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Genetic diversity, inbreeding and cancer

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Genetic diversity is essential for adaptive capacities, providing organisms with the potential of successfully responding to intrinsic and extrinsic challenges. Although a clear reciprocal link between genetic diversity and resistance to parasites and pathogens has been established across taxa, the impact of loss of genetic diversity by inbreeding on the emergence and progression of non-communicable diseases, such as cancer, has been overlooked. Here we provide an overview of such associations and show that low genetic diversity and inbreeding associate with an increased risk of cancer in both humans and animals. Cancer being a multifaceted disease, loss of genetic diversity can directly (via accumulation of oncogenic homozygous mutations) and indirectly (via increased susceptibility to oncogenic pathogens) impact abnormal cell emergence and escape of immune surveillance. The observed link between reduced genetic diversity and cancer in wildlife may further imperil the long-term survival of numerous endangered species, highlighting the need to consider the impact of cancer in conservation biology. Finally, the somewhat incongruent data originating from human studies suggest that the association between genetic diversity and cancer development is multifactorial and may be tumour specific. Further studies are therefore crucial in order to elucidate the underpinnings of the interactions between genetic diversity, inbreeding and cancer.

1. Introduction

Genetic diversity provides populations with the ability to respond to challenges, such as parasites/pathogens, predators and environmental perturbations (electronic supplementary material, table S1). Attenuation of genetic diversity has been linked to increased risk of inbreeding depression, resulting in decreased growth rate, fertility, fecundity and offspring viability [1–9], as well as in increased vulnerability to pathogens [10–12]. Loss of genetic diversity therefore has a negative impact on organismal fitness, and limits a population's ability to respond to threats in both the long and short term (for review see [13]). Akin to parasites, malignant transformations that emerge due to environmental challenges, infections and/or host genotype either in isolation or via the interaction between genotype and environment exploit the host for energy and resources, and thereby impair host fitness and pose as a significant selective force [14–16]. Indeed, recent studies have proposed that malignant cells should be regarded as a developing species that behave in a manner akin to parasites [17]. Consequently, multicellular hosts that have the genetic toolkit to recognize and control cancer causing infections and malignant cell proliferation will have a significant fitness advantage over those that lack such mechanisms. Although a clear reciprocal link between genetic diversity and vulnerability to parasites and pathogens has been widely acknowledged

across taxa, so far the vast majority of studies have overlooked how reduced genetic diversity and inbreeding may influence the appearance and progression of non-communicable diseases, such as cancer. Here we discuss how genetic diversity and inbreeding may contribute to increased risk of cancer development and progression in humans and animals.

2. Cancer aetiologies

Cancer, the uncontrolled division of neoplastic cells, is a ubiquitous disease of metazoans [18] and has been proposed to have appeared with one of the major transitions of life (i.e. the transition from unicellularity to multicellularity) [19]. Fossilized bones, mummified tissues and phylogenetic analyses of oncogenic pathogens show that malignant transformations have been afflicting human and animal populations for eons (reviewed in [20]).

Although cancer is a multifactorial disease, only a small proportion of human cancers (less than 10%) originates from inherited mutations [21]. The majority of familial human cancers have been proposed to root from high-penetrance genetic variants or polymorphisms [22]. For example, specific inherited mutations in BRCA1 and BRCA2 genes account for 5–10% of all breast cancers [23], and inherited mutations of the APC gene is associated with 1–2% of all colon cancers [24]. Similarly, cancer predisposition by rare, high-penetrance alleles (e.g. mutations in c-KIT, P53, BRCA1/2) have also been observed in animal malignancies [25–27].

The majority of human cancer cases can be attributed to advanced age [28] and/or to acquired mutations due to environmental factors (including pathogen infections, exposure to pollution or sunlight, as well as lifestyle, economic and behavioural factors) [20,21] (see also https://www.cancer.gov/about-cancer/causes-prevention/risk). Human lifestyle particularly is one of the underlying factors of cancer development as almost 25–30% of all cancer-related human deaths are due to tobacco and 30–35% are linked to diet (reviewed in [21]).

