely unknown (Rozhok & DeGregori, 2015). Furthermore, these proximate factors of carcinogenesis (i.e. (epi)genetic instability and telomere attrition) also belong to the 'primary hallmarks' of aging by being involved in the progressive deterioration of various biological functions (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). Variations in cancer prevalence between and within species should thus be mainly determined by differential somatic mutation rate and repair efficiency. As the immediate results of the proximal deteriorations occurring with age, both processes of carcinogenesis and senescence should be tightly linked. However, understanding the causality of the relationship linking cancer and senescence (at cellular, individual and population levels) and deciphering their complexity through the lenses of evolutionary biology is particularly arduous (Hofman et al., 2019). In that context, several hypotheses have recently emerged. The aim of this article is

thus to provide a critical reappraisal of these new hypotheses and to identify salient research directions that evolutionary ecologists should embrace.

Once a cancer cell is generated (even by a multistage process), cancer cell proliferation is then mediated by both the immune response and the competition between cancer and normal cell lineages. It has thus been recently argued that cancer incidence and prevalence are mostly shaped by defense mechanisms preventing tumor cells to transform into invasive cancer (Harris, Schiffman, & Boddy, 2017). Immunosenescence (i.e. the decline in immune function with increasing age) can therefore lead to increased cancer incidence due to decreasing efficiency in cancer cells' predation and increased inflammation with age. In addition, the senescence process might induce a change in the cells' adaptive landscape making healthy cells less competitive compared to cancer cells (Liggett & DeGregori, 2017). If true, mortality and cancer incidence should exhibit a similar pattern with age. However, while the current prevailing paradigm posits that all physiological functions should senesce at the same pace (Maynard Smith, 1962; Williams, 1957), recent studies have demonstrated that this may not be true (Gaillard & Lemaître, 2017), which could potentially explain differences in the shape of cancer incidence and age-specific mortality by other causes. To evaluate these different hypotheses, it is mandatory to first determine whether individual-based mechanistic theory of carcinogenesis can be embedded within a population-based evolutionary theory of senescence.

2. DOES CANCER MEDIATE THE REPRODUCTION – SENESCENCE TRADE-OFF?

The predominant hypothesis related to the evolution of senescence is based on an evolutionary trade-off between reproduction and subsequent mortality. This trade-off takes its origin in the '*antagonistic pleiotropy theory'* of aging (Williams, 1957). Based on the

assumption that the force of natural selection against fitness impairing genes decreases with age (Hamilton, 1966; Medawar, 1952), George C. Williams proposed that allele(s) can be selected by natural selection trough a positive effect on reproductive success during early life even if such allele(s) is responsible for increased senescence in late life. While detecting such alleles is challenging, experimental manipulations in laboratory models and quantitative genetic approaches performed on wild populations of animals have provided support to this theory (see Gaillard & Lemaître, 2017 for a review). The key role of reproductive allocation in shaping reproductive and actuarial senescence patterns was then emphasized in the '*disposable soma theory*' of aging (see Kirkwood, 2017 for a comprehensive review), a theory originally focusing on the maintenance of molecular and cellular integrity (Kirkwood, 1977). In its current form, the disposable soma theory adopts assumptions and predictions that are common with life history theory as they both give a pivotal role to the principle of allocation (Cody, 1966), namely that individuals need to share a finite pool of resources extracted from the environment between different functions like growth, reproduction and survival (Kirkwood & Rose, 1991; Stearns, 1992). However, the disposable soma theory explicitly involves the concept of '*somatic maintenance*' (Holliday, 1995) based on evidence that organisms have evolved dedicated but costly mechanisms (e.g. enzymatic complexes) that insure the fidelity of DNA replication and repair, as well as the accuracy of protein synthesis (Gladyshev, 2016). Therefore, resources devoted to growth and reproduction cannot be simultaneously used for somatic maintenance, which might compromise cellular integrity and, on the long-run, be responsible for a premature and/or accelerated reproductive and actuarial senescence (Kirkwood, 2017; Kirkwood & Rose, 1991).

Both the antagonistic pleiotropy and the disposable soma theories of aging (Kirkwood & Rose, 1991; Williams, 1957) jointly predict a negative relationship between reproductive effort in early-life and fitness-related traits in late-life. This prediction has been so far broadly

validated through the use of genetic and phenotypic data and across a wide range of organisms (Lemaître et al., 2015). As the occurrence of cancers impairs survival prospects, whether the development of tumor can be embedded in such early- vs late-life trade-off deserves some attention (Jacqueline et al., 2017). While this question remains largely open, it could potentially shed new lights on the genetic and physiological pathways linking reproductive allocation and age-specific survival probabilities in the elderly.

