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4

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30 tumor

31

32

34 **Abstract**

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

67 **1. THE PROBLEMATICS OF SENESCENCE AND CANCER**

68

69 The last decades have seen a burst in the number of studies providing evidence for a decrease
70 in survival and reproductive success with increasing age (processes coined actuarial and
71 reproductive senescence, respectively) in both wild and captive populations of animals (Jones
72 et al., 2014; Nussey, Froy, Lemaître, Gaillard, & Austad, 2013). Such declines in age-specific
73 life history traits are supposed to be underlined by a progressive deterioration of organism
74 along the life course (henceforth coined ‘senescence’), generally described in free-ranging
75 populations through a loss of body mass (e.g. Douhard, Gaillard, Pellerin, Jacob, & Lemaître,
76 2017) or physiological performance (e.g. immune performance, Ujvari & Madsen, 2011).
77 While the demographic senescence process appears pervasive across species, the complex
78 interplay between the deterioration of physiological functions and body condition and the
79 concomitant increase in susceptibility to diseases culminating in death, is yet to be
80 deciphered. The ‘emperor of all maladies’, cancer, illustrates this complexity.

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

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

98 Cancer originates from the (epi)genetic alterations of a given cell. The dominant
99 theory (also referred to as the ‘Doll-Armitage multistage model’, Armitage & Doll, 1954) is
100 that carcinogenesis is a multistage process of accumulation of (epi)mutations in a mitotic cell
101 lineage that liberates a cell from homeostatic mechanisms of cell division; often due to
102 inhibited attrition of telomeres. Although it has recently been argued that lifetime risk of
103 cancer correlates with the total number of cell divisions in a given tissue (Tomasetti, Li, &
104 Vogelstein, 2017; Tomasetti & Vogelstein, 2015), the kinetics of damage accumulation with
105 age and its consequences on the age-specific patterns of cancer prevalence and incidence
106 remain largely unknown (Rozhok & DeGregori, 2015). Furthermore, these proximate factors
107 of carcinogenesis (i.e. (epi)genetic instability and telomere attrition) also belong to the
108 ‘primary hallmarks’ of aging by being involved in the progressive deterioration of various
109 biological functions (López-Otín, Blasco, Partridge, Serrano, & Kroemer, 2013). Variations in
110 cancer prevalence between and within species should thus be mainly determined by
111 differential somatic mutation rate and repair efficiency. As the immediate results of the
112 proximal deteriorations occurring with age, both processes of carcinogenesis and senescence
113 should be tightly linked. However, understanding the causality of the relationship linking
114 cancer and senescence (at cellular, individual and population levels) and deciphering their
115 complexity through the lenses of evolutionary biology is particularly arduous (Hofman et al.,
116 2019). In that context, several hypotheses have recently emerged. The aim of this article is

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

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

136

137 **2. DOES CANCER MEDIATE THE REPRODUCTION – SENESCENCE TRADE-** 138 **OFF?**

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

142 assumption that the force of natural selection against fitness impairing genes decreases with
143 age (Hamilton, 1966; Medawar, 1952), George C. Williams proposed that allele(s) can be
144 selected by natural selection through a positive effect on reproductive success during early life
145 even if such allele(s) is responsible for increased senescence in late life. While detecting such
146 alleles is challenging, experimental manipulations in laboratory models and quantitative
147 genetic approaches performed on wild populations of animals have provided support to this
148 theory (see Gaillard & Lemaître, 2017 for a review). The key role of reproductive allocation
149 in shaping reproductive and actuarial senescence patterns was then emphasized in the
150 ‘*disposable soma theory*’ of aging (see Kirkwood, 2017 for a comprehensive review), a
151 theory originally focusing on the maintenance of molecular and cellular integrity (Kirkwood,
152 1977). In its current form, the disposable soma theory adopts assumptions and predictions that
153 are common with life history theory as they both give a pivotal role to the principle of
154 allocation (Cody, 1966), namely that individuals need to share a finite pool of resources
155 extracted from the environment between different functions like growth, reproduction and
156 survival (Kirkwood & Rose, 1991; Stearns, 1992). However, the disposable soma theory
157 explicitly involves the concept of ‘*somatic maintenance*’ (Holliday, 1995) based on evidence
158 that organisms have evolved dedicated but costly mechanisms (e.g. enzymatic complexes)
159 that insure the fidelity of DNA replication and repair, as well as the accuracy of protein
160 synthesis (Gladyshev, 2016). Therefore, resources devoted to growth and reproduction cannot
161 be simultaneously used for somatic maintenance, which might compromise cellular integrity
162 and, on the long-run, be responsible for a premature and/or accelerated reproductive and
163 actuarial senescence (Kirkwood, 2017; Kirkwood & Rose, 1991).

