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► **To cite this version:**

Georgina Bramwell, James Degregori, Frédéric Thomas, Beata Ujvari. Transmissible cancers, the genomes that do not melt down. *Evolution - International Journal of Organic Evolution*, 2024, qpae063. 10.1093/evolut/qpae063 . hal-04618355

**HAL Id: hal-04618355**

**<https://hal.science/hal-04618355>**

Submitted on 20 Jun 2024

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# Transmissible cancers, the genomes that do not melt down

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## Abstract

Evolutionary theory predicts that the accumulation of deleterious mutations in asexually reproducing organisms should lead to genomic decay. Clonally reproducing cell lines, i.e., transmissible cancers, when cells are transmitted as allografts/xenografts, break these rules and survive for centuries and millennia. The currently known 11 transmissible cancer lineages occur in dogs (canine venereal tumour disease), in Tasmanian devils (devil facial tumor diseases, DFT1 and DFT2), and in bivalves (bivalve transmissible neoplasia). Despite the mutation loads of these cell lines being much higher than observed in human cancers, they have not been eliminated in space and time. Here, we provide potential explanations for how these fascinating cell lines may have overcome the fitness decline due to the progressive accumulation of deleterious mutations and propose that the high mutation load may carry an indirect positive fitness outcome. We offer ideas on how these host–pathogen systems could be used to answer outstanding questions in evolutionary biology. The recent studies on the evolution of these clonal pathogens reveal key mechanistic insight into transmissible cancer genomes, information that is essential for future studies investigating how these contagious cancer cell lines can repeatedly evade immune recognition, evolve, and survive in the landscape of highly diverse hosts.

**Keywords:** Muller's ratchet, mutation load, coevolution, competition, cooperation

Evolutionary theory predicts that the accumulation of deleterious mutations in asexually reproducing organisms should lead to Muller's ratchet (Muller, 1964) and the meltdown of genomes (Smith & Maynard-Smith, 1978). Nevertheless, some clonally reproducing cell lines, i.e., transmissible cancers, can persist for centuries and even for millennia (Baez-Ortega et al., 2019; Bruzos et al., 2023; Hart et al., 2023; Stammnitz et al., 2018). Although these fascinating cell lines are perceived to be rare (but see Dujon et al., 2021) they may hold the keys to our understanding of fundamental evolutionary processes such as the emergence of sexual reproduction (Thomas et al., 2019), the immune system (Ujvari et al., 2016), and overcoming genomic decay in asexual organisms (Dujon et al., 2020).

There are currently 11 different lineages of transmissible cancers, one in dogs (canine venereal tumour disease [CTVT] [Baez-Ortega et al., 2019; Murgia et al., 2006; Rebbeck et al., 2009]), two in Tasmanian devils (*Sarcophilus harrisi*), devil facial tumor diseases (DFTDs), DFT1 (Pearse & Swift, 2006) and DFT2 (Pye et al., 2016), and eight bivalve transmissible neoplasia (BTN) in nine bivalve species (Hammel et al., 2022; Metzger et al., 2015, 2016; Michnowska et al., 2022; Skazina et al., 2022; Yonemitsu et al., 2019). CTVT is of histocytic origin (Olusola et al., 2018), and DFT1 and DFT2 are derived from Schwann cells in different differentiation states (Owen et al., 2021). BTNs are cancers of the hemolymphatic system (the circulatory system of bivalves), and they have derived

from either hemic progenitor cells or somatic hemocytes (Bruzos et al., 2023; Hart et al., 2023).

These clonal cell lines are transmitted as allografts and/or xenografts (BTN) via direct contact (via biting in devils and copulation in dogs) or indirectly by releasing and filter-feeding the neoplastic cells from seawater by bivalves. Transmissible cancers have been able to breakdown geographic (CTVT [Baez-Ortega et al., 2019]) and species (BTN [Garcia-Souto et al., 2022; Metzger et al., 2016]) barriers as they spread across continents.