At the genetic level, a few alleles involved in carcinogenesis but conferring advantages in terms of reproductive success have been identified (i.e. Inherited Cancer Mutant Alleles, see Arnal et al., 2016 for a review). Among them, the *Xmrk* melanoma-promoting oncogene found in fish from the genus *Xiphophorus* constitutes an iconic example. In *Xiphophorus cortezi*, the presence of melanoma on the male caudal fin exacerbates the spotted caudal melanin pattern, which ultimately increases female preference during mate choice experiments, even if it shortens the duration of reproductive lifespan (Fernandez & Morris, 2008). Although this example suggests that cancer might mediate the genetic trade-off between reproduction and survival predicted by the antagonistic pleiotropy of aging, it is important to notice that such clear-cut examples remain rare, sometimes equivocal, and mostly limited to human and laboratory models (e.g. *BRCA1/2* mutations, see Smith, Hanson, Mineau, & Buys, 2012).

In non-model organisms, fine-scale genetic data are generally unavailable and most supports for early- vs late-life trade-offs rely on covariation patterns between life-history traits depicting reproductive effort and lifespan and/or senescence measurements (Lemaître et al., 2015). Interestingly, reproductive effort has also been associated with the risk of developing cancer in wild populations of animals (Jacqueline et al., 2017). For instance, in Tasmanian devils (*Sarcophilus harrisii*), female fecundity rates were positively associated with the risk of contracting facial tumors (the Tasmanian devil facial tumor disease, DFTD, one of the very

rare example of transmissible cancer) during their lifetime (Wells et al., 2017), and males that are the most aggressive during intersexual competition suffer from a stronger risk of contracting the disease through bites (Hamede, McCallum, & Jones, 2013; Figure 1). Currently, it is unclear whether a resource allocation trade-off *per se* mitigates the relationship between reproductive expenditure and cancer occurrence observed in Tasmanian devils. Indeed, under a 'disposable soma' framework, individuals that direct resources towards growth and reproduction might compromise the allocation of resources to costly DNA repair mechanisms (e.g. Vilchez, Saez, & Dillin, 2014), which can increase DNA damages and ultimately open the door for the development of cancer (Freitas & de Magalhães, 2011, Figure 1). Although the relative importance of facial tumor occurrence in terms of actuarial and reproductive senescence (e.g. Russell et al., 2018) have not yet been quantified, the stronger decline in body condition in affected male Tasmanian devils compared to affected females suggests that this cancer influences sex differences in lifespan and actuarial senescence patterns (Ruiz-Aravena et al., 2018).

A higher risk of carcinogenesis when the level of intraspecific competition is high has been theoretically investigated by Boddy and colleagues (2015) in a model where competitiveness is a declining function of allocation into cancer defenses. This model predicts that cancer should be more prevalent in males than in females (as observed in humans, see Clocchiatti, Cora, Zhang, & Dotto, 2016). As the increased cell proliferation associated with the rapid growth of body size or secondary sexual traits can also increase cancer susceptibility (De Magalhães, 2013), males who grow faster and also develop and maintain conspicuous sexual traits might be at higher risk of cancers, especially malignancies of the reproductive system (e.g. testes cancer, antleromas). This also suggests that, in such species, cancer might potentially trigger male reproductive senescence rather than actuarial senescence, and potentially contributes to the observed uncoupling between these two processes (Gaillard &

Lemaître, 2017). Taken together, these predictions from theoretical approaches combined with evidence that both reproductive allocation and cancer defense mechanisms are energetically costly, strongly highlight that the development of some cancers might be seen as a long-term reproductive cost (Boddy, Kokko, Breden, Wilkinson, & Aktipis, 2015). The picture might be even more complex, at least in females, where an absence or a very low rate of reproduction might itself increase the risk of developing cancers of the reproductive system (Pesavento, Agnew, Keel, & Woolard, 2018). Basically, females that do not reproduce will experience a higher number of oestrous cycles and thus a greater exposure to oestrogen, which can ultimately lead to higher risk of cancers, as observed in humans (Britt & Short, 2012) and captive mammals (Pesavento et al., 2018).

Although the fine-scale quantifications of cancer prevalence in the wild remains challenging (Madsen et al., 2017), theoretical predictions and the availability of long-term physiological and demographic data on free-ranging populations now provide parts of the necessary material for studying the relationship between both reproductive and actuarial senescence and cancer in the light of early- and late-life trade-offs. In addition, such datasets should also open up opportunities to investigate in depth the genetic and physiological bases of these processes. In the next section, we argue that among the physiological mechanisms underlying these relationships immunosenescence might play a critical role.

