The guardians of inherited oncogenic vulnerabilities

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Similar to seemingly maladaptive genes in general, the persistence of inherited cancer-causing mutant alleles in populations remains a challenging question for evolutionary biologists. In addition to traditional explanations such as senescence or antagonistic pleiotropy, here we put forward a new hypothesis to explain the retention of oncogenic mutations. We propose that although natural defenses evolve to prevent neoplasm formation and progression thus increasing organismal fitness, they also conceal the effects of cancer-causing mutant alleles on fitness and concomitantly protect inherited ones from purging by purifying selection. We also argue for the importance of the ecological contexts experienced by individuals and/or species. These contexts determine the locally predominant fitness-reducing risks, and hence can aid the prediction of how natural selection will influence cancer outcomes.

KEY WORDS: Cancer, natural defenses, purifying selection, somatic mutations.

The "war on cancer" commenced more than half a billion years ago with the evolution of multicellular organisms (Nunney 2013). Indeed, at the dawn of Metazoans, cancer suppression represented a significant selection advantage to those individuals who were able to control unregulated cell division over those who were not

(Aktipis and Nesse 2013). Although most cancer-causing mutant alleles are somatically acquired during a lifetime (thereafter SCMA for somatic cancer-causing mutant allele), certain cancers are caused by congenital mutations, that is, germinally inherited cancer-causing mutant alleles (ICMA; Table 1). Why has evolution not done a "better job" at eliminating them? In spite of several studies on the topic, it is still not clear whether most ICMA, like
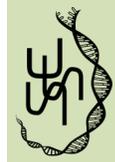
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Table 1. The three types of genes that are known to play a role in cancer susceptibility.

Gene types	Mutation types	Genes	Example of cancer susceptibility (syndrome or main tumor type)	References
Proto-oncogenes	Inherited	Ret XMRK	MEN II Melanoma (fish)	Huang et al. (2000), Fernandez and Morris (2008), Fernandez and Bowser (2010)
	Acquired	K Ras HER2 Braf EGFR	Colon Breast Melanoma Lung	Giampuzzi et al. (2001), Paez et al. (2004), Geyer et al. (2006), Thomas et al. (2007)
Tumor suppressor genes	Inherited	APC P53 Rb PTEN	Familial adenomatous polyposis Li Fraumeni Retinoblastoma Breast	Bandara and La Thangue (1991), Lal and Gallinger (2000), Nochols et al. (2001), Zhou et al. (2007)
	Acquired	P53 APC PTEN	Breast, lung, ovary, colon . . . Colorectal Prostate	Fodde et al. (2001), Nochols et al. (2001), Wang et al. (2003)
DNA repair genes	Inherited	XPA, XPB, XPC, XPD BRCA1, BRCA2 hMLH1, hMSH2, hMSH6 ATM PalB2	Xeroderma pigmentosum Breast, ovary Colon, uterus Breast Breast	Grady et al. (2001), Antoniou et al. (2003), Renwick et al. (2006), Tischkowitz et al. (2007), Feltes and Bonatto (2014)
	Acquired	hMLH1, hMSH2 BRCA1, BRCA2	Colon Ovary	Grady et al. (2001), King et al. (2003)

A proto-oncogene is a normal gene that can become an oncogene due to mutations or increased expression. When this happens, the cell grows out of control, which can lead to cancer. Tumor suppressor genes are normal genes that slow down cell division, repair DNA mistakes, or tell cells when to die (a process known as apoptosis or programed cell death). When tumor suppressor genes do not work properly, cells can grow out of control, which can lead to cancer. DNA repair genes are genes linked to the recognition and repair of damaged DNA. Defects in these genes enable cancer cells to accumulate genomic alterations that contribute to their aggressive phenotype (see http://www.cancer.org/acs/groups/cid/documents/webcontent/002550-pdf.pdf).

any rare disadvantageous mutation, are maintained at levels predicted by mutation–selection balance (Nunney 2003) and/or are maintained by selection (potentially at a higher frequency than that expected; see Bodmer 2006; Risch et al. 2006). Recent advances in evolutionary medicine have highlighted that ICMA, similar to other maladaptive mutations, can in fact be maintained in populations through various processes. For instance, it has been suggested that natural selection is unlikely to act on ICMA when their detrimental effects occur after the reproductive life (Nunney 2003; Frank 2004). In addition, antagonistic pleiotropy (the expression of a gene resulting in multiple competing effects) might be important if late acting oncogenic mutations, including inherited ones, have beneficial effects at younger ages (Boddy et al.

