Evolutionary Approaches to Understanding Cancer Persistence in Human Populations

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BIO 425 – Evolution

Introduction

The first written description of cancer dates back to approximately 3000 B.C. to the Edwin Smith Papyrus, an ancient Egyptian textbook on trauma surgery (Di Lonardo et al., 2015). This text described eight different types of cancers and declared that the disease had no cure. Since then, our understanding of cancer, a disease characterized by uncontrolled cellular proliferation, has progressed. Now over 100 types of human cancers are recognized, most of which are classified by their organ of origin, the cell types involved, and their metastatic capabilities (National Cancer Institute, 2021). Some of these cancers, such as acute lymphoblastic leukemia, (ALL) can be cured through a variety of methods such as radiation therapy, immunotherapy, and chemotherapy, while other cancers, such as glioblastoma multiforme, have limited treatment options and a poor prognosis (Scott et al., 1998; Simone, 2006; Stupp et al., 2005).

Despite all the progress that has been made in both treatment and diagnostics, approximately 10 million people die annually from cancer, with over 600,000 deaths occurring in the United States of America alone. On top of this, approximately 1.9 million new cancer cases are diagnosed annually (Siegel et al., 2022). Studies have also shown that in recent years, cancer rates have increased, with the incidence of female breast cancer increasing by 0.5% annually from 2014-2018, and the incidence of cancer cases in individuals under the age of 50 rising by 80% (Siegel et al., 2022). Furthermore, the incidence of people under the age of 40 dying from cancer has increased by 27% over the last three decades (Siegel et al., 2022; Zhao et al., 2023).

In general, there are some key characteristics that distinguish cancer cells from healthy cells, one of which is the reduced requirement for extracellular growth factors in comparison to healthy cells (Cooper, 2000). This is due to the fact that cancer cells can produce their own growth factors (autocrine growth stimulation). Additionally, cancer cells are insensitive to both density dependent inhibition and contact inhibition. These are phenomena exhibited by normal cells that restrict their growth to a single confluent monolayer when cultured *in vitro* and that prevent excessive proliferation *in vivo*. Cancer cells are also less regulated by cell-cell and cell-matrix interactions since they are less adhesive than normal cells. In many cases, this is due to the loss of epithelial cadherin (E-cadherin), a molecule associated with cell adhesion. This lack of adhesion is, in part, what gives some cancer cells metastatic capabilities. The final factor that differentiates cancer cells from normal cells is that they can release chemical signals that stimulate angiogenesis, which is the formation of new blood vessels (Cooper, 2000). Angiogenesis is vital for solid tumor formation.

Due to the severity of this disease and its mortality rate, there exists a strong selective pressure against cancer within human populations. To put it simply, cancer should no longer exist, yet it has persisted throughout human evolution. Therefore, evolutionary biologists are interested in determining why this has been possible, and in describing the mechanisms involved (Roser & Ritchie, 2015). Additionally, within an individual, the development of cancer is an evolutionary process. Within populations, speciation occurs through mutation and natural selection acting on species. Within an individual, oncogenesis occurs through mutation and natural selection acting on cells/tissues (Casás-Selves & DeGregori, 2011). As such, viewing

cancer though an evolutionary lens, and understanding the mechanisms behind oncogenesis, may help explain the persistence of cancer within human populations.

Addressed here are two potential explanations for the persistence of cancer: antagonistic pleiotropy, and evolutionary tradeoffs. With regards to cancer, antagonistic pleiotropy is a phenomenon in which genes that differentially impact fitness during the lifespan of an organism promote oncogenesis, meaning that a gene that is useful during embryogenesis/development may promote cancer development later in life (Gaillard & Lemaître, 2017; Tuminello & Han, 2011; Williams, 1957). Evolutionary tradeoffs occur when the optimization of fitness in one area simultaneously decreases fitness in another.

Antagonistic Pleiotropy

One explanation for the persistence of cancer in human populations is antagonistic pleiotropy. This phenomenon occurs when natural gene variants within a population are pleiotropic (when one gene has multiple effects), and while some effects may be beneficial, others can be detrimental. Furthermore, these negative effects can manifest at different life stages (Gaillard & Lemaître, 2017; Tuminello & Han, 2011; Williams, 1957). If these positive and negative effects were equal in magnitude, the trait would, functionally, be selectively neutral, however, if the positive effects outweigh the corresponding negative effects, then through natural selection, these alleles will be selected for allowing them to spread throughout the population (Cohen & Holmes, 2014). Similarly, if the positive effects of the gene operate early in the life history of the organism, while a majority of the negative effects manifest later in life, that trait will selected for. This makes sense when one considers the fact that natural selection

acts strongest on traits that are directly related to an organism's reproductive value, while acting less strongly on traits that arise after peak reproductive age (Carter & Nguyen, 2011).

Experimentally, the existence of antagonistic pleiotropy has been shown by the fact that inactivating an antagonistic pleiotropic gene generally increases lifespan, while decreasing early-life fitness (Blagosklonny, 2010). A series of experiments on *Drosophila melanogaster* conducted throughout the 1980s and 1990s showed that populations selected for an extended lifespan generally had a simultaneous decrease in early-life fitness, as measured by the presence of developmental abnormalities and reduced fertility (Rose, 1984; Sgrò & Partridge, 1999). These experiments marked some of the earliest experimental evidence for antagonistic pleiotropy, and while they do not directly relate to cancer, they laid the foundations for the research conducted relating antagonistic pleiotropy to cancer. Since then, antagonistic pleiotropic genes have been linked to many different human diseases, lending additional support to the notion that they may be involved in cancer development (Table 1, Byars & Voskarides 2020). Furthermore, two antagonistic pleotropic genes/gene pathways in humans are directly related to cancer; **p53** and **MTOR**[1].

Table 1. Cases of antagonistic pleiotropy in human disease. These diseases have a clear genetic basis, a late age of onset, and are linked with reproductive success. Adapted from, Byars & Voskarides (2020).

Gene Variant	Fitness Benefit	Deleterious Cost	Age of Onset
HTT, CAG trinucleotide repeat	Increased fertility and reduced cancer risk	Huntington's Disease	~ 30-40 years
[2] **BCRA** 1/2	Increased fertility	Breast and ovarian cancer	~ 30-50 years

[1] Bold names reference genes, italicized names reference the resulting protein product.

[2] Highly debated, with more recent analyses showing that **BCRA1** and **BCRA2** have no effect on fertility. Historic accounts of it enhancing fertility may be contributed to the lack of family planning resources being available during that time period (Smith et al., 2013).