3. DOES CANCER RESULTS FROM IMMUNOSENESCENCE?

Immunosenescence involves the progressive morpho-functional involution of organs, as well as an age-related deterioration of cellular and humoral immune functions (Malaguarnera et al., 2001). The atrophy of the thymus (the key organ for T-cell maturation) leads to decreased number of lymphoid precursor T-cells and to the impairment of T-cell proliferative capacity with increasing age (see Malaguarnera et al., 2001 for a review). By acting as antibody-

specific antigen presenting cells, T-cells provide support to the development of antibody responses by B-cells (i.e. T cell-dependent B cell activation (Parker, 1993)). CD4+ T cells provide helper signal to B cells to initiate their proliferation (Kurosaki, Kometani, & Ise, 2015), and the lack of T cells can result in minimal memory B cell development (Lafrenz & Feldbush, 1981). Therefore reduced functioning of T-cells can limit the production of specific high-affinity antibodies potentially leading to a more restricted antibody repertoire (Rubelt et al., 2012; van Dijk-Härd, Söderström, Feld, Holmberg, & Lundkvist, 1997). In parallel, with advancing age, the number of naïve lymphocytes and early progenitor B-cells in the bone marrow also decrease, and the rate of B-cell maturation and generation decline (Allman & Miller, 2005; Linton & Dorshkind, 2004). The decreased productions of T and B immune cells ultimately limit the efficiency of the adaptive immune system to cope with pathogens (Weksler, 2000). In addition, while the efficiency of the humoral immune system's also generally declines with increasing age (Ujvari & Madsen, 2011; Weksler, 2000), other arms of the immune system follow different age-specific trajectories. For example, the number of other key innate immune cells may actually increase with age or remain constant over the lifecourse (e.g. Cheynel et al., 2017 in two wild populations of roe deer, *Capreolus capreolus*). Overall, immunosenescence has now been documented in a wide range of species (e.g. Garschall & Flatt, 2018; Ujvari & Madsen, 2011) and is believed to strongly impair reproductive and survival prospects at late ages.

Because malignant cells are immunogenic, the immune system has the potential to recognize and to suppress carcinogenesis. In other words, the immune system not only plays a crucial role in recognizing, controlling and eliminating foreign pathogens, but also has the ability to recognize and remove malignant cells (Muenst *et al.* 2016). Therefore, age associated waning of immunity has been proposed to contribute to increased cancer incidence in older individuals (Pawelec 2017; see Figure 1 and Box 2 for further details on the

mechanistic pathways involved). Moreover, the persistent antigenic stimulation caused by infection with pathogens (e.g. Cytomegalovirus) throughout the lifetime of an organism may also generate an inflammatory environment favorable for tumor growth, and also concurrently to direct resources from tumor surveillance to elimination of pathogens (Fulop et al., 2013; Mancuso et al., 2018; Box 2). The dysfunction of immunity as the organism grows older will thus impair their ability to respond to diverse challenges, such as parasites and malignant cells.

The functional relationships linking immunosenescence and cancer emphasize that life-history and evolutionary theories of aging can illuminate our understanding of carcinogenesis. Indeed, between-individual variation in immunosenescence patterns (and thus in cancer resistance) can thus be explained by differential allocation of resources towards costly biological functions such as growth or reproduction, in line with predictions of the disposable soma theory of aging (Figure 1). There is now a tremendous amount of evidence that maintaining baseline immunity or mounting an immune response is energetically costly (Lochmiller & Deerenberg, 2000) and might be impaired by increased allocation to growth or reproduction, as evidenced by experimental manipulations of brood size in birds (Demas, Greives, Chester, & French, 2012; Knowles, Nakagawa, & Sheldon, 2009). For instance, experimental increase in brood size in collared flycatcher (*Ficedula albicolis*) reduced their level of antibody response against Newcastle disease virus (Nordling, Andersson, Zohari, & Lars, 1998). A decrease in immunocompetence following reproductive allocation has also been observed in European rabbits (*Oryctolagus cuniculus*) where both neutrophils and lymphocytes counts were lower in females that allocated heavily to reproduction (Rödel, Zapka, Stefanski, & Holst, 2016). Moreover, several phylogenetic comparative studies have highlighted that immunocompetence is superior in species exhibiting slow pace-of-life (Pap et al., 2015; Tella, Scheuerlein, & Ricklefs, 2002) indicating that an efficient immune system is

a key to a long life. Further studies, that investigate the association between life history strategies and immunosenescence, not only from the classical host-parasite spectrum, but also by considering malignant cells (i.e. the oncobiota) as selective force (Russell *et al.* 2018; Thomas *et al.* 2018), are thus urgently needed.

4. FROM MOSAIC AGING TO ASYNCHRONICITY OF AGE-SPECIFIC CANCER INCIDENCE

Predictions from early evolutionary studies suggest that senescence should be a highly synchronized process among phenotypic traits or biological functions (Maynard Smith, 1962; Williams, 1957). However, increasing amount of evidence show that age-specific patterns of senescence might be asynchronous between and among physiological and demographic traits (Gaillard & Lemaître, 2017; Hayward et al., 2015). In line with this observation, age- and site- specific cancer incidences are exemplary of such asynchronicity.