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

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

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

185 In non-model organisms, fine-scale genetic data are generally unavailable and most
186 supports for early- vs late-life trade-offs rely on covariation patterns between life-history traits
187 depicting reproductive effort and lifespan and/or senescence measurements (Lemaître et al.,
188 2015). Interestingly, reproductive effort has also been associated with the risk of developing
189 cancer in wild populations of animals (Jacqueline et al., 2017). For instance, in Tasmanian
190 devils (*Sarcophilus harrisi*), female fecundity rates were positively associated with the risk
191 of contracting facial tumors (the Tasmanian devil facial tumor disease, DFTD, one of the very

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

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

217 Lemaître, 2017). Taken together, these predictions from theoretical approaches combined
218 with evidence that both reproductive allocation and cancer defense mechanisms are
219 energetically costly, strongly highlight that the development of some cancers might be seen as
220 a long-term reproductive cost (Boddy, Kokko, Breden, Wilkinson, & Aktipis, 2015). The
221 picture might be even more complex, at least in females, where an absence or a very low rate
222 of reproduction might itself increase the risk of developing cancers of the reproductive system
223 (Pesavento, Agnew, Keel, & Woolard, 2018). Basically, females that do not reproduce will
224 experience a higher number of oestrous cycles and thus a greater exposure to oestrogen,
225 which can ultimately lead to higher risk of cancers, as observed in humans (Britt & Short,
226 2012) and captive mammals (Pesavento et al., 2018).

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

235

236 **3. DOES CANCER RESULTS FROM IMMUNOSENESCENCE?**

237 Immunosenescence involves the progressive morpho-functional involution of organs, as well
238 as an age-related deterioration of cellular and humoral immune functions (Malaguarnera et al.,
239 2001). The atrophy of the thymus (the key organ for T-cell maturation) leads to decreased
240 number of lymphoid precursor T-cells and to the impairment of T-cell proliferative capacity
241 with increasing age (see Malaguarnera et al., 2001 for a review). By acting as antibody-

242 specific antigen presenting cells, T-cells provide support to the development of antibody
243 responses by B-cells (i.e. T cell-dependent B cell activation (Parker, 1993)). CD4+ T cells
244 provide helper signal to B cells to initiate their proliferation (Kurosaki, Kometani, & Ise,
245 2015), and the lack of T cells can result in minimal memory B cell development (Lafrenz &
246 Feldbush, 1981). Therefore reduced functioning of T-cells can limit the production of specific
247 high-affinity antibodies potentially leading to a more restricted antibody repertoire (Rubelt et
248 al., 2012; van Dijk-Hård, Söderström, Feld, Holmberg, & Lundkvist, 1997). In parallel, with
249 advancing age, the number of naïve lymphocytes and early progenitor B-cells in the bone
250 marrow also decrease, and the rate of B-cell maturation and generation decline (Allman &
251 Miller, 2005; Linton & Dorshkind, 2004). The decreased productions of T and B immune
252 cells ultimately limit the efficiency of the adaptive immune system to cope with pathogens
253 (Weksler, 2000). In addition, while the efficiency of the humoral immune system's also
254 generally declines with increasing age (Ujvari & Madsen, 2011; Weksler, 2000), other arms
255 of the immune system follow different age-specific trajectories. For example, the number of
256 other key innate immune cells may actually increase with age or remain constant over the
257 lifecourse (e.g. Cheynel et al., 2017 in two wild populations of roe deer, *Capreolus*
258 *capreolus*). Overall, immunosenescence has now been documented in a wide range of species
259 (e.g. Garschall & Flatt, 2018; Ujvari & Madsen, 2011) and is believed to strongly impair
260 reproductive and survival prospects at late ages.

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

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

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

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

296

297 **4. FROM MOSAIC AGING TO ASYNCHRONICITY OF AGE-SPECIFIC CANCER** 298 **INCIDENCE**

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

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

317 efficiency of their natural defenses against cancer. Mosaic aging (sensu Walker & Herndon,
318 2010), the heterogenous and idiosyncratic pattern of age on different cells, organs and system,
319 therefore could also be extended to cancer.