~ 56 **CHD** Loci	Increased fertility	Coronary heart disease	40-50+ years

p53 *and Antagonistic Pleiotropy*

p53 is a tumor suppressor gene located on the short arm of chromosome 17 that codes for the transcription factor, *p53* (Chang et al., 1993). *p53* binds DNA to stimulate the production of another protein called *p21*. *p21* then interacts with the cell division stimulating-protein, *cdk2,* (cyclin-dependent kinase 2)**.** When *p21* and *cdk2* are complexed, the cell cannot divide, leading to cell cycle arrest. Mutant **p53**, however, cannot properly bind to DNA, meaning that *p21* is not made, and the cell is then able to divide uncontrollably (cancer) (National Center for Biotechnology Information, 1998) (Figure 1). Current estimates suggest that mutated versions of **p53** are found in half of all human cancers (Hollstein et al., 1991).

p53 has been shown to have antagonistic pleotropic effects in *D. melanogaster*, whose **p53** shares a very similar structure to human **p53** making this a valid model system. Both systems have two promoters, and protein products of a similar size, with human *p53* being 393 amino acids, and *D. melanogaster p53* being 358 amino acids (Waskar et al., 2009). In *D. melanogaster* adults, **WTp53** (Wild-Type p53) overexpression reduced lifespan in females by 16%, while simultaneously increasing lifespan in males by 6%. Additionally, **WTp53** overexpression in females provided an early life benefit in the form of increased larval survival compared to males (3 adult flies resulting from the female larva vs 0 adult flies resulting from the male larva) (Figure 2). This supports the claim that p53 exhibits antagonistic pleiotropy in female *D. melanogaster* since despite it being linked to a shorter lifespan, it provides an early-life benefit that is selected for. Furthermore, **MTp53** (Mutant p53) increased the lifespan

of both males and females, by 12% and 11% respectively, suggesting antagonistic pleotropic effects, since as previously stated, inactivation of an antagonistic pleiotropic gene should increase lifespan (Waskar et al., 2009). While more evidence is necessary to determine the effects of **MTp53** on early-life fitness, preliminary evidence does support the conclusion that **p53** exhibits antagonistic pleiotropy.

Furthermore, in humans, evidence suggests that increased expression of **p53**, and therefore enhanced tumor suppression, is actively selected against due to antagonistic pleiotropic effects. As previously stated, **p21** expression is positively regulated by the binding of *p53* to one or multiple of the five *p53* binding sites located on **p21.** It has been shown that elevated *p21* levels, while potentially enhancing tumor suppression later in life by leading to cell cycle arrest (Figure 1 & Supplemental Figure 1), can have deleterious effects during development on the proliferation of lymphocytes leading to a 50% decrease in $CD4^+$ T-cell proliferation (Figure 3a & Figure 3b), and a decrease in stem cell proliferation, preventing wound healing and tissue homeostasis, negatively impacting early life fitness (Balomenos et al., 2000; Deng et al., 1995; Ozaki & Nakagawara, 2011; Ungewitter & Scrable, 2009). Since these deleterious effects manifest before an individual reaches sexual maturity, there is a negative selection pressure against the evolution of more than one copy of **p53** in the human genome.

mTOR Pathway and Antagonistic Pleiotropy

Aside from single genes exerting antagonistic pleiotropic effects, biochemical pathways can as well. An example of this is the *mTOR* (mammalian target of rapamycin) pathway found in mammalian cells, which has been linked to many diseases including neck, lung, and breast cancer (Tian et al., 2019). The primary protein in this pathway, *mTOR*, is a 290 kDa

serine-threonine kinase (a protein that preferentially phosphorylates serine and threonine residues within proteins) (The UniProt Consortium et al., 2023). This pathway is known to be one of the central regulators of cellular metabolism, growth, and hormone response. ***mTOR*** is also known to regulate proliferation, autophagy, and apoptosis (Figure 4), by controlling translational machinery via the activation of *p70 ribosomal S6 kinase* and through the inhibition of *eukaryotic initiation factor-4E-binding protein* (Lian et al., 2008; Zou et al., 2020). Deletion of the **mTOR** pathway has proven to be lethal during embryogenesis (post-implantation lethality) by severely impacting the formation and proliferation of the inner cell mass and trophoblast (Figure 5A). Additionally, deletion of *mTOR* reduces cell size and causes cell-cycle arrest in embryonic stem cells (Figure 5B) (Murakami et al., 2004). These findings suggest that the presence of **mTOR** is selected for early in life. Later in life however, the *mTOR* pathway is involved in ageing, senescence (irreversible cell cycle arrest), and cancer development (Blagosklonny, 2010; Ramachandran & Balakrishnan, 2021). One pathway through which **mTOR** promotes cancer development is by positively regulating *glutamate dehydrogenase (GDH)* and repressing *sirtuin 4 (SIRT4)*, a *GDH* inhibitor. This means that *mTOR* promotes the synthesis of glutamate which then acts as the primary carbon and nitrogen source for anaerobic glycolysis and cell growth. The utilization of aerobic glycolysis is a hallmark of cancer cells (Warburg Effect), so a pathway that promotes it also promotes cancer growth (Vander Heiden et al., 2009; Warburg, 1956). Combined, the effects of **p53** and **mTOR** suggest that antagonistic pleiotropy plays a significant role in the persistence of cancer in human populations.

Evolutionary Tradeoffs

Cancer is subject to the same framework as most other diseases. Due to this, selection should place organisms under pressure to avoid the disease, encourage the development of mechanisms to prevent disease progression, and if the disease is unavoidable, alleviate some of associated fitness costs (Ujvari et al., 2016). One way that cancer differs from this traditional framework, however, is that cancer is a disease involving an individual's own cells. As such, it is subject to the evolutionary tradeoffs that many other traits are subject to. Evolutionary tradeoffs serve as a second explanation for the persistence of cancer in human populations. Evolutionary tradeoffs are a compromise between the functions of multiple traits, in which increasing fitness in one trait negatively affects fitness in another. It is due to these tradeoffs that optimal health in all domains may not be possible. Similar to antagonistic pleiotropy, this phenomenon has been linked to a variety of human illnesses, including breast cancer (Table 2) (Ellison, 2014). Despite sharing many similarities, evolutionary tradeoffs differ from antagonistic pleiotropy in that evolutionary tradeoffs consider the organism as a whole, while antagonistic pleiotropy focuses on single genes/pathways. It is also worth noting that antagonistic pleiotropy involves one gene having two different effects, hence, the effects are antagonistic, but in evolutionary tradeoffs, the tradeoffs can involve traits governed by completely different mechanisms and is more dictated by resource allocation rather than antagonistic effects.

Table 2. Cases of evolutionary tradeoffs and human illness.