2015). For example, in *Xiphophorus* fish, melanoma-promoting oncogene alleles are associated with larger body size and aggressiveness and confer early life advantages in male–male competition and female mate choice (see Fernandez and Morris 2008; Fernandez and Bowser 2010). Women with *BRCA1/2* mutations have a significantly higher lifetime risk of developing breast or ovarian cancer, but elevated fertility of mutation carriers indicates that these women are also more fecund despite their elevated postreproductive mortality risks (Smith et al. 2012). It has also been suggested that the maintenance of ICMA can be a by-product of genomic conflict ("selfish" genes: Kleene 2005) and/or antagonistic coevolution (e.g., maternal–fetal interactions; Summers and Crespi 2005). Also, when ICMA are rare, their purge by

natural selection is slow and/or difficult, and this may explain why they persist in natural populations. Finally, ICMA can be present due to being caused by recent germline mutations for which insufficient time has passed to remove them from gene pools.

In this article, we aim to highlight the paradoxical role of natural protective mechanisms that not only guard organisms from cancer, but on the other hand, also protect ICMA from being counterselected by alleviating their detrimental effect on fitness. Additionally, we argue that ecological contexts experienced by individuals and/or species are crucial to be considered because they could potentially determine locally occurring fitness-reducing risk factors (e.g., somatic diseases related to aging, parasite infections, predation, or adverse environmental conditions), and hence also influence the intensity with which natural selection will be acting on both tumor burden and ICMA.

Natural Cancer Prevention Mechanisms Potentially Protecting ICMA

Natural selection has favored a variety of heritable adaptations that either prevent the formation of neoplasms or control their growth and progression (Nunney 1999). The defense mechanisms against cancer therefore fall into two conceptually different components: (1) the ability to eliminate tumors and (2) the ability to limit their proliferative potential (DeGregori 2011). Although both somatic defense (how cells avoid becoming malignant) and broader intrinsic defenses (cancer avoidance at the level of tissues and the whole organism) have the potential to suppress cancer and the associated detrimental consequences, they do not however eliminate, nor cure SCMA and ICMA. Because of the typically slow progression of malignancy, evolution's solutions against cancer are rather similar to those used in therapeutic strategies: both targeting symptoms rather than sources, and therefore rendering selection "myopic" to the mutations responsible for the disease. Recent studies based on autopsies of individuals who died of unrelated causes confirm that during our lifetime most of us steadily accumulate benign in situ tumors that do not necessarily lead to the development of malignant cancers (Folkman and Kalluri 2004). This supports the idea that evolutionary processes have been acting to suppress cancers occurring in prereproductive life by preventing tumors from becoming fatal, rather than by eliminating SCMA and ICMA.

Natural selection is not always "myopic" to germinally inherited deleterious mutations. For instance Duchenne muscular dystrophy is an X-linked muscular dystrophy for which there is currently no treatment to prevent or arrest the progressive muscle weakness. It affects one in 3500 male live births and patients rarely survive beyond their teens as the condition also causes progressive respiratory muscle weakness and respiratory failure (Eagle et al.

2002). Not surprisingly, because the disease sufferers generally do not survive to reproductive age, selective purging takes place and the prevalence of Duchenne muscular dystrophy remains low in human populations. Other examples could include Fanconi anemia (Kutler et al. 2003; Meetei et al. 2003), Bloom syndrome (Hickson et al. 2004) and ataxia telangiectasia (Domazet-Loso and Tautz 2010), diseases which all affect the sufferers prior to reaching reproductive age.

The reasons why natural selection tends to eliminate disease-causing genes in certain situations (e.g., Duchenne muscular dystrophy) and instead favors compensatory mechanisms that hide their deleterious effects in other instances (e.g., cancer) is explained by the evolutionary history of the pathology. Rare deleterious alleles do not promote compensation; however, common alleles that are initially neutral (or even advantageous) that become disadvantageous due to changing conditions may result in compensatory evolution.