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

340 These concepts are fundamental to understand organ and age-specific incidences and
341 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

367 through time, it is the state of the tissue environment that becomes the key determinant that
368 either favors or disfavors cancer development. For instance, introduction of oncogenes into
369 old bone marrow progenitors in an old bone marrow environment in mice, often leads to
370 clonal expansion and leukemia. Conversely, this is not observed when oncogenes are
371 introduced into young bone marrow progenitors in a young bone marrow environment in mice
372 (Henry et al., 2015). Therefore, the age-related decline in tissues and organs (e.g. Lui et al.,
373 2019 for a case study on skin senescence) promotes selection for new cellular phenotypes
374 adapted to the new microenvironment. Interestingly, alteration in cellular niches due to aging
375 seems to be specific compared to other causes. For instance, lung cancers in the elderly and in
376 smokers rely on different mutations (on EGFR and KRAS, respectively), while it is not
377 expected that carcinogens from smoking induce KRAS mutations only (DeGregori, 2018).

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

385

386

387 **5. DYNAMIC INTERPLAY AND TRADE-OFF BETWEEN SENESCENCE AND** 388 **CANCER**

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

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

397 Although the accumulation of numerous oncogenic manifestations, (e.g. precancerous
398 lesions and *in situ* carcinoma) throughout the life (being therefore highly prevalent before
399 individuals are old, e.g. Bissell & Hines, 2011) might be seen as a direct expression of
400 cellular, tissues or organs senescence, it might be only indirectly linked to the decline in
401 fitness with age. Indeed, assuming that natural defenses against malignant progression are
402 associated with trade-offs for the host (Jacqueline et al., 2017), one must also admit that
403 oncogenic processes can be a cause, rather than a consequence of senescence. For instance,
404 even when a cancer is apparently not invasive, we cannot exclude that it is energetically
405 costly to keep such a cancer sub-lethal (Vittecoq et al. 2013). Under the current evolutionary
406 theories of aging, the amount of resources devoted to limit malignant progression should,
407 everything else being equal, impair somatic maintenance (e.g. the efficiency of the immune
408 system) and ultimately lead to a much more pronounced reproductive and actuarial
409 senescence. For instance, Arnal and colleagues (2017) found that females in *Drosophila* flies
410 harbouring early stages of a gut cancer lay their eggs earlier than healthy females prior to their
411 concomitantly earlier death (Arnal et al., 2017). Since early ages at first reproduction are
412 often associated with long-term reproductive and survival costs in animals (Lemaître et al.,
413 2015), this example suggests that cancer development during early-life might strengthen
414 demographic senescence. Another illustration of cancer-induced alteration in life-history
415 strategies involves the Tasmanian devil and their aforementioned transmissible facial tumor
416 disease. Basically, Tasmanian devil populations have responded to the cancer-induced

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

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

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

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

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

463

464 **6. CONCLUSIONS**

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

467 theories proposed to explain the evolution of senescence provide a solid background to better
468 understand both cancer prevalence (e.g. if strong allocation to growth and reproduction
469 facilitate cancer development) and timing (e.g. if the asynchrony in senescence patterns
470 parallels the age-specific patterns of cancer development across organs). At the same time, we
471 demonstrate that cancer might itself promote senescence or can even be embedded in a trade-
472 off with senescence. Whether the directionality of the relationship between senescence and
473 cancer varies among individuals, populations or species is currently unknown. However, we
474 argue that research programs aiming to embrace this question are particularly timely since
475 modifications of the environmental conditions (especially significant perturbations caused by
476 human activities) have been associated with increased cancer rates in wild populations.
477 Although we are currently only scratching the surface of the potential importance of
478 oncobiota in wild populations living in human-impacted habitats (Giraudeau, Sepp, Ujvari,
479 Ewald, & Thomas, 2018; Hochberg & Noble, 2017; Pesavento et al., 2018; Vittecoq et al.,
480 2018), cancer in wildlife has also been suggested to be associated with other anthropogenic
481 activities, such as nocturnal light pollution, intentional or accidental wildlife feeding, or
482 reduction of genetic diversity in human-impacted habitats (Giraudeau et al., 2018; Sepp,
483 Ujvari, Ewald, Thomas, & Giraudeau, 2019). Since both cancer prevalence and demographic
484 senescence patterns can be modulated by environmental conditions (e.g. Garrott, Eberhardt,
485 Otton, White, & Chaffee, 2002; Tidière et al., 2016), possibly through the trade-off between
486 reproduction and somatic maintenance (Lemaître et al., 2015), a greater understanding of the
487 dynamic interplay between senescence and cancer will become a major question for diverse
488 research areas such as population dynamics, conservation biology, epidemiology or public
489 health.