Disease/Illness	Tradeoff	Consequences
Elevated serum C-reactive protein (CRP) levels (McDade et al., 2008)	Energy allocation to the immune system vs allocation to growth	The elevated immune response leads to slowed growth
Increased risk of obstetric complications in teenage pregnancy (Scholl et al., 1994)	Energy tradeoff between maternal and fetal growth	Teenage girls allocate less energy to fetal development than older women. This leads

		to an elevated risk of obstetric complications.
Increased risk of breast cancer (Banks et al., 2004)	Tradeoff between bone health and cancer risk	Using prescription hormone replacement therapy (HRT) as a post-menopausal woman can reduce the risk of osteoporosis and ovarian cancer but increases breast cancer risk.

Cancer Prevention and Evolutionary Tradeoffs

When a trait is both essential to survival and reproduction, but it increases cancer risk, it will be subject to tradeoffs. One such example can be seen with Tasmanian Devil *(Sarcophilus harrisii*) Facial Tumor Disease (DFTD). DTFD is an infectious cancer, first described in 1996, that is characterized by the development of primary facial, neck, and oral tumors which grow to be larger than 3 cm and ulcerate (Hawkins et al., 2006; Murchison, 2008). Death usually occurs within months of the first symptoms appearing. In natural populations, DTFT is spread by biting, as evidenced by the presence of DTFD cells on the canine teeth of affected individuals and the observation of tumors developing from lesions caused by bite wounds (Obendorf & McGlashan, 2008). This biting behavior, however, is also a regular part of Tasmanian devil mating in multiple different aspects; male-male competition, and female evasion of male guarding, while also being common during copulation itself (Hamede et al., 2008). In this case, there is a tradeoff between mating success and the fact that biting also spreads DFTD. This tradeoff is what maintains DFTD in Tasmanian devil populations.

This disease can serve as natural model for human cancers since some of the genes involved in the occasional spontaneous regression of the disease (**$RASL_{11}A$***)* in infected individuals are also active in human prostate and colon cancers (Margres et al., 2020). As such, viewing the disease through an evolutionary lens can provide insight into the persistence of cancer in human populations. Additionally, understanding the tradeoffs influencing DFTD may provide insight into the tradeoffs governing cancers linked to bacterial and viral infections in humans, such as the 99% of cervical cancer cases that are caused by human papillomavirus (HPV), or the increased risk of gastric adenocarcinoma linked to chronic infections with *Helicobacter pylori* (Sharafadeen, 2020; Wroblewski et al., 2010).

In a similar vein, Canine Transmissible Venereal Tumor (CTVT), is a sexually transmitted cancer characterized by the appearance of lesions around the external genitalia of either sex of any breed of dog (*Canis familiaris*) first described in 1876 (Murchison, 2008). These lesions then result in the development of multinodular tumors that are delimited but not encapsulated (tumors with a rough/lumpy appearance that have a clear border, but no distinct external casing (Supplemental Figure 2)), which can grow to be larger than 10 cm (Murchison, 2008; Zayas et al., 2019). While CTVT is not usually fatal, it provokes a cell-mediated and humoral immune response, resulting in the downregulation of MHC, the suppression of Natural Killer (NK) cells, the killing of B-cells, and slowed maturation of dendritic cells, which serve as the initiators of the immune response and as the branch between innate and adaptive immunity. Studies have shown that CTVT can increase monocyte apoptosis by 31% (Figure 6), while also dramatically reducing the levels of dendritic cells in draining lymph nodes from 4.65% in healthy individuals to 0.54% in individuals with P-phase tumors (tumors that are increasing in volume), and 1.21%

in individuals with R-phase tumors (tumors that are decreasing in volume) (Figure 7) (Liu et al., 2008). Combined, these effects weaken the immune system, leaving affected individuals more susceptible to secondary infections and reduced tumor suppression which could prove lethal. In this case, the evolutionary tradeoff is between mating success and the immune cost of this cancer. The tradeoff between the fitness benefit of biting on mating success outweighs the detrimental effects of potentially spreading CTVT, allowing this type of cancer to persist within canine populations.

While humans do not get CTVT, preliminary research indicates that it and DFTD could serve as valuable models for the development of human cancers. This is because CTVT and DFTD express different lineage markers (histiocytic origin for CTVT and neural crest origin for DFTD), which can be used to investigate cancer-stem cell processes in human cancers (O'Neill, 2011). Additionally, many of the core mutations found in CTVT are directly linked to human cancers, such as Signature D. Signature D is characterized by C>T and CC>TT mutations. It is prevalent in many human skin cancers and its presence has been directly linked to exposure to ultraviolet light. These mutations comprise 42% of the mutations observed in CTVT (Murchison et al., 2014). So, while humans do not get CTVT, the mechanisms underlying cancer development in both cases are similar, thus, studying one disease can provide valuable information about the other.

As previously mentioned, pathogens can also directly cause cancer in humans, an example of which is human papillomavirus. Human papillomavirus is a sexually transmitted DNA virus with an 8 kb genome, that integrates into the host genome (Münger et al., 2004). Once integrated, expression of the viral **E7** and **E6** oncogenes are maintained, and cells expressing

these viral oncogenes have a growth advantage over cells not expressing these genes. Additionally, host cells can also lose expression of the HPV **E2** transcriptional regulator. This can lead to dysregulated **E6** and **E7** expression. It is currently thought that this loss of **E2** is critical for malignant progression in cervical cancer caused by human papilloma virus (Münger et al., 2004; Pal & Kundu, 2020). The tradeoff in these instances is very similar to those found in CTVT and DFTD: reproductive success vs increased cancer risk.

Cancer Suppression and Evolutionary Tradeoffs

Similar to how cancer prevention is subject to evolutionary tradeoffs, cancer suppression is as well, with the evolution of larger, multicellular organisms with longer lifespans making effective cancer suppression increasingly difficult. In response to this, humans have evolved multiple modes of tumor suppression such as the evolution of tumor suppressor genes (such as **p53**) and lower somatic mutation rates. In humans, there are currently 1,217 genes linked, in some way, to tumor suppression, 1,018 of which are protein coding genes, and 199 of which are non-coding genes (Yeo, 1999; Zhao et al., 2016). Despite this, these mechanisms are not perfect, and they may come at a cost by preventing the cellular proliferation necessary for reproduction and growth (Harris et al., 2017).

There also exists a tradeoff between rapid growth/maturation and somatic maintenance. In many species, early puberty and rapid growth can be advantageous for increased mating success/reproductive output and predator avoidance. The extra energetic cost of this rapid growth leaves less energy available for somatic maintenance leading to increased

cancer risk (Arora et al., 2011). This tradeoff can be seen by the fact that rapidly growing teenagers, as measured by accelerated pubertal longitudinal bone growth, have an increased osteosarcoma risk, with male adolescents who had early onset growth spurt showing the highest risk increase (Age and sex-adjusted odds ratio of 7.1, $p = 0.01$) (Arora et al., 2011; Troisi et al., 2006). Furthermore, high birth weight (Figure 8a), early puberty (Figure 8b), and accelerated adolescent growth (Figure 8c) are all independently associated with an increased breast cancer risk in females (Ahlgren et al., 2004). Since these tradeoffs are directly linked to the increased risk of cancer, these examples serve as clear evidence for the role of evolutionary tradeoffs in the continued existence of cancer in human populations.