Several of the factors resulting in increased cancer prevalence in humans such as smoking, alcohol and diet are highly unlikely to cause cancer in animals (but see [29,30]), whereas stress [31–33], infections (reviewed in [34]) and exposure to environmental carcinogens have been found to increase cancer prevalence in other vertebrates, such as the brown bullhead (*Ameiurus nebulosus*) [35], California sea lion (*Zalophus californianus*) [36] and beluga whales (*Delphinapterus leucas*) [37].

Infections are the direct or indirect underlying factors of a substantial proportion of both human and animal cancers [38]. Pathogens (particularly intracellular parasites) that alter cellular regulatory mechanisms (e.g. apoptosis, cell-cycle arrest), increase cell proliferation rates and break down cellular controls that would prevent oncogenesis can directly contribute to neoplasm formation. Inflammatory responses initiated by pathogen infections may also increase mutation rates and alter proliferation signals, and hence indirectly initiate malignant transformations (reviewed in [38,39]).

Viruses are the major agents of infection-initiated vertebrate cancers, and seven viruses have been now acknowledged as infectious causes of human cancers (e.g. gamma herpes virus indicated in nasopharyngeal, gastric cancers; Hodgkin's lymphoma, Burkitt's lymphoma) [38]. Similarly, many oncogenic viruses have been associated with malignancies in domestic and wild animals, such as the oncogenic papillomavirus in rabbits [40] and a gamma herpesvirus associated with urogenital carcinoma in California sea lions (*Zalophus californianus*) [41].

Apart from viruses, the most frequent sources of infection-induced cancers are protozoans (e.g. *Plasmodium falciparum*) [42], bacteria (e.g. *Helicobacter pylori*) [43,44] and trematodes (e.g. *Schistosoma haematobium*) [43,45] have all been shown to directly or indirectly cause malignancies. Although rare, contagious cancers without underlying infectious aetiologies do occur in the wild, and eight naturally occurring transmissible cancers—one lineage in dogs [46], two lineages in Tasmanian devils (*Sarcophilus harrisii*) [47,48] and five lineages in bivalves [49]—have so far been recorded.

3. Genetic diversity, inbreeding and cancer in humans

Several reports provide evidence that low genetic diversity and inbreeding may increase cancer risk and that cancer may have a recessive basis in humans [50–52]. For example, thyroid cancer has been found to be associated with significantly higher levels of inbreeding as well as a higher number and longer runs of homozygosity (ROH) [53], and acute leukaemia have been found to be linked to low levels of genetic diversity and inbreeding [54]. Moreover, extended germline homozygosity has been shown to result in an increased risk of lung cancer [55] and homozygosity of the MTHFR gene has been found to be associated with an increased risk of breast cancer [56].

Genome-wide association studies have also found a significant association between recessive alleles/inbreeding and cancer such as Hodgkin's lymphoma [57]. Based on the same methodology, two studies observed that inbreeding and ROH resulted in an increased risk of colorectal cancer [58,59], whereas a third study could not find such an association [60]. Similar disconsonant results have been reported from studies focusing on countries with high close-kin unions such as the United Arab Emirates and Qatar, with up to 54% consanguinity prevalence [52,53]. The two studies showed that reduced genetic diversity and inbreeding was associated with a reduced risk of breast, skin, thyroid and female genital cancers, but an increased risk of developing leukaemia, lymphoma, colorectal and prostate cancer [61,62]. The incongruous results observed in some human studies suggest that the effect of genetic diversity and inbreeding on cancer development may be tumour specific.