Despite extensive research over the last 50 years, it remains unclear why certain tissues are significantly more vulnerable than others to developing or hosting malignancies. While Tomasetti and Vogelstein (2015) suggested that two-thirds of cancer types can be explained by tissue-specific stem-cell division rates, Wu and colleagues (2016) rather proposed that cancer risk is heavily influenced by environmental factors. More recently, Thomas and colleagues (2016) suggested an alternative explanation based on the evolutionary ecology of organs that could explain why some neoplasms develop into lethal tumors while others remain benign for decades. This approach considers that the ecological conditions that characterize each organ, along with the way natural selection has optimized organs to maximize the individual's fitness, contribute to explaining the spatial and temporal patterns of cancer occurrences in the body. Furthermore, through time, cellular and tissue senescence may alter differently the various ecological parameters inside the organs as well as the

efficiency of their natural defenses against cancer. Mosaic aging (sensu Walker & Herndon, 2010), the heterogenous and idiosyncratic pattern of age on different cells, organs and system, therefore could also be extended to cancer.

In complex multicellular organisms, organs correspond to ecosystems with their own distinct ecologies (Thomas et al., 2016). For instance, organs are characterized by particular structures, functions, abiotic (e.g., glucose, oxygen gradients, temperature, pH) and biotic conditions (microbial community), the extent of carrying capacity and spatial distribution of resources, the dimensions of networks with other organs, and last but not least, by the expanse of contact with the external world. Furthermore, organs differ in the way they relate to fitness, some being more essential than others for keeping the organism alive and reproduce efficiently (Thomas et al., 2016). For instance, vital organs such as the heart, brain, and pancreas are essential for survival, while others, such as the gallbladder and spleen, are not. In addition, organs found in pairs (lungs or kidneys) can still function even if only one is damaged. The assumption that organs are perfect by design and intended to maximize health and lifespan is a common misconception in medicine (Brüne & Hochberg, 2013). The evolutionary perspective (Nesse & Williams, 1996) emphasizes that trade-offs and constraints limit the perfection of every organ, and that selection maximizes reproductive success at the expense of health and lifespan. This implies that organs less crucial for survival and reproduction should be more vulnerable to pathologies (Thomas et al., 2016). Alternatively, the strong selection for efficient reproduction that operates on reproductive organs, possibly associated with a higher expression of genes with antagonistic effects (see Section 2), might explain why, once standardized for organ mass, prostate and ovaries show the highest rates of cancer incidence in humans (Silva et al., 2011).

These concepts are fundamental to understand organ and age-specific incidences and prevalence of cancer in different organs. Akin to microbes, cancer cells depend on their tissue

342 environment for sustenance and proliferation. The local ecological conditions in organs
343 should therefore substantially influence cancer dynamics. In accordance with this idea, it is
344 increasingly recognized that tumor development, progression, and metastasis are strongly
345 dependent on the microenvironmental conditions experienced by cancer cells (Bissell &
346 Hines, 2011). Interactions such as competition, mutualism, and antagonism are likely to shape
347 the somatic evolution of cancer cells (Crespi & Summers, 2005; Marusyk & Polyak, 2010).
348 Deterioration of organs with age may also favor malignant proliferation. Reduced cell
349 proliferation and increased cell death with aging display substantial variations among organs,
350 as illustrated by Richardson and colleagues (2014). These authors showed that the loss of
351 functional mass in tissues with aging, which is related to the mitotic rate or rates of tissue
352 turnover, is organ specific. With aging, highly proliferative tissues also exhibit greater
353 telomere erosion and hence replicative senescence (Ishii et al., 2006). In young persons, tissue
354 maintenance involves the removal of old and/or damaged cells, followed by their replacement
355 by stem cells providing progenitors. Conversely, in the elderly, the most proliferative tissues
356 display a lack of homeostasis and lose functional mass due to mutations of TP53, a
357 mechanism/process that is also frequently involved in the age-related rise of cancer incidences
358 (Richardson, Allan, & Le, 2014).