Tissue Repair and Evolutionary Tradeoffs

There also exists a tradeoff between tissue repair and cancer development. In general, wound healing consists of four integrated and overlapping stages: hemostasis, inflammation, proliferation, and resolution (tissue remodeling) (Gosain & DiPietro, 2004). The need for rapid mesenchymal cell differentiation (which requires an epithelial-mesenchymal transition (EMT)), proliferation, and migration in wound healing leaves organisms more prone to cancer development since cancer cells can use these same pathways during oncogenesis (Thiery, 2002). More specifically, the EMTs required for the resolution phase of wound healing, which produces migratory mesenchymal cell types due to the loss of E cadherin, is believed to play an active role in cancer invasion, metastasis, and chemoresistance. Clinically, this is shown by patients with progressive forms of metastatic breast cancer (ductal, lobular, and $HER2^{+}$) having a higher proportion of mesenchymal circulating tumor cells (CTCs) remaining after treatment with

conventional chemotherapy, **PI3K** inhibitors, and **mTOR** and **MEK** inhibitors (Figure 9) (Haensel & Dai, 2018; Yu et al., 2013).

Discussion

Based on the evidence provided, the hypothesis suggesting that cancer persists in human populations due to evolutionary tradeoffs is better supported. This is because for many cancers, multiple genetic factors are involved, and at present, not all of the genetic mechanisms underlying cancer are fully understood. Due to this, only two clear examples of antagonistic pleiotropic genes/pathways can be discussed in relation to cancer: **p53** and the **mTOR pathway**. The effects of two genes, when it is known that a minimum of 5-10 genetic alterations are necessary for the development of a malignant phenotype (Fearon & Vogelstein, 1990), with some carcinomas having as many as 11,000 mutations (Stoler et al., 1999), are insufficient to explain the persistence of cancer within human populations. Furthermore, the effects of evolutionary tradeoffs can be seen across all animals. Antagonistic pleiotropy may also be ubiquitous across all animal species; however, the same gene can have different effects in different animals. This is highlighted by the fact that elephants have 20 copies of **p53**, suggesting that the negative effects seen in humans could be species-specific (Callaway, 2015). Since incidences of cancer can be found in all animals, it makes sense that a mechanism that can be observed in all animals is behind the persistence of cancer (Vincze et al., 2022).

Many questions, however, remain to be answered. One such question is the cause of geographic variation in cancer incidence with there being a 50-fold difference in cancer incidence between some geographic areas (Bray et al., 2017). There also exist some sex-disparities between cancer mortality rates, with the mortality rate for cancer generally

being higher for men than for women. Recent studies estimate that men have a mortality rate of 189.5 per 100,000 individuals, while females have a mortality rate of 135.7 per 100,000 individuals. When these values are further broken down by race, it becomes clear that the highest mortality rate is among African American men (227.3 per 100,000 individuals). The lowest mortality rate is among Asian/Pacific Islander women (85.6 per 100,000 individuals) (National Cancer Institute, 2015). Understanding the source of this variation is important to developing novel, targeted therapies, that work best for an individual based on their life circumstances, with environmental factors playing a large role.

To address these disparities and to answer the question as to why cancer persists in human populations, additional research needs to continue to investigate the genetic basis of cancer development. This is especially necessary to determine the role of antagonistic pleiotropy in the disease. Additionally, more effort needs to be made to understand cancer as an evolutionary process (Casás-Selves & DeGregori, 2011). This is necessary since the application of Darwinian theory may be beneficial to understanding neoplastic progression and the development of therapeutic resistance (Pepper et al., 2009). Using evolutionary theory to obtain a better understanding of the development of therapeutic resistance could potentially help with drug design, as it could allow for the development of mathematical models which can be used to design “adaptive therapies” which seek to control the spread of therapeutic resistance by adjusting treatment cycles based on tumor evolution (Belkhir et al., 2021). These adaptive approaches have already shown success in clinical trials when treating metastatic castrate-resistant prostate cancer. In these trials, time to progression (TTP) was extended from 16 to 27 months, using less than half of the standard dose of the drug (Abiraterone) (Zhang et

al., 2017). Adaptive therapies have also shown promise when it comes to treating preclinical models of breast cancer (Enriquez-Navas et al., 2016).

Being a disease that kills over half a million people annually in the United States alone, there is a strong selective pressure against cancer, yet it persists in human populations (Siegel et al., 2022). The shortcomings of modern medicine alone cannot explain this persistence, however, evolution can; due to evolutionary tradeoffs and antagonistic pleiotropy cancer is able to persist, with evolutionary tradeoffs likely having a larger effect on this persistence. Since this phenomenon only makes sense when viewed through an evolutionary lens, effective treatment must also be developed through the same lens. At an organismal level, cancer is selected against, however, within the tumor, proliferation and survival are selected for. This means that, at the cellular level, cancer cells are selfish. Knowing this and how tumors evolve is necessary to developing effective treatments.

Conclusion

Cancer is a class of 100+ diseases characterized by unrestricted cell proliferation; the first recorded case of which dates back to ~3000 BC in ancient Egypt. Cancer cells are unique in that they can produce their own growth factors to stimulate proliferation, are insensitive to density dependent inhibition, and are less constrained by cell-cell or cell-matrix interactions. Combined these factors give them malignant and metastatic capabilities. Despite there being strong selection against cancer within human populations, it persists, killing over half a million people annually in the United States.

While there are many hypotheses on why this persistence continues, the most common ones involve antagonistic pleiotropy and evolutionary tradeoffs. Based on this analysis, the

evolutionary tradeoff hypothesis is the best supported due to the fact that tradeoffs can be seen in all animals, and specific tradeoffs can be connected to increased risks of certain cancers. That being said, many questions regarding the persistence of cancer within human populations remain unanswered such as the observed geographic variation in cancer incidence and the sex-dependent differences in mortality rate. Future research into the genetic basis for cancer may help explain these differences. Additionally, applying evolutionary theory to the study of cancer will aid in the development of more effective treatment strategies. Examining why cancer continues to plague humanity is vital to understanding evolution. Based purely on selection, it seems that cancer should have gone extinct within humans, but it has not, and that is not just due to the shortcomings of medicine. It is because evolution shapes cancer; antagonistic pleiotropy and evolutionary tradeoffs shape cancer, and they have made it so that cancer will never naturally go extinct within human populations.