The mammalian cancer lineages appear to be the youngest and oldest, with the Tasmanian devil cancers estimated to have emerged in the 1980s (DFT1) and 2010s (DFT2) (Stammnitz et al., 2023) and CTVT estimated to have appeared between 4,000 and 8,500 years ago (Baez-Ortega et al., 2019). The recent genome sequencing of two BTN lineages revealed them to be centenarians, MarBTN (from soft-shell clam *Mya arenaria*) being at least 200 years old (Hart et al., 2023) and CedBTN in the common cockle (*Cerastoderma edule*) proposed to have emerged centuries or millennia ago (Bruzos et al., 2023).

Not surprisingly, being neoplastic, all known transmissible cancer cell lineages possess chromosomal abnormalities, polyploidy, and high mutation rates (approximated with substitution rates like in human cancers [Loeb, 2016]) in their genomes. Interestingly, however, the mutation density of MarBTN is between those observed in the mammalian

Received November 5, 2023; revisions received April 8, 2024; accepted April 19, 2024

Associate Editor: Kirk Lohmueller; Handling Editor: Jason Wolf

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transmissible cancer lineages: 440–450 mutations per Mb for the minimum two-hundred-year-old MarBTN lineages, between <1.3 and 3.1 mutations per Mb for the <40-year-old DFTD lineages (Stammnitz et al., 2018), and >850 mutations per Mb (from exome data) for the >4,000-year-old CTVT (Baez-Ortega et al., 2019) (no data was provided for CedBTN). Apart from the DFTDs, these mutation loads are much higher than observed in human cancers, where mutation frequency ranges between approximately 1.5 and 150 mutations per Mb (Chalmers et al., 2017; Kandoth et al., 2013). Close to 2 million mutations (1.9 million) have been estimated in CTVT (Murchison et al., 2014), and 15,000–17,000 somatic base substitution mutations were observed in DFTDs (Murchison et al., 2012; Storfer et al., 2018). Hart et al. (2023) identified 10.7 million single nucleotide variants shared by all MarBTN studied, of which 8.1 million most likely have originated in the founder clam. Accordingly, we estimate that 2.6 million single nucleotide variants may have occurred in MarBTN since it emerged from the founder an average of 400 years ago. These numbers, particularly in CTVT and MarBTN are much higher than those observed in human cancer cells, where the number of observed mutations varies between tumor types: 500 in acute myelogenous leukemia to 100,000 in melanomas (reviewed in [Loeb, 2016]). By a rough calculation, these mutation burdens equate to rates of 500/year in CTVT and ~6,500/year in MarBTN. In a recent study, Stammnitz et al. (2023) have used Bayesian phylogenetic approach to calculate substitutions and have shown a mutation rate of 215.5 in DFT1 and 516.7 in DFT2. The latter study also identified a hypermutator clade that carries six more substitutions and 10 times more indels than other DFT1 investigated.

Although it is difficult to compare mutation rates among normal and tumor cells as they grow and age at different rates (Lengauer et al., 1998), these values are higher than those observed in human and dog somatic cells: 47.17 and 229.46 somatic substitutions per genome per year, respectively (Abascal et al., 2021; Cagan et al., 2022). Estimating a rate of mutation accumulation per year, MarBTN's mutation rate appears to be 10 times higher than that of DFTD, CTVT, and nonmutator human tumors (assuming ~2 mutations/Mb and ~10 years for tumor development), recognizing that “ages” of these cancers are based on estimates. Based on the cancer mutator phenotype theory, put forward 50 years ago by Loeb et al. (1974), even a twofold increase in mutation accumulation can have a significant impact on disease progression and host survival (Loeb, 2016).