Contrary to many genetic disorders, uncontrolled cell growth is a pathological manifestation that is concurrent with the dawn of multicellularity, it can even be viewed as an ancestral challenge for building viable multicellular organisms (Nunney 1999). Indeed cancer has been with us ever since multicellular organisms evolved. The emergence of proto-oncogenes facilitated cell cooperation by coordination, while the evolution of tumor suppressor genes kept tight control on cheater cells, contributing fundamentally to the establishment of stable multicellularity (Domazet-Loso and Tautz 2010). However, proper operation of multicellular organisms requires a constant balancing of such genes and precise regulation of overall cell proliferation levels and cell numbers (Leroi et al. 2003).

The evolution of ICMA is constrained by the effects on their bearers. If ICMA cause cancer while their bearers are still reproductive, they may impair the reproduction of their carriers, and therefore impair their own transmission. But if their oncogenic effect is delayed until after reproduction has ceased due to other causes (e.g., senescence, death, or diseases), then they have no effect on the individual's fitness, and can be passed on to the offspring. As tumor suppressor genes slow down cancer progression, but are progressively inactivated by somatic mutations, the more effective they are early in life, the later cancer will arise in the organism. Therefore, ICMA can be further passed on when compensatory mechanisms (such as tumor suppressor genes, immune system) are able to mask their oncogenic effects until a postreproductive period.

The concealment of oncogenic phenotypes likely explains why natural selection did not *only* systematically eliminate individuals with alleles causing uncontrolled cell proliferation (both SCMA and ICMA) prior to the end of reproduction, but also favored individuals that were able to keep developing malignancies under control and below the detrimental thresholds. Cancers

that are controlled to grow slowly enough not to endanger hosts within the time frame when natural selection can be effective, are not per se decreasing fitness. Individuals who could tolerate the early stages of late-acting cancers without suffering significant fitness reduction were then likely to be favored by selection over those unable to activate compensatory mechanisms.

ICMA (at least highly penetrant ones) are actually a direct cause of only a small proportion of cancers. Because most cancers instead originate from SCMA, it could be predicted that cancer preventing selective pressures were/are mostly directed toward tumor growth. This may be the reason why natural selection presumably favored compensatory mechanisms (at least against those oncogenic mutations that were not purged during the course of evolution). If this process has, from a human individual health perspective, the desirable effect to prevent cancer progression due to SCMA and ICMA, it will also have the undesirable effect of protecting ICMA, that is, the mutation–selection balance shifts so that a higher frequency of oncogenic alleles results (Nunney 2003). If this reasoning is correct, other genetic diseases initiated by both acquired and inherited mutations could face the same challenge: as soon as acquired mutations induce the disease with sufficient frequency, selection will favor compensatory mechanisms that in return protect abnormal genes/alleles from being eliminated across generations.

Therapies against malignancies (as for other pathologies, e.g., Type I Diabetes) act in the same way because even those targeting mutated genes do not eliminate nor cure ICMA. Thus, ICMA responsible for cancer early in life, instead of being counterselected, will rather become neutral if therapies are efficient. It is also interesting to consider treatments targeting symptoms rather than sources, that self-medication against cancer in animals (see Vittecoq et al. 2015) also renders selection "myopic" to the genes responsible for the disease. The existence of self-medication could also help to understand the persistence across generations of ICMA in wildlife genomes.

Frequency and Diversity of Intrinsic and Extrinsic Fitness Limiting Factors

Various internal and/or external factors influence the reproductive life span of individuals and species in natural environments (Thomas et al. 2004). As recently highlighted by Roche et al. (2012) and Vittecoq et al. (2013), cancer, depending on species/populations and/or their habitat, is a more or less likely cause of death. For instance, small rodents in nature may succumb to cancer, but only if they do not first die from any one of numerous other causes, such as predators, infectious diseases, environmental causes (e.g., floods, extreme temperatures), etc. For those species, selection on both oncogenic mutation elimination and on genes responsible for natural defenses against tumor emer-