Figures

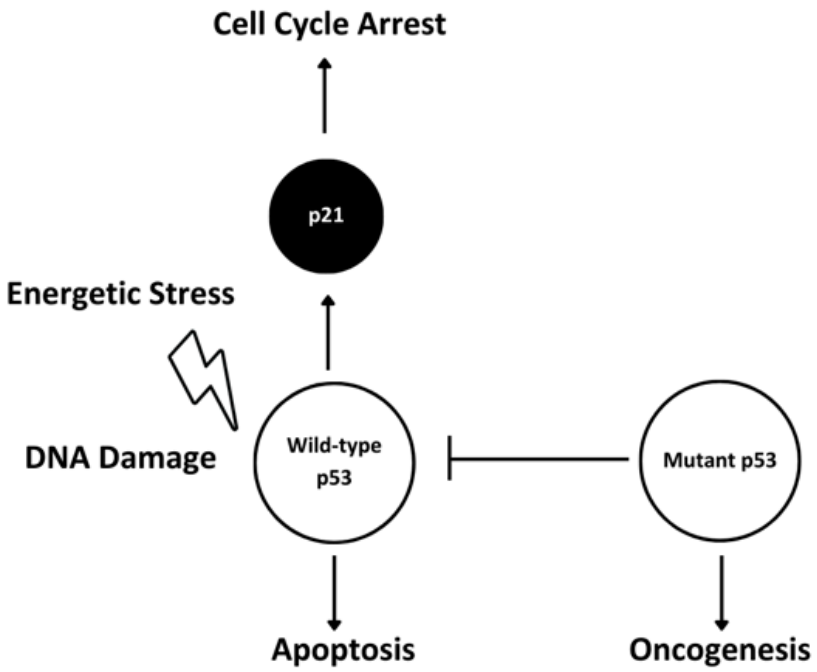


Figure 1. The role of **p53** as a tumor suppressor. **Wild-type p53** can stimulate the production of *p21* which can lead to cell-cycle arrest or, it can induce apoptosis. **Mutant p53** can do neither of these things, often leading to oncogenesis. Adapted from, Ozaki & Nakagawara (2011).

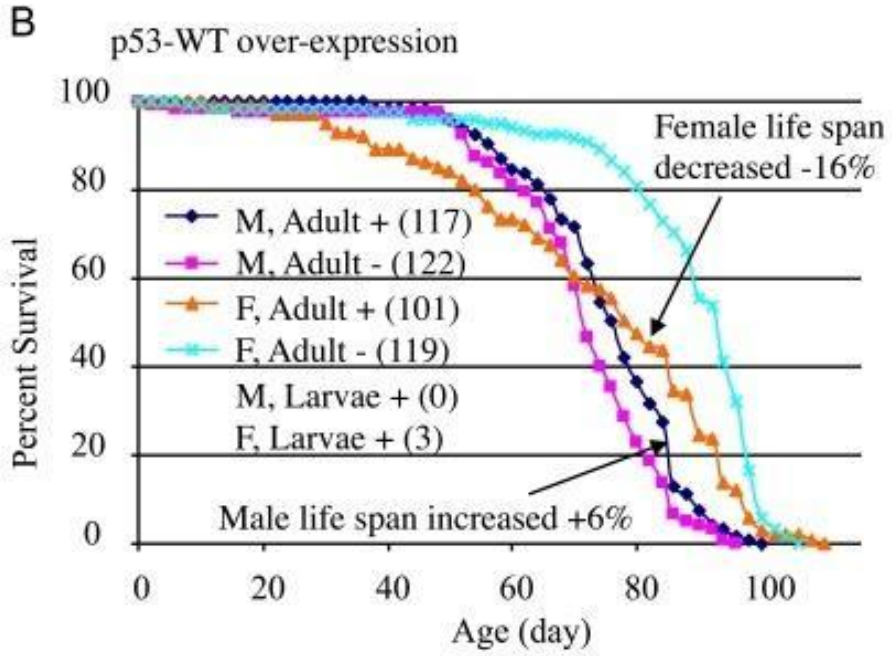


Figure 2. The overexpression of **WTp53** (wild type **p53**) decreased lifespan in females while increasing lifespan in males (Waskar et al., 2009). + denotes **p53** overexpression.

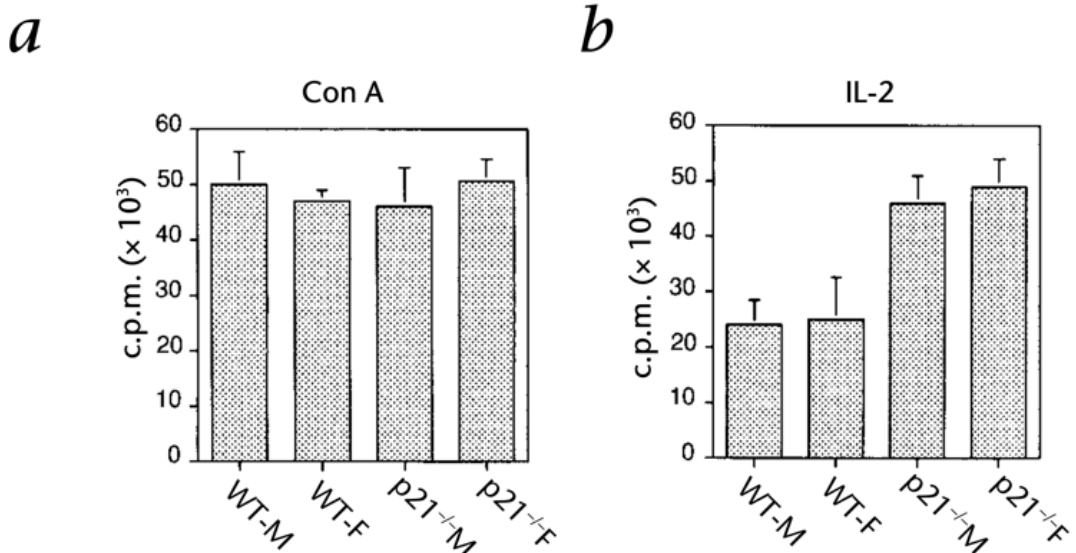


Figure 3. Proliferative responses of $CD4^+$ T-cells when **p21** is active (WT) or inactive (**p21**$^{-/-}$) quantified by [^{3}H] thymidine incorporation over a 12-hour period. (a) Proliferation rates 3 days post stimulation with Con A (Concanavalin A) and IL-2 (Interlukin-2). (b) Proliferation rates 6 days after the Con A stimulated cells were further stimulated using IL-2 (Balomenos et al., 2000). Cells lacking **p21** had enhanced proliferation following stimulation.