359 The adaptive theory proposed by DeGregori (2018) also provides an interesting
360 conceptual framework to understand why the general of process of senescence can locally
361 promote cells carrying malignant mutations and hence cancer. In this theory, tissues and
362 organs are equivalent to adaptive landscapes, and healthy cells are best adapted to live in
363 healthy young tissue. However, age-specific decline in tissue and organ structures or
364 functions alter the adaptive landscapes, so that cells with oncogenic mutations may suddenly
365 find themselves better adapted to their surroundings and hence may be able to out-compete
366 healthy cells. Thus, while oncogenic mutations may always be present and/or accumulate

through time, it is the state of the tissue environment that becomes the key determinant that either favors or disfavors cancer development. For instance, introduction of oncogenes into old bone marrow progenitors in an old bone marrow environment in mice, often leads to clonal expansion and leukamia. Conversely, this is not observed when oncogenes are introduced into young bone marrow progenitors in a young bone marrow environment in mice (Henry et al., 2015). Therefore, the age-related decline in tissues and organs (e.g. Lui et al., 2019 for a case study on skin senescence) promotes selection for new cellular phenotypes adapted to the new microenvironment. Interestingly, alteration in cellular niches due to aging seems to be specific compared to other causes. For instance, lung cancers in the elderly and in smokers rely on different mutations (on EGFR and KRAS, respectively), while it is not expected that carcinogens from smoking induce KRAS mutations only (DeGregori, 2018).

To conclude, eco-evolutionary approaches offer promising frameworks to investigate variations is cancer risk between organs and tissues. However, to go further, one would need to extend the classical evolutionary theory of aging that aggregates all causes of death at the organism level and predict synchronisation of senescence of physiological functions (Maynard Smith, 1962; Williams, 1957) to a model which encompasses the potential asynchronicity of senescence and trade-offs between physiological functions and anatomical sites.

5. DYNAMIC INTERPLAY AND TRADE-OFF BETWEEN SENESCENCE AND CANCER

Because age is the strongest predictor of metastatic cancer development, it is usually assumed that cancer is a pathology of old ages (Frank, 2004; Rozhok & DeGregori, 2016). This correlation may indeed involve causal processes, when for instance advancing age predisposes cells to accumulate oncogenic mutations, alters tissue microenvironments in a

way that favors cells carrying oncogenic mutations (Section 4), and /or alter the efficiency of the mechanisms that normally hold in situ tumors in check (Section 3 and Box 2). However malignant pathologies also display a range of characteristics suggesting that the occurrence of cancer might not automatically be a consequence of senescence (Thomas, Vavre, et al., 2018).

Although the accumulation of numerous oncogenic manifestations, (e.g. precancerous lesions and *in situ* carcinoma) throughout the life (being therefore highly prevalent before individuals are old, e.g. Bissell & Hines, 2011) might be seen as a direct expression of cellular, tissues or organs senescence, it might be only indirectly linked to the decline in fitness with age. Indeed, assuming that natural defenses against malignant progression are associated with trade-offs for the host (Jacqueline et al., 2017), one must also admit that oncogenic processes can be a cause, rather than a consequence of senescence. For instance, even when a cancer is apparently not invasive, we cannot exclude that it is energetically costly to keep such a cancer sub-lethal (Vittecoq et al. 2013). Under the current evolutionary theories of aging, the amount of resources devoted to limit malignant progression should, everything else being equal, impair somatic maintenance (e.g. the efficiency of the immune system) and ultimately lead to a much more pronounced reproductive and actuarial senescence. For instance, Arnal and colleagues (2017) found that females in Drosophila flies harbouring early stages of a gut cancer lay their eggs earlier than healthy females prior to their concomitantly earlier death (Arnal et al., 2017). Since early ages at first reproduction are often associated with long-term reproductive and survival costs in animals (Lemaître et al., 2015), this example suggests that cancer development during early-life might strengthen demographic senescence. Another illustration of cancer-induced alteration in life-history strategies involves the Tasmanian devil and their aforementioned transmissible facial tumor disease. Basically, Tasmanian devil populations have responded to the cancer-induced

mortality by transitioning from an iteroparous (multiple reproductive cycles) to a semelparous (single breeding at one year of age) reproduction (Jones et al., 2008).

Using an eco-evolutionary perspective to investigate how different hosts (with different life-history strategies) manage non-invasive (sub-lethal) malignant cells should help to understand the dynamic relationship linking cancer and senescence. More generally, it is important to adopt a novel view of malignant pathologies, and recognize not only invasive/metastatic cancers as selective force, but rather to consider the entire oncobiota (Thomas et al., 2017). Oncogenic phenomena, taken in their totality, may indeed influence various aspects of individual fitness and thus modulate the numerous trade-offs occurring at the individual level (Stearns, 1992), long before negative impacts on age-specific survival and reproductive probabilities become apparent (Thomas et al., 2017). Embracing this view will be particularly relevant to understand how the great majority of cancers occurs late in life even if common malignancies in youth can still impair fitness on the long-run.