Knowing that high mutation load can pose a threat to the long-term fitness of any living entities (e.g., lethal mutagenesis, see Anciaux et al., 2019 and references therein), including transmissible cancers (see, for example, the case of CTVT, Baez-Ortega et al., 2019), transmissible cancers such as MarBTN, with such high mutation rate and burden, should have been eliminated in space and time (Ujvari et al., 2016). Over half a century ago, Muller proposed that the progressive accumulation of deleterious mutations in asexual organisms would lead to their inevitable fitness decline (Muller, 1964), known as Muller's ratchet (Gabriel et al., 1993; Lynch & Gabriel, 1990; Lynch et al., 1993). Nevertheless, the BTN and CTVT lineages appear to have existed for centuries, even millennia, despite the continuous accumulation of mutations due to their asexuality.

In the early 1970s, Loeb et al. (1974) put forward the possibility of causality between increased rate of errors in DNA synthesis and malignancy, and 30 years later, they provided evidence for a 200-fold higher rate of point mutations in cancer cells compared to normal cells (Bielas & Loeb, 2005). Using an elegant approach, random mutation capture, the authors showed that as a consequence of the elevated mutation rate in human cancers, they harbor larger numbers of random point mutations and such a higher mutation load (Bielas & Loeb, 2005). Here, we extend the observations in human cancers and propose potential explanations for the persistence of transmissible cancers. We start with the idea that mutations accrued by these asexual cell lines are still subjected to purifying selection, with the elimination of cells with mutations decreasing fitness and large population sizes (cell numbers) buffering the effects of Muller's ratchet. In addition, given that a substantial portion of the genome is likely nonessential in transmissible cancers, mutations can readily accumulate in these regions without a substantial decrease in the cell's fitness. Furthermore, the observed chromosome duplications in these cell lines (Hart et al., 2023; Stammnitz et al., 2023) may have rescued cells from the potentially lethal mutations in the affected regions, as seen in human cancers (reviewed by Merlo et al., 2010). Hart et al. (2023) proposed that the two MarBTN sublineages arrived at polyploidy largely via independent duplication events, further supporting the genomic rescue theory by chromosome expansions.

Alternatively, here we propose that having a mutator phenotype (originally postulated as excessive accumulation of point mutations in nonrepetitive sequences (Loeb et al., 1974), now extended to microsatellite, chromosomal and point mutation instability (Klein, 2006)) may actually carry an indirect positive fitness outcome for transmissible cancer cell lines like it has been proposed for human cancers (Loeb, 2016; Loeb et al., 1974) and as it has been observed in other organisms. For example, in their elegant experiments, Wiser et al. (2013) and McDonald et al. (2012) propagated mutator strains of *Escherichia coli* and *Saccharomyces cerevisiae* for thousands of generations without loss of fitness. Direct competition between strains with different mutation rates may be behind the maintenance of high mutation rates, as proposed by Good and Desai (2016). High mutation rate in novel and fluctuating environments, as well as in populations of asexual species subjected to strong cyclical competition, has also been found to be advantageous by increasing the frequency of adaptive phenotypes in both mathematical and experimental studies (Anciaux et al., 2019; Rosenbloom & Allen, 2014; Rozhok et al., 2021). Host–pathogen coevolution and competition between different populations can present cyclical competition and drive the evolution of mutation rates (Rosenbloom & Allen, 2014).

Based on the theories outlined above, we propose that cocirculation of transmissible cancer cell lineages in and between hosts and being exposed to harsh environments may have created conditions in which high mutation rates are advantageous. Specifically, bivalves being filter feeders and inhabiting particularly exposed environments, as well as the spread of BTN cells via seawater (Giersch et al., 2022), may deliver consistently fluctuating environments and rapidly changing selection pressure that are necessary for these mutator BTNs to persist. Indeed, structural rearrangements and copy number alterations are pervasive in both BTN lineages, which can have even more dramatic phenotypic consequences. BTN

genomes appear to be more unstable than the mammalian cancer lineages, with the potential to rapidly mutate (and thus evolve quickly), facilitating their long-term survival (Bruzos et al., 2023; Hart et al., 2023). In contrast to BTN, the mammalian transmissible cancer cells are transmitted directly by the host, and as such, they might not experience such challenging conditions that facilitate the maintenance of high mutators, although both DFTD and CTVT must repeatedly overcome host immune defenses. Coinfection of the same host with two different cancer lineages has been observed in both bivalves (Bruzos et al., 2023) and in devils (James et al., 2019; Stammnitz et al., 2023), and such, competition between the cancer lineages may also contribute to the perfect conditions to maintain high mutation rates.