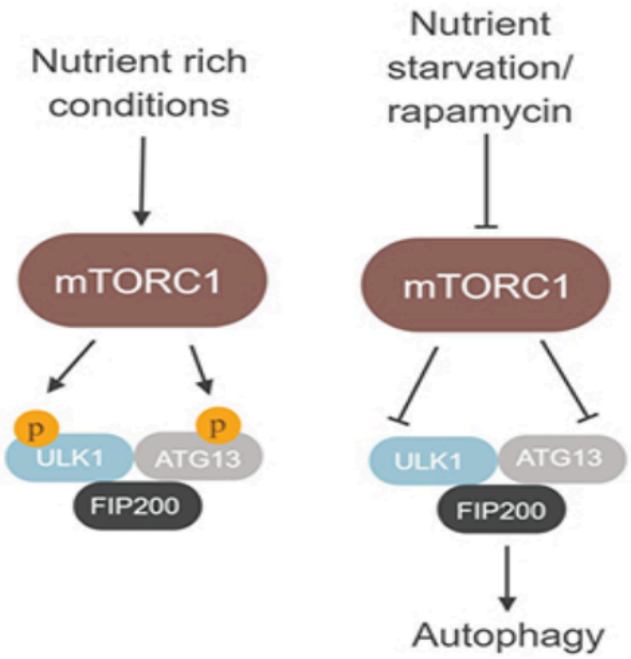


Figure 4. A snapshot of the autophagy arm of the **mTOR** pathway. When nutrients are present, *mTORC1* is able to phosphorylate *ULK1* (an autophagy inducing kinase) and *ATG13* (an autophagy factor responsible for phagosome formation), but not *FIP200* (a protein required for autophagosome formation). When nutrients are not present, this phosphorylation is unable to occur, and autophagy is induced. Adapted from Bio-Rad (2020).

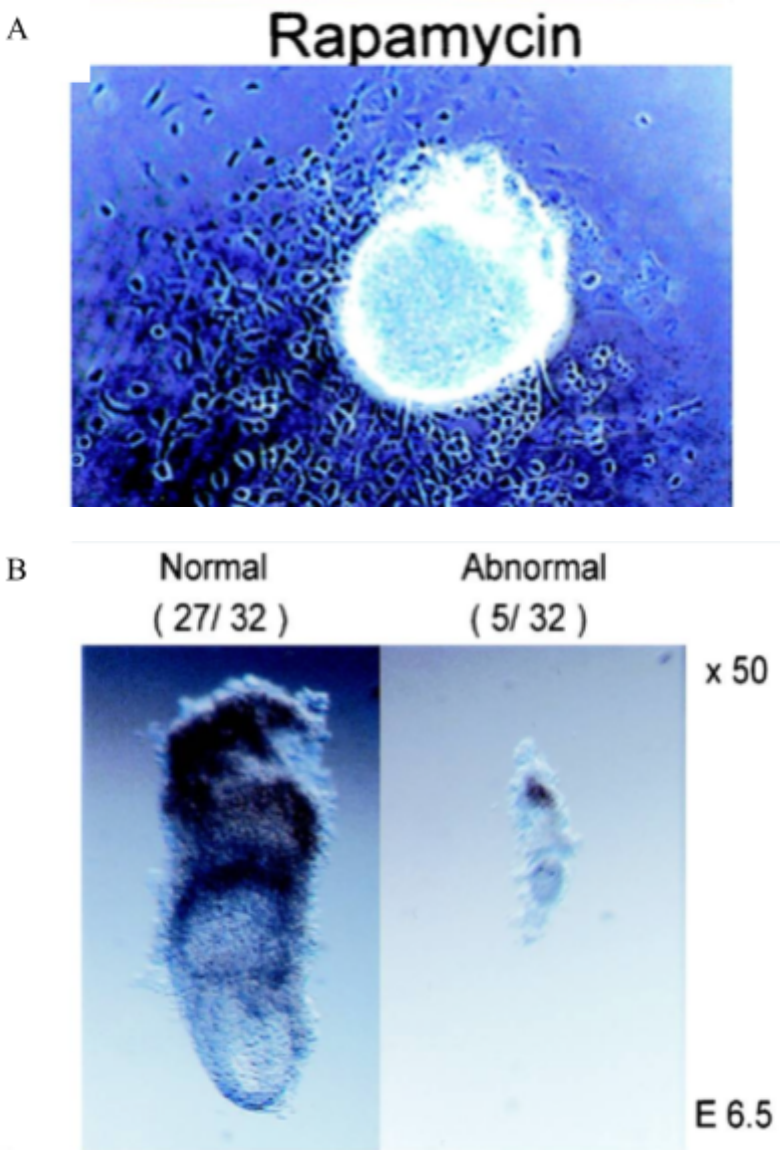


Figure 5. Effects of **mTOR** deletion on embryo development. (A) When using Rapamycin to mimic the effects of an **mTOR** deletion, trophoblast proliferation was inhibited. (B) An **mTOR**$^{-}$ (right) embryo dissected 6.5 days post-coitum was much smaller than an **mTOR**$^{+}$ embryo dissected within the same time frame (Murakami et al., 2004).