Finally, the causal link between oncogenic processes and senescence may also be mediated by trade-offs resulting from our constitutive defenses against cancer as for instance trade-off between morbidity by cancers and other senescence-related causes of death. One possible mechanism mediating such trade-off could stem from the senescent-cell's theory of aging (Van Deursen, 2014). Senescent cells are stem/progenitor cells that stop replication and cease participating in tissue functioning, and accumulate in tissues with age. Senescent state is seen as a mean to divert a cell potentially at risk of carcinogenesis to a 'safe' state where, avoiding replication, it is not a risk of accumulating further mutations. Hence the genes controlling for the entrance into the senescent state are mainly tumor suppressor genes. However this has a cost: increased proportion of senescent cells compromises tissue renewing, functioning and therefore the organism's survival (Baker et al., 2016). Thus, molecular and cellular theories predict a physiological trade-off between mortality

components (dying from cancer or from other causes) mediated by the proportion of senescent cells (Finkel, Serrano, & Blasco, 2007). For instance, apart from its well-known cancer-suppressive function, activation of TP53 also modulates (together with other alternative molecular pathways) cellular senescence and organismal aging (Rufini, Tucci, Celardo, & Melino, 2013), leading to reduced tissue renewal and repair, stem cell deletion, and organismal aging through an antagonistic pleiotropy effect (Campisi, 2003; García-Cao et al., 2002). Accordingly, mutated mice with a phenotypic effect analogous to the up-regulation of the TP53 gene have a reduced risk of cancer but in return display earlier onset of tissue atrophy and shortened lifespan (Donehower, 2002; Tyner et al., 2002).

Over evolutionary time, selection might also have favored compensatory adaptations, as illustrated by elephants (*Loxodonta africana*) that are long lived mammals with a high number of copies of the TP53 gene coding p53 proteins (Abegglen et al., 2015). Although the relatively low number of vertebrates at the same position as elephants along the slow-fast life history trait continuum makes it difficult to draw general conclusions, slow species (e.g. long-lived birds) generally show limited functional and actuarial senescence (Jones et al., 2008). These examples clearly suggest that focusing on non-classical model organisms offer exciting opportunities to decipher the intimate relationship linking senescence and cancer, from the molecular to the whole-organism level. Overall, further studies are needed to determine the extent to which inter-individual variability in the vulnerability to carcinogenesis (due to strictly intrinsic or environmentally-driven factors) correlates with differential senescence rates.

6. CONCLUSIONS

Our perspective article highlights that the study of the relationship between senescence and cancer is still at its infancy. More specifically, we emphasize that the current evolutionary

theories proposed to explain the evolution of senescence provide a solid background to better understand both cancer prevalence (e.g. if strong allocation to growth and reproduction facilitate cancer development) and timing (e.g. if the asynchrony in senescence patterns parallels the age-specific patterns of cancer development across organs). At the same time, we demonstrate that cancer might itself promote senescence or can even be embedded in a trade-off with senescence. Whether the directionality of the relationship between senescence and cancer varies among individuals, populations or species is currently unknown. However, we argue that research programs aiming to embrace this question are particularly timely since modifications of the environmental conditions (especially significant perturbations caused by human activities) have been associated with increased cancer rates in wild populations. Although we are currently only scratching the surface of the potential importance of oncobiota in wild populations living in human-impacted habitats (Giraudeau, Sepp, Ujvari, Ewald, & Thomas, 2018; Hochberg & Noble, 2017; Pesavento et al., 2018; Vittecoq et al., 2018), cancer in wildlife has also been suggested to be associated with other anthropogenic activities, such as nocturnal light pollution, intentional or accidental wildlife feeding, or reduction of genetic diversity in human-impacted habitats (Giraudeau et al., 2018; Sepp, Ujvari, Ewald, Thomas, & Giraudeau, 2019). Since both cancer prevalence and demographic senescence patterns can be modulated by environmental conditions (e.g. Garrott, Eberhardt, Otton, White, & Chaffee, 2002; Tidière et al., 2016), possibly through the trade-off between reproduction and somatic maintenance (Lemaître et al., 2015), a greater understanding of the dynamic interplay between senescence and cancer will become a major question for diverse research areas such as population dynamics, conservation biology, epidemiology or public health.

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AUTHORS' CONTRIBUTION

All co-authors conceived the research ideas and contributed to the writing of the manuscript.