While it is well-established that dynamically changing environments, especially adverse ones, present as a positive selection for an elevated mutation rate (Metzgar & Wills, 2000), the corollary of this observation is that a high mutation rate in a stable environment tends to lead to the generation of diversity that is often poorly adapted. Indeed, Lynch (2010) has argued that selection favors a lower mutation rate to the extent dictated by the population size imposed drift barrier. From an evolutionary point of view, the key is the alignment between the instability/adversity of the environment and the mutation rate. Also important to consider that while high mutation rates can offer short-term benefits, they can also lead to burdens later in life (Stefania et al., 2023). With cancer cells, it is the same: the mutation rate is adjusted, it is optimal and not maximal, which avoids maladaptation or even genetic disaster. On the other hand, if the environment changes drastically and becomes adverse, for example, as a result of therapy (or changing water temperature and salinity in the case of BTN, as described above), then cancer cells may have an advantage if they suddenly increase their mutation rate (Russo et al., 2019), just like the bacteria mentioned above. Thus, the problem is complex and diversified, and there is no unique rule that can be applied to all organisms.

As genetic mutations create new alleles and, therefore, new traits, a high mutation rate may allow a species to explore a wide range of potential traits, increasing the likelihood of access to adaptive characteristics. This might be even more relevant for asexually reproducing diploid lineages, where Meselson predicts homologous chromosomes to accumulate mutations at different rates and, such, evolve independently from each other (Birky, 1996). Given the potential importance of these traits to the lifestyle of transmissible cancer, we suggest that natural selection is likely to favor their maintenance, resulting in consistent traits in transmissible cancers. Also, not only must transmissible cancers overcome the individual defenses of new hosts (of the same species or not) each time they are transmitted, but as transmissible cancers evolve as parasites *sensu stricto* (described by Burioli et al. (2021)), they are engaged in an ongoing evolutionary arms race with their hosts (Red Queen hypothesis [Van Valen, 1973]). Explicitly, oncogenesis is often compared to a speciation process in which somatic cells disassociate from other cells and embark on a distinct evolutionary trajectory (Capp & Thomas, 2020; Gatenby et al., 2020; Vincent, 2011). This is even more relevant for transmissible cancers, whose evolutionary trajectory continues after the death of the host (Dujon et al., 2020). BTN has even been shown to overcome host defenses by jumping species and assuming a parasitic role in a new host (Garcia-Souto et al., 2022; Metzger et al., 2016).

Transmissible cells, therefore, are under the influence of new selective pressures (as they move between hosts and even across species) to pursue their parasitic lifestyle (e.g., Burioli et al., 2021). Consequently, akin to microparasites, transmissible cancers also undergo coevolution both in real-time with the host immune systems and on evolutionary timescales with their hosts (Dujon et al., 2020; Russell et al., 2018).

Cancers, in general, appeared at the dawn of multicellularity (Domazet-Loso & Tautz, 2010), and, as a result, metazoan hosts have had long evolutionary times to develop effective anticancer defenses against them. As far as we know, today's transmissible cancers are, on the contrary, life forms that have more recently emerged than their host. These cell lines have originated via oncogenesis and survived via an internal speciation process that is more recent in relation to the appearance of the host species themselves. Therefore, they must overcome a form of evolutionary lag in order to survive in the presence of the host's highly effective defenses. To compensate for this "Red Queen disadvantage," we ask the question, could transmissible cancers benefit from a very high mutation rate to speed up evolution and/or to bypass the host's defenses? A parasite that has only recently appeared in relation to its host, which has evolved to cope with parasitic exploitation, in one way or another, must compensate for its lack of adaptation to successfully exploit the host and survive over time. We propose that this evolutionary disadvantage in the "Red Queen race" could be compensated for by the high mutation rate, which generates a substrate on which selection can favor winning combinations despite the inherent disadvantages that come with it.