4. Genetic diversity, inbreeding and cancer in domestic animals

Strong artificial selection and small founder population size during domestication of animals have had the unintentional effect of diminishing genetic diversity, and resulted in the accumulation of deleterious genetic variants. For example, despite their exceptional phenotypic diversity, both domestic dogs and cats have significantly lower genetic diversity compared with their wild conspecifics, and/or their wild ancestors [63–69]. Apart from additional factors, such as anthropogenically induced longer lifespan and altered environment (e.g. diet and exposure to tobacco smoke), the loss of genetic diversity has been linked to the observed

relatively high cancer prevalence in both cats and dogs [70–73]. Data originating from the histopathology analyses of more than 30 000 malignant neoplastic cases of cats and dogs revelead skin being the most frequently affected tissue in both species, and purebred dogs being more prone to develop neoplasms in general [72]. The latter finding has been further supported by a survey from Italy that showed an almost twofold higher incidence rate of malignant tumours in both purebred cats and dogs compared with mixed breeds [73]. These results are not surpising since selective breeding of dogs led to some breeds descending from a few founders with documented increased risk for certain diseases, such as osteosarcoma, histiocytic sarcoma and squamous cell carcinoma [74]. Recent genomic comparison of healthy golden retrievers with golden retrievers suffering from mast cell tumours (MCT) identified potential causative genetic variations in multiple hyaluronidase genes [75], while an other study demonstarted significant association between germline mutations of BRAC1/2 genes and mammary cancer in English springer spaniels [27].

Lymphoma, the most common haematopoietic cancer of cats, can be initiated by retroviral infections—such as feline leukaemia virus (FeLV) and feline immunodeficiency virus (FIV)—or by additional factors, such as chronic cigarette smoke exposure and chronic inflammation (revewied in [76]). In addition, similar to dogs, breed-specific predisposition for lymphoma with a recessive pattern of inheritance has been observed in Siamese cats and Oriental shorthair cats (revewied in [76]). Selecting phenotypic traits and specific functions may have inadvertently contributed to the increased suceptibility of our feline and canine companions to both infectious and heritable oncogenesis.

5. Genetic diversity, inbreeding and cancer in wildlife

Despite neoplasia being recorded in most metazoans [77], and being common in domesticated animals, it has generally been assumed to be rare in the wild. In our view this is most likely to be due to the fact that cancer prevalence in wildlife is extremely difficult to identify and reports are highly scattered in the scientific literature, and hence challenging to access [18]. In some fish populations cancer prevalence can actually reach 100%, being caused by contagious agents, pollution, inbreeding or the combination of all these factors [18,78]. Moreover, the high cancer prevalence (26%) recorded in some populations of California sea lions (*Zalophus californianus*) has been suggested to be caused by a herpesvirus and/or persistent organic pollutants, but a high prevalence of urogenital carcinoma has been linked to loss of genetic diversity at a single locus, the heparanase 2 gene (HPSE2) [79]. Additionally, two recent studies have observed a link between low genetic diversity and high cancer prevalence (greater than 50%) in Santa Catalina Island foxes (*Urocyon littoralis catalinae*) [80,81] and the South African Cape mountain zebra (*Equus zebra zebra*) [82–84].

6. Genetic diversity, inbreeding and cancer development

Cancer being a multifaceted disease, loss of genetic diversity and inbreeding can impact cancer emergence both directly and indirectly (electronic supplementary material, table S2). Reduction of population size, cultural traditions promoting consanguineous marriages and natural selection purging favouring certain haplotypes contribute to an increased likelihood of a reduction in genetic diversity, which may result in a higher frequency of long stretches of ROH regions [85,86]. ROH harbour disproportionately more deleterious homozygotes than other parts of the genome [85], and the presence of identical pathogenic variants of both alleles have been shown to result in recessive disorders [51,87]. Reduced genetic diversity magnifies the impact of deleterious homozygous mutations [85], and genomic studies suggest that homozygosity of some germline low-penetrance cancer genes act as significant contributing factors to the development of human oesophageal [88], oral [89], lung [90,91], bladder [92], acute lymphocytic leukaemia [93] and breast cancers [61,94,95].