gence/growth is expected to be strong on a shorter period of the life. Natural selection leads to different investments in longevity (and the avoidance of cancer and other diseases) to the extent that maximizes reproductive success. Thus, selection is expected to act to lower the incidence of cancer (and other manifestations of aging) only up to the age when most of these animals ceased reproduction or died from other causes (Hamilton 1966). In accordance with this statement, when in protective captive conditions species such as wild mice (*Mus musculus*) have elevated incidences of cancer (46%; Andervont and Dunn 1962). Thus, with respect to the predominating factors limiting fitness, different predictions can be made on how natural selection should adjust the levels of cancer resistance: either through defenses against tumor development and progression or through selecting against ICMA. Somatic diseases such as cancer are likely to be an important source of fitness variation between individuals mainly in stable, well-resourced, environments with low pathogen loads and low predation rates. Selection pressures to prevent the formation and uncontrolled growth of tumors prior to old age should then be the highest in those habitats. It is however unclear if this will lead to more and more sophisticated defenses against cancer or to direct selection against ICMA, or both. There are several animal species which potentially present examples for this scenario: for instance elephants (*Loxodonta africana)*, whose large size makes them nearly invulnerable to predators as adults (Shoshani and Eisenberg 1982) possess 20 copies of the tumor suppressor TP53 gene (Belyi et al. 2010). Although, the increased number of TP53 gene copies in elephants (compared to other mammals) has been attributed to their elevated risk of cancer resulting from their body size, their increased longevity has probably been an even more important driver of increased cancer suppression. It is therefore probable that these genetic defenses against cancer have, at least partially, evolved because of the selective advantage conferred by resistance to somatic diseases in this animal with low predation risk (and hence extended life span). Other organisms, supporting the idea that ecological context rather than only body size extends life span, are long-lived rodents, that is, the naked mole rat (*Heterocephalus glaber*) and the (unrelated) blind mole rat (*Spalax* spp., Gorbunova et al. 2014). Naked mole rats have no known cancer, even in captivity (Kim et al. 2011). This rodent lives underground, digging intricate tunnel networks in which they have virtually no chance of falling to predation, and has evolved some unique anticancer defenses, including enhanced cell contact inhibition. The blind mole rat has evolved a unique trade-off, boosting the immune system's necrotic defense, by expanding and duplicating immune genes to attack cancer cells while apparently weakening the key mediators of the normal cell-shutdown defense, the tumor suppressor TP53 (Fang et al. 2014).

Thus, in the light of the ideas developed above, a crucial question is: Are there any ecological contexts that could favor

the purge of ICMA? Basically, our hypothesis suggests that perfect tumor suppression (which theoretically removes the effects of ICMA) is equivalent to elimination of ICMA from a population (which is of course impossible because of mutation). Because cancerous lesions contained by compensatory mechanisms generally trigger little to no fitness reduction, abolition of a postreproductive period could potentially contribute to the increased purging of ICMA. If individuals suffer from a cancer without impact on their lifetime reproductive output, that is, fitness, then ICMA do not cause any fitness reduction and are unlikely to be selected against. However, if postponed breeding and postreproductive care significantly increase the fitness of the organism, then even ICMA with late oncogenic expression will be detrimental to fitness and selected against. A converse strategy could consist of constraining selection on compensatory mechanisms. Indeed, compensatory mechanisms are associated with antagonistic effects. Notably, tumor suppression and anticancer immunity can be associated with severe trade-offs with reproduction, such as senescence (Campisi 2001), and they can even promote carcinogenesis when unregulated (Coussens and Werb 2002; Coppé et al. 2010). Oncogenic effects of ICMA could therefore be unmasked by contexts where compensatory mechanisms are no longer beneficial. Moreover, for ICMA to cause fitness reduction, they must cause death or impair reproduction before other factors. Thus, a mandatory condition of ICMA elimination is that the associated cancer is a significant cause of mortality before or during the reproductive period. This requires driving the multigenic mutation–selection equilibrium for the set of genes responsible for a given cancer to near zero (Nunney 2003). Therefore, future research should explore how the frequency of ICMA could depend on other fitness reduction processes (such as predation and diseases, accidents, and the somatic mutation rate) possibly by focusing on a limited range of wildlife species in different ecosystems.

Concluding Remarks

More empirical data are needed to explore the extent to which ICMA have higher frequencies in natural populations than expected by mutation–selection balance. Mutation–selection balance predicts a link between the frequency of ICMA and their deleterious effects. Indeed, an important assumption involved in our hypothesis is that ICMA effects on fitness are not related to their frequency. Because some equivalence could exist between having few highly deleterious alleles or several less deleterious ones, this issue should be clarified with empirical data. Because large and/or long-lived organisms have evolved more tumor suppression mechanisms (since cancer risk increases with size/age), according to our hypothesis, it is expected that the frequency of ICMA is higher in those species. We encourage further research to empirically test this prediction, for example, in species such as

naked mole rats or elephants. Finally, a promising research direction will be to explore whether human populations experiencing a historically higher risk of cancer due to ecological conditions would have additional tumor suppression mechanisms and higher ICMA frequencies.

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