These clonally replicating cancer cell lines also contain another asexually reproducing organelle that is known to succumb to Muller's ratchet, the mitochondrion. Mitochondrial DNA capture and rescue from genomic decay has been detected in CedBTN (Bruzos et al., 2023), in another BTN affecting the *Mytilus* species complex (Yonemitsu et al., 2019) and in CTVT, with reoccurring horizontal transfer, and positive selection on a particular haplotype, in the latter (Strakova et al., 2016, 2020). The possibility of mitochondrial genome rescue via periodically acquiring and recombining with host mtDNA, as shown in CTVT by Strakova et al. (2016), while the nuclear genome remains riddled with mutations, poses a fascinating question. In somatic cells, asexually reproducing mitochondria coexist with nuclear genomes that have originated from recombined germlines that have potentially been purged of many deleterious mutations. Thus, mitochondrial and nuclear genomes have very different evolutionary trajectories in nonmalignant/nontransmissible cells—so how do these different propensities to "refresh" the mitochondrial and nuclear genomes impact the evolution and persistence of transmissible cancers?

Chou and Leu (2015) proposed that in sexual organisms, selfish mtDNA with a higher proliferation rate can outcompete the inherited mtDNA but also potentially compromise host fitness if it carries deleterious mutations. When the frequency of selfish mtDNA increases in the population, compensating mutations may occur in the nuclear genome to offset the negative fitness effects of the selfish mtDNA, resulting in accelerated cytonuclear coevolution, where the nuclear genome has to repeatedly evolve in order to maintain fitness, a Red Queen effect (Chou & Leu, 2015).

We expand on Chou and Leu's (2015) ideas and propose that the replacement of partial or full mitochondrial

genomes may unbalance the cooperation between mitochondrial and nuclear genomes in transmissible cancer cells, and such contributes to the high mutation rate and burden observed in them. Strakova et al. (2020) recently showed that one canine mtDNA haplotype repeatedly infiltrates CTVT cells and replaces incumbent CTVT haplotypes. In addition, horizontal mtDNA transfer has also been observed in bivalve transmissible cancers (Bruzos et al., 2023; Yonemitsu et al., 2019). The success of the given CTVT mitochondrial haplotype infiltrating CTVT cells (as shown by Strakova et al. (2020)) may lay in its higher proliferation rate and its capacity to increase its frequency in CTVT cells, and such it may be a selfish mtDNA. In addition, horizontal mtDNA transfer can cause cytonuclear incompatibility, and such, changes in the nuclear genome need to be pursued due to the inseparable interactions between these two genomes.

Would the high mutation rate and selfish behavior of mitochondria help drive the high mutation rates observed in the nuclear genomes of transmissible cancers to maintain fitness despite mitochondrial change? Would further evolutionary scenario emerge where only the mtDNA can be rescued via recombination or where deleterious mutations are also removed from the nuclear genome via horizontal transfer aided by extracellular vesicles (Valcz et al., 2022) and/or by spontaneous fusions, as seen in human cancer cells (Miroshnychenko et al., 2021)? While conventional views hold that vertically inherited mutations largely shape tumor genome properties, emerging evidence on human cancers shows tumor cells can acquire external, nonvertically inherited genetic properties via horizontal gene transfer. The transfer of DNA occurs with the help of small extracellular vesicles and leads to genome and phenotype modification and potentially genomic rescue of recipient cells (Valcz et al., 2022). In addition, in vitro cell culture and in vivo xenograft studies of human cancer cell lines have shown that spontaneous cell fusion could result in para(sexual) recombination, providing a new source of genetic diversification to tumor cell populations (Miroshnychenko et al., 2021). By using in silico simulations, Miroshnychenko et al. (2021) have also demonstrated that fusion-mediated recombination can result in higher numbers of mutations observed within a single lineage. Whether cytonuclear incompatibility and cytonuclear coevolution contribute to the higher mutation burden in transmissible cancers is a fascinating evolutionary question that remains to be answered. Coinvestigation of nuclear and mitochondrial genomes in bivalve transmissible cancers exposed to diverse environmental conditions that evoke different selective pressures on the cancer cells and the host (e.g., changing water temperature and salinity) in addition to investigating the mitonuclear conflict and cooperation in transmissible cancer cell lines might hold the key to deciphering which evolutionary scenario provides the highest adaptive advantage.