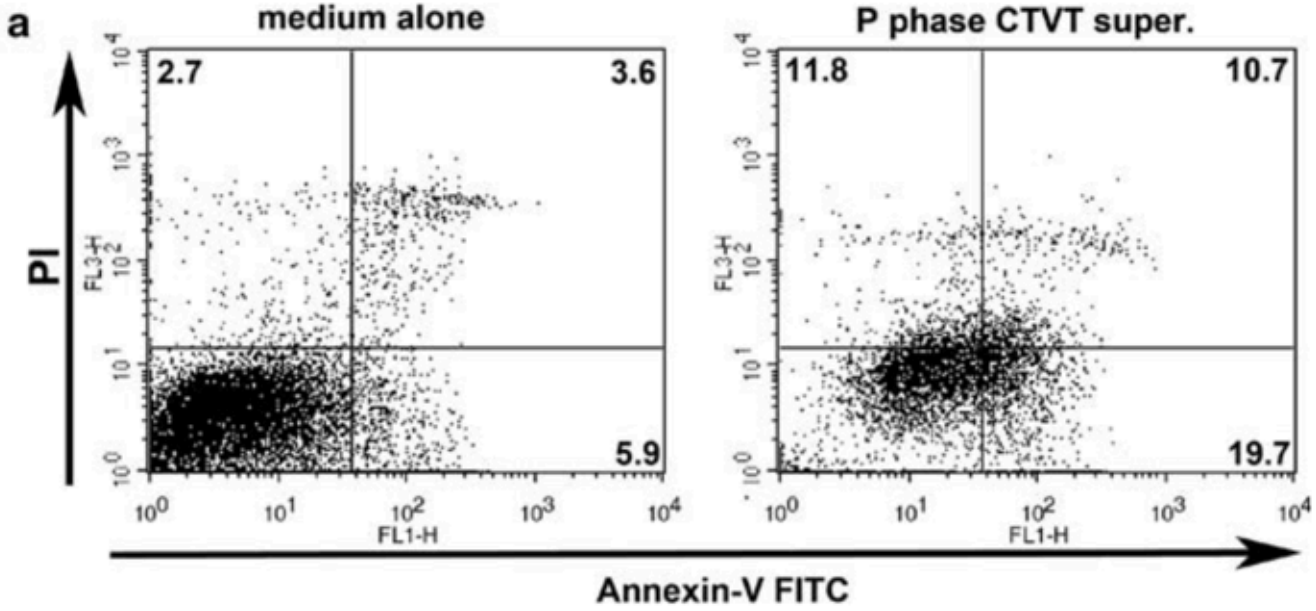


Figure 6. Supernatant isolated from P-phase CTVT tumors increased monocyte apoptosis, as measured by flow cytometric analysis of Annexin-V FITC staining. Annexin is commonly used to stain necrotic cells. Elevated Annexin-V FITC values indicate high levels of apoptosis (Liu et al., 2008).

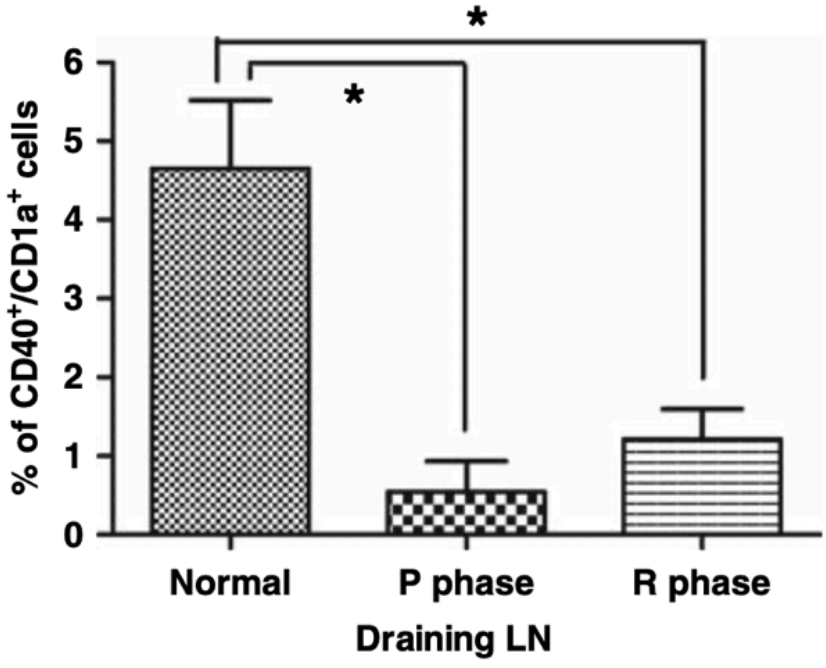
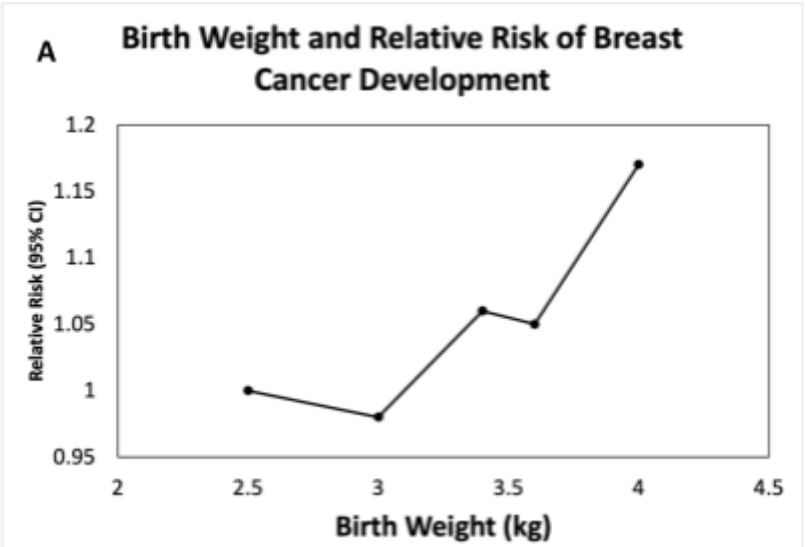
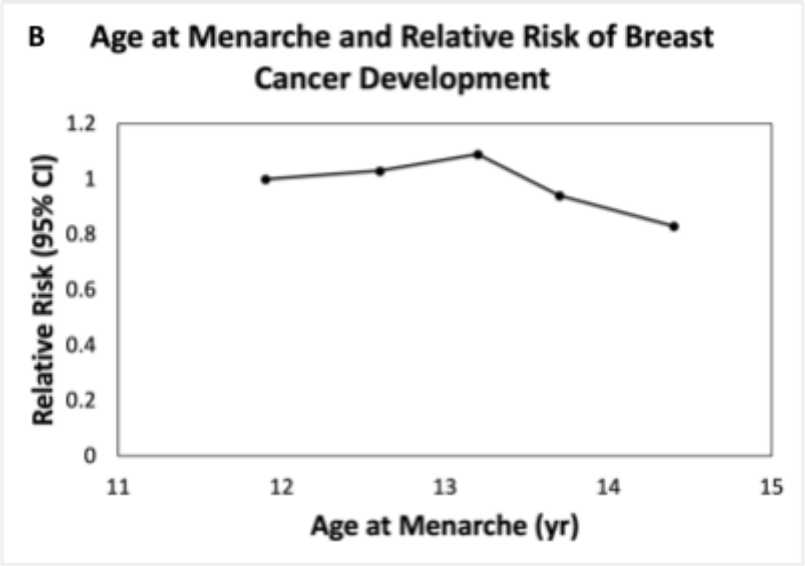


Figure 7. Individuals with P-phase and R-phase tumors had impaired dendritic cell proliferation, as shown by the reduced levels of dendritic cells ($CD40^+$ and $CD1a^+$ cells) found in samples taken from draining lymph nodes (Liu et al., 2008).





