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Cancer: a missing link in ecosystem functioning?

Marion Vittecoq[1,2,3], Benjamin Roche[3,4], Simon P. Daoust[5], Hugo Ducasse[1,3], Dorothée Missé[1], Jérome Abadie[6], Sophie Labrut[6], François Renaud[1], Michel Gauthier-Clerc[2,7], and Frédéric Thomas[1,3]

[1] Maladies Infectieuses et Vecteurs: Écologie, Génétique, Évolution et Contrôle (MIVEGEC), Unité Mixte de Recherche (UMR), Institut de Recherche pour le Développement (IRD)/Centre National de la Recherche Scientifique (CNRS)/Unité Mixte 5290, 911 Avenue Agropolis, BP 64501, 34394 Montpellier CEDEX 5, France
[2] Centre de Recherche de la Tour du Valat, le Sambuc, 13200, Arles, France
[3] Centre for Ecological and Evolutionary Cancer Research (CREEC), 95 rue de la Galera, 34090, Montpellier, France
[4] International Center for Mathematical and Computational Modeling of Complex Systems, Unité Mixte Internationale (UMI), Institut de Recherche pour le Développement (IRD)/Université Pierre et Marie Curie (UPMC)/Unité de Modélisation Mathématique et Informatique des Systèmes Complexes (UMMISCO), 32 Avenue Henri Varagnat, 93143 Bondy CEDEX, France
[5] Aquatic Biodiversity Section, Watershed Hydrology and Ecology Research Division, St Lawrence Centre, Environment Canada, 105 McGill, 7th floor, Montréal, Québec H2Y 2E7, Canada
[6] L'Université Nantes Angers Le Mans (LUNAM), Oniris, Animaux Modèles pour la Recherche en Oncologie (AMaROC), 44307, Nantes, France
[7] Chrono-Environment UMR CNRS Unité 6249, University of Franche-Comté (UFC), Place Leclerc, 25000, Besançon, France

Cancer is a disease that affects the majority of metazoan species and, before directly causing host death, is likely to influence the competitive abilities of individuals, their susceptibility to pathogens, their vulnerability to predators, and their ability to disperse. Despite the potential importance of these ecological impacts, cancer is rarely incorporated into model ecosystems. We describe here the diversity of ways in which oncogenic phenomena, from precancerous lesions to generalized metastatic cancers, may affect ecological processes that govern biotic interactions. We argue that oncogenic phenomena, despite their complexity, can have significant and sometimes predictable ecological consequences. Our aim is to provide a new perspective on the ecological and evolutionary significance of cancer in wildlife, and to stimulate research on this topic.

The ecological paradox of cancer: inconspicuous although ubiquitous

Cancer is a disease associated with clonal evolution and cell competition within the body and probably appeared with the transition to multicellularity more than half a billion years ago [1]. Despite the evolution of numerous natural mechanisms that suppress cancer (see [2]), it has been observed in nearly the entire animal kingdom, from bivalves to whales [3]. In fact, cancer-causing genes (oncogenes) can be maintained in populations through various processes (Box 1). In addition, mounting evidence suggests that metastatic cancers are a relatively rare (although often the most severe) oncogenic manifestation (Box 2 gives an overview of different cancer stages). For instance, several autopsy-based studies of humans and other animals that died of immediate causes other than cancer indicate that most individuals accumulate precancerous lesions and *in situ* tumors in many organs (e.g., prostate, lung, thyroid, breast, pancreas) as they age (see [4–6]). Precancerous lesions and *in situ* tumors might persist throughout the life of an individual without necessarily resulting in death. This persistence may occur because natural selection is too weak to eliminate them – the fitness costs of controlling them could be too high or the fitness benefits of eliminating them too small (e.g., [2,7]).

Whatever the exact reasons for the persistence of oncogenic processes over evolutionary time, it might appear surprising, given their occurrence in a range of species, that their influences on species dynamics and ecosystem functioning are largely unexplored. In fact, with few exceptions (e.g., Tasmanian devil facial tumor disease [8]), cancer in wildlife is difficult to study because pathological manifestations are usually unapparent. Indeed, most animals affected by cancer in the wild probably die unseen, for instance being disproportionately predated upon before overt clinical signs appear. A similar conclusion was reached in the 1970s and 1980s by Anderson and May with regard to infectious diseases [9,10]. Evaluating the ecological significance of oncogenic phenomena in ecosystems is undoubtedly a complex and technically challenging task, but to some extent this complexity is observed in parasitic diseases [11]. Indeed, despite several major differences between overtly infectious diseases and cancers, the progression of cancer can, in many ways, be compared to an overtly infectious disease and lead to similar health

Corresponding author: Thomas, F. (frederic.thomas2@ird.fr).
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Box 1. Why has cancer not been eliminated over evolutionary history?