490

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504 **AUTHORS’ CONTRIBUTION**

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

506

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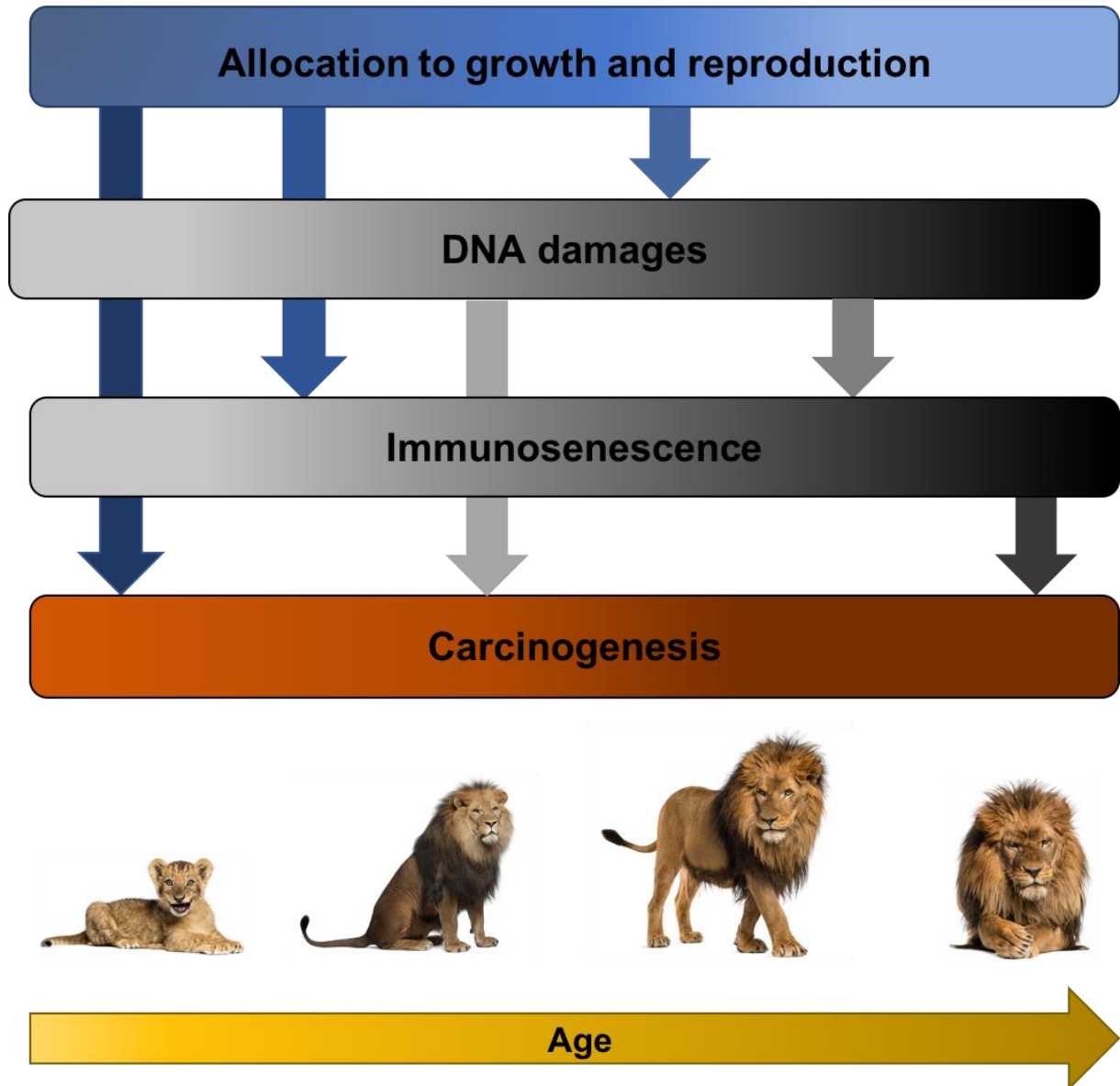
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Figure 1: The life-history origins of carcinogenesis. An individual's allocation to growth and reproduction can increase cancer risk through multiple pathways. The relationship can sometimes be direct if, for example, higher rates of antagonistic interactions 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.

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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).