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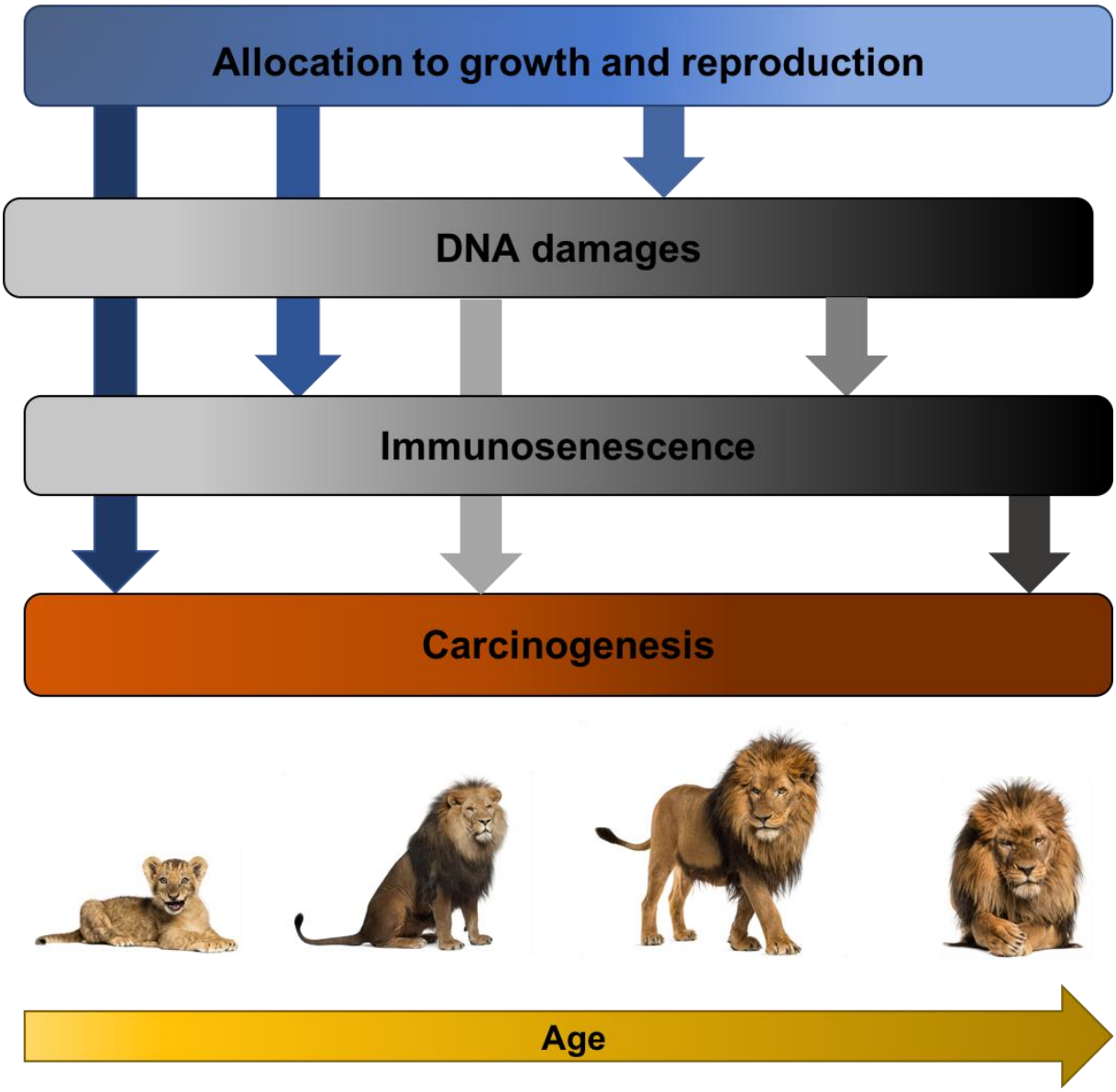

Figure 1: The life-history origins of carcinogenesis. An individual's allocation to growth and reproduction can increase cancer risk through multiple pathways. The relationship can sometimes be direct if, for example, higher rates of antagonistic interactions during sexual competition elevate the risk of contracting cancers (as observed in Tasmanian devils). More generally, the functional relationships linking the allocation of resources to growth and reproduction might ensue increased DNA damages that can either directly or indirectly (via higher rate of immunosenescence) augment the risk of carcinogenesis. Taken together, this suggests that cancer risk worsens with chronological age.

Box 1 – The paradox of cancer prevalence and age-specific incidence across the tree of life

Peto's paradox: Multistage carcinogenesis predicts that a species' cancer prevalence should be a function of the number of cell divisions (then of species size) per unit of time (then of lifespan). As first noted by Sir Richard Peto (Peto, Roe, Lee, Levy, & Clack, 1975), this prediction seems not to be supported when comparing mice and humans. Mice are about 1000 times smaller and about 30 times shorter lived than humans but cancer incidence is about the same in the two species. This led Peto to ask whether our stem cells are "a billion or a trillion times more "cancer-proof" than murine stem cells?" and "Why don't we all die of multiple carcinoma at an early age? (Peto, 1976, pp 1413-1414). Scarcity of data and more specifically age-specific data yet prevent to properly test whether Peto's paradox holds across taxa (but see (Abegglen et al., 2015). Indeed, while multistage carcinogenesis theory predicts a positive correlation between cancer prevalence and lifespan, cancer morbidity is by contrast obviously negatively correlated to lifespan, an effect never properly accounted for. So far the best hypothesis that accommodates for both the multistage theory and also solves Peto's paradox is the existence of better cancer suppression in larger species compared to small ones (Abegglen et al., 2015; but see Caulin, Graham, Wang, & Maley, 2015). For instance, bowhead whale (*Balaena mysticetus*) carry specific genes involved in DNA repair and cell-cycle regulation that potentially confer advantages against cancers (Keane et al., 2015), which is in line with repeated evidence that long-lived species show more efficient DNA repair mechanisms (Freitas & de Magalhães, 2011). However, many alternative but so far untested hypotheses have also been proposed (see Nunney, Maley, Breen, Hochberg, & Schiffman, 2015 for a synthesis).