As mentioned above, some BTN lineages have been able to spread across species as xenografts, i.e., *Mytilus trossulus* cancer cell lines have infected sister species *M. chilensis* and *M. edulis* (Yonemitsu et al., 2019) and the cancer lineage in *Polititapes aureus* originated in a different species, *Venerupis corrugata*, that itself is no longer affected by neoplasia (Metzger et al., 2016). It appears that the neoplastic cells originated in *V. corrugata* that became resistant to BTN, and the disease survived by colonizing the neighboring species that coexist in the same bed, suggesting that transmissible

cancers have been a significant selective force in the evolution of multicellular organisms (Metzger et al., 2016).

BTN cells can be collected with noninvasive techniques (Lauren et al., 2023), and they can be kept in cell cultures and introduced across individuals (Giersch et al., 2022), hence potentially presenting as model systems to study the evolutionary arms race between mitochondrial and nuclear genomes. Artificial transmission of BTN cell lines into more or less evolutionarily distanced species and simultaneous investigation of host and BTN (mitochondrial and nuclear) genotypes and phenotypes could elucidate the evolutionary dynamics between transmissible cancer cell lines and their hosts. Such experiments may also reveal whether transmissible cancer cells cooperate to achieve higher fitness, as observed in human cancers (Archetti & Pienta, 2019).

In conclusion, the recent studies on the evolution of these fascinating clonal pathogens reveal key mechanistic insight into transmissible cancer genomes, information that is essential for future studies investigating how these contagious cancer cell lines can repeatedly evade immune recognition, evolve, and survive in the landscape of highly diverse hosts. As Hart et al. (2023) worded beautifully, studies on transmissible cancers “Highlight the fact that oncogenesis is not a single event, but an ongoing evolutionary process.” Given that we only observe transmissible cancers that have successfully evolved from many potential candidates, the high mutation rates of those that persist suggest that this characteristic is crucial to their emergence and evolution over the long term. Consequently, rather than seeing it as a genetic disadvantage that needs to be corrected for long-term persistence, we should strive to understand how this characteristic is most likely adaptive in transmissible cancers. The challenge of continuing this research, aimed at elucidating this apparent evolutionary paradox, lies in a deeper understanding of the hidden advantages that compensate for the inevitable production of mutations and their consequences.

## Data availability

No data was generated for this article.

## Author contributions

G.B. and B.U. initiated the original idea, and F.T. and J.D. contributed with discussions on evolutionary theories and information from the human cancer literature. All authors contributed to the writing, editing, revision, and proofreading of the manuscript.

## Funding

This work was funded by the CNRS (IRP CANECEV). F.T. is supported by the Hoffmann Family, and by the following grant: EVOSEXCAN project (ANR-23-CE13-0007). J.D. was supported by grants from the Veteran’s Administration (1 I01 BX004495) and the National Institute of Aging (R01AG067584). B.U. and G.B. were supported by Deakin SEBE\_RGS\_2019, the Holsworth Wildlife Research Endowment, the Save the Tasmanian devil Appeal, Eric Guiler Research Grant, and Australian Research Council (ARC) DP230100162 and LP170101105.

*Conflict of interest:* The authors declare no conflict of interest.

## Acknowledgments

The authors would like to thank Prof. Kirk Lohmueller and two anonymous reviewers for their valuable comments on the manuscript.

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