Apart from the direct role of cancer increasing homozygous genomic regions, a general reduction in genetic diversity can also contribute to the development of tumours via infectious agents such as viruses (e.g. [34,38,96]). Loss of genetic diversity at important immune gene loci such as the major histocompatibility complex (MHC), Toll-like receptors (TLRs) and type I and II interferons [12,97], can increase the risk of pathogen infections that either directly or indirectly initiate malignant transformations. For example, genetic variants of interferon genes have not only been associated with pathogen resistance (including carcinogenic helminth infections) [98–102], but have also been shown to influence melanoma progression and survival in humans [103]. Furthermore, hepatitis C virus (HCV), one of the most common chronic blood-borne infections, results in chronic hepatitis in approximately 80% of infected patients, and leads to death in up to 5% of these patients from hepatocellular carcinoma (HCC) or liver cancer [104]. A complex interplay between host genetics, immunology and viral factors has been proposed to determine the outcome of HCV infection [104–107]. Ethnic background, immune gene polymorphism as well as the presence of specific alleles (e.g. interleukin 28B, inhibitory natural killer cell receptors and MHC classes I and II, and variants of interferon (IFN)L3-IFNL4, etc.) have been identified as key elements of HCV clearance, and consequent disease progression [104–107].

Helicobacter pylori infections, an underlying factor of gastric cancer, provide an excellent example of how the host genotype may indirectly contribute to initiation of malignant transformations. *Helicobacter pylori* affects at least 50% of humans worldwide, and hence owns the uncoveted title of being 'the most common single chronic bacterial infection in the world' [108]. The bacteria and their human host have a long evolutionary history; anatomically modern humans were already infected by *H. pylori* prior to leaving Africa and the close association remains ever since [109]. The majority of infected individuals develop no significant disease, but clinical outcomes range from asymptomatic gastritis to peptic ulcer disease and gastric cancer [108]. Risk of infection, prevalence and disease outcomes have been linked to ethnicity, socioeconomic status, and behavioural and genetic variables [110]. One of the most challenging scientific conundrums is to explain individual predisposition to the disease—why some individuals develop serious sequelae of *H. pylori* infections, while others don't [108].

Considerable focus has been placed on understanding bacterial and host genetic factors, and a twin study showed that both host genetic and environmental factors ('rearing environment') influence the acquisition of *H. pylori* infection [111]. Importantly, host proinflammatory genetic makeup appears to have a major contribution to the pathogenesis of gastric cancer. Individuals with proinflammatory genotypes (IL-1B-511*T carriers/IL-1RN*2 homozygotes) have an increased risk for gastric carcinoma. The carriers of the specific genotypes generate heightened inflammatory response to *H. pylori* infection, which ultimately creates a chronically inflamed environment with elevated oxidative/genotoxic stress (due to hypochlorhydria) and eventually initiates a proneoplastic drive [108,112]. Apart from the genetic factors, socioeconomic variables and industrialized environments have also been associated with chronic gastritis, peptic ulcer disease and gastric cancers [110]. While gastric carcinoma is more common in the developing world, the less severe chronic gastritis and peptic ulcers are more frequently reported from the developed world [110]. These might be due to reporting, or due to disease presentation being related to the age of infection (i.e. early childhood infections are postulated to develop over time into pre-malignant changes and eventually gastric carcinoma, in contrast to infection during adulthood, which is more likely to result in ulcer disease [110]). Regional and ethnic variations of *H. pylori* aetiology have been observed and discussed since the links between infection, peptic ulcer disease and gastric adenocarcinomas [113] have been established (reviewed in [114]). More recent studies identify environmental factors such as food preservation and diet as primary determinants of disease outcomes [114]. *Helicobacter pylori* infection is clearly a complex disease with a long coevolutionary history between the host and its parasite, which requires further studies to determine prevention and treatment strategies [115].