At the beginning of the 20th century it was thought that cancer was associated with senescence, being one degenerative mechanism among others that is predominantly observed in older people [68,69]. It was then acknowledged that tumors were also detected in young people, even in babies (e.g., [70]). Thus, it became clear that cancer represent a much more complex process than previously thought. Paradoxically, if cancer is not strictly limited to old individuals we may suppose that it should have been eliminated throughout species evolution. That being said, natural selection can only favor the best options available in a particular environment. It allows species to adapt to changing conditions but it does not lead to perfection. Indeed, evolution is constrained by previous templates available and diverse trade-offs. Therefore, it is for this reason that cancer, although dating back from the dawn of multicellularity, was not wiped out over millennia. Here are described the major mechanisms currently known to underlie this apparent paradox.

Antagonistic pleiotropy: particular genes have opposite effects on fitness at different ages, such that their effects are beneficial in early life, when natural selection is strong, but harmful at later ages, when selection weakens. As an illustration, melanoma-promoting oncogene *Xmrk* alleles in the fish genus *Xiphophorus* (Figure I) are under positive selection because they are associated with large size and particular pigmentation that confer advantages in male–male competition and female mate choice [71].

Genomic conflicts: some genes have important functions, such as cell proliferation or angiogenesis regulation, that may favor tumor development when their expression is modified. As an example, some genes of the ADAM family are essential for fetus implantation and placentation but they exhibit highly dysregulated expression in prostate and breast cancers, where they appear to play key roles in invasion and metastasis due to their protease activity [72].

Mismatches: mismatches between genotype and environment or lifestyle arise when a characteristic that was selected in a particular context becomes detrimental in a new environment or due to a novel lifestyle. Some mismatches can lead to increased cancer risk. As an illustration, pale skin is thought to be a positive adaptation to cloudy northern climes, resulting in increased UV-dependent vitamin D synthesis. The mismatch arises when these individuals migrate to sunnier latitudes and fail to protect themselves from excess UV exposure which leads to highly increased skin cancer risk [73].

Figure I. *Xiphophorus cortezi* exhibiting the phenotype associated with the *Xmrk* oncogene. Reproduced with permission from A. Fernandez.

consequences (e.g., reduced viability and survival) for the host. Due in part to these similarities, it is predicted that particular oncogenic phenomena should also influence ecological dynamics in ecosystems. As we argue below, these influences may be considerably underestimated. We propose that oncogenic phenomena, depending on their magnitude, are likely to influence the competitive abilities of individuals, their susceptibility to pathogens, their vulnerability to predators, and their ability to disperse, and thus cannot be neutral on ecosystem functioning, stability, and diversity.

Cancer in wildlife: why is our knowledge so limited?

Relatively precise statistics are now available on the profile (e.g., incidence and mortality) of most cancers in humans (e.g., International Agency for Research on Cancer; IARC GLOBOCAN project, year 2008, http://globocan.iarc.fr/), as well as in domesticated animals [12]. By contrast, the incidence of cancers in wildlife is poorly understood because data are difficult to collect and interpret.

Cancer can be lethal, but ascertaining how it contributes to mortality in wildlife is complex for several reasons. A first difficulty lies in the fact that death in natural conditions can be ascribed to several contributing factors (e.g., predation, infectious diseases, somatic diseases, abiotic perturbations, etc.) and that identification of the contribution of one cause of death cannot be used as evidence that others did not play a role. For instance, while the rate of tumor development can be stable in a prey species occupying different habitats, mortality due to cancer is likely to be revealed in habitats where predator abundance is low; otherwise predation will be recorded as the main cause of mortality. Therefore, on a geographical scale, relative causes of death for a given species can vary from one location to another, meaning that cancer might be apparent as a significant cause of mortality in some areas but not others. Establishing causation is also difficult because of the complex network of interactions between oncogenic phenomena and other variables acting on individuals and species in ecosystems [13]. For example, fatal cancers might have an infectious origin (e.g., [14,15]). By contrast, the immunosuppression frequently associated with cancers [16–18] might promote infections that kill the host before it dies from the cancer *per se*, for example, by increasing its vulnerability to predators.

Cancer statistics from captive animals constitute an interesting source of information to evaluate both cancer incidence and mortality in wildlife, but their interpretation requires caution. Cancer mortalities may be higher in captivity than in nature because this situation is an extreme illustration of a predator/pathogen-free habitat where cancer mortalities are likely to be overestimated. For example, cancer probably rarely develops to an advanced stage in small rodents in nature because the vast majority of individuals first die from any one of a number of other causes, such as predators, infectious diseases, or environmental perturbations (e.g., floods, extreme temperatures, drought, etc.); nevertheless, when in protected captive conditions, species such as wild mice (*Mus musculus*) can have elevated incidences of cancer (e.g., 46%) [19]. Thus, depending on the source of the information, conclusions pertaining to cancer susceptibility of a given species can differ significantly.

Other limitations of data collected from captive animals come from the fact that captivity can artificially modify the prevalence of particular cancers because they impose artificial conditions (e.g., altered level of activity, novel food,