The paradox of deceleration and decline of cancer incidence with age. Multistage carcinogenesis indeed predicts that cancer incidence with age should closely match in shape the increase of mortality with age. However, this is not the case in humans: after a phase of increase, the cancer incidence curve decelerates and even declines in very old ages (Smith, 1996). As a consequence, the proportion of death by cancer decreases after age 60-70, making cancer less responsible for actuarial senescence and eventually cancer becomes one of the least prevalent cause of death in centenarians (Nolen et al., 2017). This has long been explained by population biases, as the selective disappearance with age of individuals genetically/environmentally more susceptible to cancer (Vaupel & Yashin, 1999). However, such deceleration has also been observed in domestic dog breeds (Fleming, Creevy, & Promislow, 2011) and homogenic rats under controlled environment (Anisimov, Ukraintseva, & Yashin, 2005), leading researchers to argue that this paradox may have some physiological grounds. Here again, its generality across species need to be assessed.

Box 2 – An overview of the mechanistic pathway linking immunosenescence and cancer

The first line of defense against both intrinsic and extrinsic challenges is generated by the innate immune system that is able to recognize pathogen-associated molecular patterns (PAMP) conserved among microbes as well as damage-associated molecular patterns (DAMP) generated by damaged cells and tissues (Muenst et al., 2016). The innate immune system produces a fast and low-cost response that ultimately initiates an adaptive immune response during infection and tissue damage/inflammation (Liu & Zeng, 2012).

The first immune effector cells from the innate response that directly target cancer cells include: natural killer cells (NK), dendritic cells (DC), macrophages, polymorphonuclear leukocytes (PMN, such as neutrophils, eosinophils, and basophils), mast cells, and cytotoxic T lymphocytes (Liu & Zeng, 2012). Direct molecular interactions between innate immune cells and cancer have been demonstrated in numerous studies. For example, NK cells kill non-MHC (Major Histocompatibility Complex) expressing cancer cells by producing cytotoxic proteins (i.e. perforin and granzyme) that initiate the apoptosis of cancer cells. NK cells produce stimulatory receptors (e.g. natural killer group 2D), on their cell surface that attaches to ligands on the cancer cell surface and the binding stimulates NK cells to secrete inflammatory cytokines, and induce the death of cancer cells (Yokoyama & Plougastel, 2003). PMN leukocytes and mast cells interact with antibody coated antigens on tumor cells and induce the release of cytokines and chemo-attractants that will recruit DC and macrophages to the cancer cells (Amulic, Cazalet, Hayes, Metzler, & Zychlinsky, 2012; Anisimov et al., 2005; Gregory & Houghton, 2011). DC and macrophages recognize the so called "eat me" signals on apoptotic cells through specific receptors and eliminate the malignant cells by phagocytizing them (reviewed in Liu & Zeng, 2012).

Natural killer T cells (NKT) and DCs also create a bridge between innate and adaptive immune systems by secreting cytokines and chemokines, and stimulate T – and B – cell responses to cancer cells (Palucka, Banchereau, & Mellman, 2010). Tumor associated antigens (TAAs), originating from the large genetic alterations of tumors, are presented via the MHC on the tumor surface and trigger T-cell responses. Secretion of chemokines and cytokines leads to expansion of T cells, and ultimately the malignant cells are destroyed by either cell-mediated or by indirect antibody complement-mediated cytotoxicity (Spurrell & Lockley, 2014). TAA specific adaptive immune responses can be generated by various subsets of T cells such as CD4+ T cells modulating the efficiency of the immune reaction and CD8+ T cells directly destroying TAA expressing cancer cells (Reuschenbach, von Knebel Doeberitz, & Wentzensen, 2009).

Overall, the involution of thymus with advancing age, the production of naïve immune cells (T cells) ceases, reserves of naïve cells become depleted, and susceptibility not only to previously un-encountered pathogens but also to antigens expressed by newly-arising cancers can increase (Fulop et al., 2013; Pawelec, Derhovanessian, & Larbi, 2010).