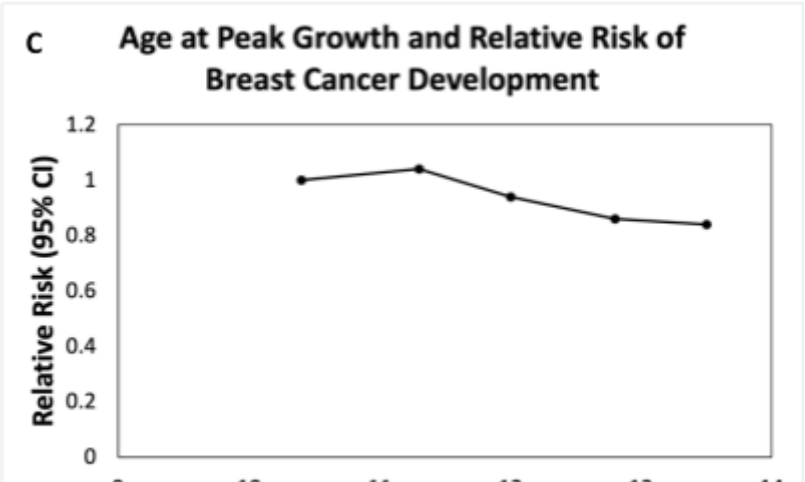


Figure 8. The association between three growth variables and relative breast cancer risk (95% CI). (A) The relationship between birth weight (kg) and relative breast cancer risk based on the analysis of 2074 cases. (B) The relationship between age at menarche (yr) and relative breast cancer risk based on the analysis of 950 cases. (C) The relationship between age at peak growth (yr) and relative breast cancer risk based on the analysis of 3340 cases. Full confidence intervals omitted for simplicity. Graphs

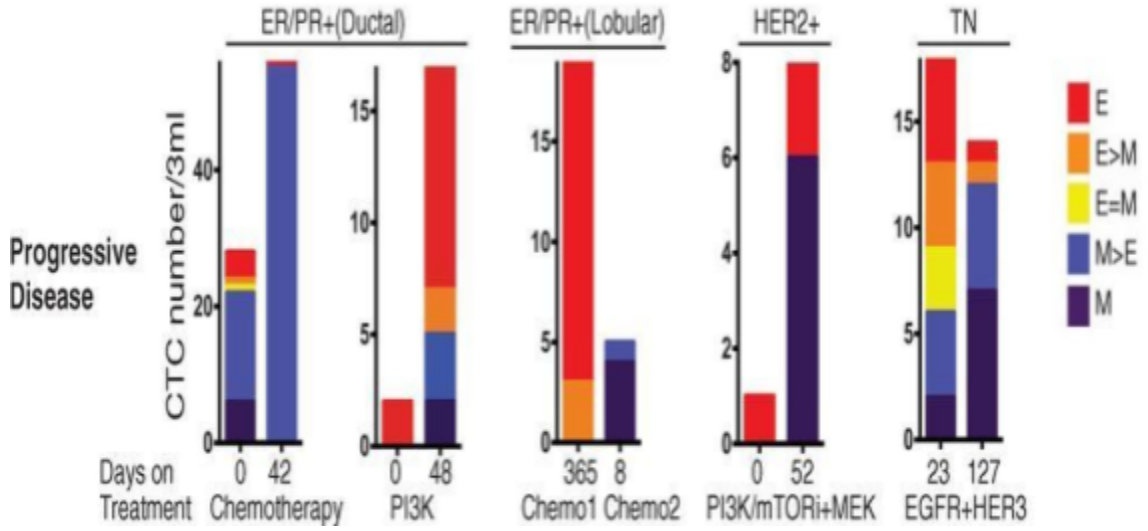


Figure 9. The proportion of epithelial to mesenchymal circulating tumor cells in patients with progressive forms of metastatic cancer (ductal, lobular, and HER2^{+}) before and after treatment with conventional chemotherapy, PI3K inhibitors (phosphatidylinositol 3-kinase), mTOR and MEK (MAP kinase) inhibitors. Days on treatment shown along with color scheme used. ER = estrogen receptor. PR = progesterone receptor. HER2 = receptor tyrosine-protein kinase erbB-2. TN = triple negative (Yu et al., 2013).

Supplemental Figures

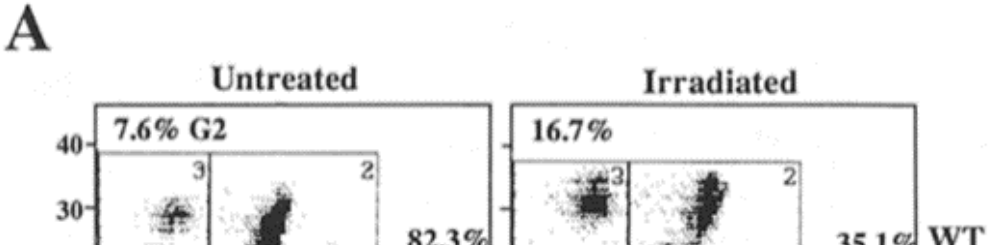


Figure S1. Cells lacking functional **p21** were 1.6 times more likely to bypass the G1 checkpoint after sustaining DNA damage. (A) Flow cytometric analysis of irradiated mouse embryonic fibroblast (MEF) cells 24 hours after exposure to γ – radiation. (B) Quantitative analysis of the percent of cells entering S-phase before and after irradiation across the three genotypes examined (Deng et al., 1995).

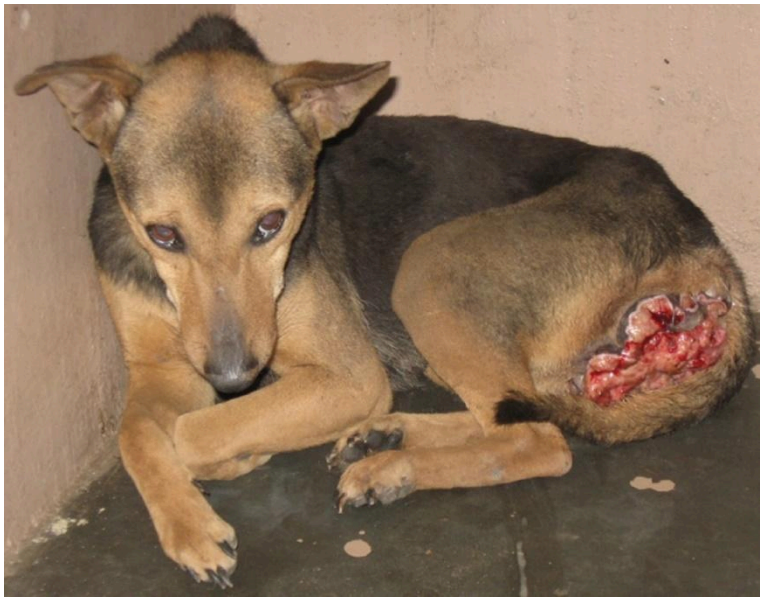


Figure S2. A dog with CTVT. The multinodular (rough/lumpy appearance), delimited but non-encapsulated (has clear boarders but no distinct outer casing) presentation of the tumor is easily visible (Ganguly et al., 2016).

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