Reduced genetic diversity may also increase susceptibility of endangered wildlife species to pathogens and their associated cancers both in captive populations as well as in the wild. For example, the low genetic diversity of the Australian western barred bandicoots (*Perameles bougainville*) (WBB) [116] has been proposed to be one of the potential underlying factors of high prevalence of papillomatosis and carcinomatosis syndrome (up to 61.4% prevalence in captive breeding facilities) [117]. By using microsatellite markers, Smith & Hughes [116] estimated the WBB's genetic diversity to be one of the lowest ever recorded in marsupials, and Woolford *et al*. [117] proposed that the reduced genetic diversity may contribute to the species's susceptibility to (oncogenic) viruses.

Low genetic diversity at microsatellite loci and lack of variations in mitochondrial DNA (mtDNA) indicate that another endangered species, the snow leopard (*Uncia uncia*), has undergone a genetic bottleneck approximately 8000 years ago [118]. Although no information on cancer prevalence is available from wild snow leopards, a survey by Joslin *et al*. [119] revealed that 9% of mortalities in 66 institutions involved with the Snow Leopard Species Survival Plan (SSP) was due to squamous cell carcinomas (SCC). Papillomas with viral aetiology have been identified as precursors to SCC in felines, including cats and snow leopards [119]. Low genetic diversity of snow leopards may therefore potentially be a contributing factor to viral infections and ultimately the development of SCCs observed in captivity [119]. Comparative genetics of sarcoid tumour-affected and non-affected mountain zebra (*Equus zebra*) populations revealed that tumour-affected populations had higher homozygosity and relatedness, and lower gene diversity and polymorphism, at 16 microsatellite loci compared with healthy populations (although the levels were not significant ($p = 0.05$) [83]). A study of 371 stranded California sea lions (*Zalophus californianus*) also found a clear association between carcinoma incidence and close genetic relatedness when analysing 11 microsatellite markers [120]. Furthermore, as discussed above, inbreeding depression (estimated based on microsatellite multilocus heterozygosity) and homozygosity of the heparanase 2 gene (HPSE2) locus have been identified as predictors of urogenital carcinoma in sea lions [121]. Finally, the high cancer prevalence observed in the highly inbred Santa Catalina Island foxes [80,81] also strongly suggest an association between loss of genetic diversity and cancer development in wildlife (electronic supplementary material, table S2).

7. Conclusion

As mentioned above, maintenance of genetic diversity is fundamental for adaptive capacities and provides organisms with an ability to successfully respond to challenges caused by parasites/pathogens [122], habitat fragmentation [3,123] and global climate change [124,125]. In contrast to parasites and pathogens cancer, has so far been largely overlooked as a significant determinant of wildlife fitness. The present review, however, suggests that low genetic diversity and inbreeding may elevate cancer development in wildlife, further imperilling the long-term survival of the numerous species presently suffering from low genetic diversity. Our review hence demonstrates the need to consider the effects of cancer in conservation biology.

The results originating from human studies indicate that the effects of genetic diversity and inbreeding on the development of a complex disease such as cancer may be tumour specific. Importantly, by reducing immune function, and thereby increasing the vulnerability to cancer causing parasite/pathogen infections, overall loss of genetic diversity and inbreeding may therefore constitute a significant underpinning of cancer development in humans as well as in other organisms [126,127]. Finally, the link between low genetic diversity/inbreeding and cancer may be just as arduous as the disease itself, and further studies, including genome-wide association studies on both domestic and wild animals, population genetic and genomic analyses of species affected by high prevalence of cancer, and epidemiological studies likening infectious diseases to cancer prevalence, are therefore urgently needed to decipher the underpinnings of such associations.

Ethics. As the manuscript is a review of published work, the study did not require any ethics approval.

Data accessibility. The manuscript is a review of published work and the data used can therefore be accessed from the referred publications.

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