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Evolving Resistance: How Natural Selection Evolved Cancer Suppression Across Species and Within Organisms

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Evolving Resistance: How Natural Selection Evolved Cancer Suppression Across Species and Within Organisms

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Bio 141: Evolution

Dr. Emily McTavish and Dr. Iolanda Da Silva

May 9th, 2025

EVOLVING RESISTANCE 3

Abstract

Cancer is frequently regarded as a modern illness; however, its origins are intertwined with the evolutionary background of multicellular organisms. The persistence of cancer reflects a fundamental evolutionary challenge: how organisms maintain cooperation among billions of cells while preventing the rise of selfish, malignant ones. In this review paper, we will examine how natural selection influences the development of cancer suppression mechanisms within individual organisms and across various species. We will concentrate on two key areas: first, the Darwinian characteristics of cancer as a clonal evolutionary process driven by mutation, competition, and selection within the body; and second, the evolution of the immune and genetic defense system that inhibits tumor formation to a limit. The development of somatic defenses that have delayed cancer's progression in long-lived species usually entails trade-offs such as aging, diminished regenerative abilities, and reduced reproductive capacity. We will also mention comparative studies that show that species such as naked mole rats, elephants, and whales have independently evolved distinct anti-cancer mechanisms, illustrating the varied approaches to a shared issue. Considering cancer from an evolutionary perspective can broaden understandings of its original traces and endurance. It also provides valuable insight into how organisms balance longevity and cellular integrity. Ultimately, integrating evolutionary theory with oncology may guide the development of more adaptive therapies and preventive approaches inspired by nature's own long-term solutions.

Keywords: Cancer suppression, Immune surveillance, Trade-offs, Tumor biology, Somatic evolution

A War Within: Cancer as a Darwinian Process

Cancer signifies a failure in the collaborative function of multicellular organisms. In healthy tissues, somatic cells undergo division, differentiation, and death in a meticulously managed process. However, when cells get a mutation that enables them to avoid these regulations, they could selfishly deviate and start growing for their own benefit, which harms the organism as a whole in the process. This phenomenon poses an evolutionary challenge because the organism needs to inhibit the self-serving actions of its own cells to preserve organismal integrity (DeGregori 2011).

The same fundamental concepts that underpin species evolution: variation, inheritance, and selection, also determine how cancer develops within the body. There is a probability that with each cell division, mutations may occur. Some mutations may be deleterious and remain undetectable by the immune system until it is too late. Within the tumor microenvironment, some mutations could form and offer a special advantage, such as resistance to cell death, accelerated growth, or the capacity to improve blood flow (angiogenesis). Clonal evolution is a term used to describe dominant and aggressive lineages as a result of certain advantageous traits within the clones (Greaves & Maley, 2012). Resistance has two kinds: intrinsic and acquired resistance. Intrinsic resistance happens when one of the founder cells pre-exists before the treatment and causes cancerous cells to be pre-resistant before the first treatment, which gives it an advantage. The other form of resistance is acquired resistance, and that happens when not all cells are pre-resistant, and they slowly acquire resistance with different treatment cycles (S. A et al. 2022). These resistance cycles cause heterogeneous tumors, which make treatment and therapies hard and ineffective.

Due to competition for nutrients, oxygen, and space, the tumor habitat is constantly changing and exerting selection pressures. Treatments and therapies provide selection pressures on resistant subclones (Guo et al. 2024). The immune surveillance system acts as a barrier that removes visible or easily detected cells (Danilova 2006). This immune selection in turn promotes selection pressures because the immune system removes weaker cancerous cells, but those that survive build more resistance and evolve new mechanisms to evade the immune system. As a result, tumors are often extremely adaptable and genetically varied, which makes it harder to find a cure (Greaves & Maley, 2012; Guo et al., 2024).

Treatment pressures naturally favor resistant mutations; this Darwinian perspective explains why tumors recur and defy treatments (Guo et al. 2024). Redefining cancer as an evolutionary process in the body shifts our perspective. Rather than viewing it as a static disease to be eradicated, we view it as a dynamic target influenced by natural selection.

Evolved Defenses: Immune and Genetic Suppression Mechanisms

Multicellular organisms have evolved complex defense mechanisms that mitigate the potential risks of somatic evolution or the evolution process in general. Originating in unicellular organisms' previous generations, these defenses evolved alongside the complexity of organisms. As they grew larger and lived longer, the defenses also grew in complexity, and the immune system added more layers of defense (Danilova 2006). Defenses include both a layered immune system and specialized DNA repair mechanisms. During cellular replication, specifically meiosis and mitosis, there are multiple checkpoints in place. DNA repair strategies, such as proofreading by polymerases and other specialized structures, play a key role in maintaining genomic integrity. These structures have one primary job: to ensure that the DNA remains free of errors. This is critical because any unrepaired errors can turn into mutations. If these mutations are not corrected, they can lead to the production of deformed proteins, which in turn affect all other cellular processes. Ultimately, DNA repair processes work to resolve replication errors at the molecular level before they become translated into proteins and become mutations. If the mistakes persist, then the cell may enter senescence. Senescence is a permanent state of growth arrest that prevents future proliferation, or apoptosis, a process for programmed cell death where the cell self-destructs (Campisi 2005). When senescence happens more than usual, it causes the accumulation of dead cells, which speeds up the aging process and causes other health complications.

Another important factor in preventing cancer is the immune system. Natural Killer (NK) cells and macrophages which can identify and destroy aberrant cells. These Natural Killer cells and macrophages are part of the innate immunity as a first line of defense (Danilova 2006). The adaptive immune system is the second line of defense, which is more specific because B and T cells recognize antigens presented by tumor cells on their surface. Evolutionary processes that aim to eliminate newly forming cancers before they are clinically detected and have caused irreversible damage have been suggested to have an impact on this surveillance mechanism (DeGregori 2011; Danilova 2006). Unicellular organisms started with only antimicrobial antibodies and proteins. Then, as the organisms started evolving and becoming more complex, the immune system started to gain more layers of defense to protect the body from the new viruses that were also evolving in complexity. Phagocytosis started to develop, which is the process of engulfing and destroying solid particles, such as bacteria or cellular debris. The immune system became specific by adding TLRs, NLRs, CLRs, and RLRs. These are all forms of pattern recognition receptors (PRRs) (Guryanova 2022). The adaptive immune system formed later and uses B and T cell receptors, which are more specific and include memory cells that remember viruses or pathogens from past encounters.

Furthermore, there are costs associated with these defense mechanisms. Senescent cells contribute to aging by promoting chronic inflammation and compromising tissue function (Campisi 2005). The accumulation of dead cells can also contribute to the development of age-associated pathologies (Aquino-Martinez et al. 2021). Another mechanism that also has a downside is apoptosis. If apoptosis is overactivated, it could prevent tissue regeneration (DeGregori 2011). Autoimmune disorders can emerge as a result of immune monitoring’s

high

energy requirements and occasional failures (Jacqueline et al. 2016). These trade-offs emphasize the limitations of natural selection: other vital processes for survival and procreation must be considered while suppressing cancer.

Trade-offs and Comparative Insights

Despite the fact that humans have created effective, if imperfect, cancer-fighting mechanisms, different species develop different strategies. Studies suggest that due to their size and longevity, large long-lived animals like whales and elephants have an increased chance of developing cancer (Tollis et al. 2017). This is due to more cell divisions happening, leading to a higher risk of deleterious mutations that could cause uncontrolled cellular division. Nevertheless, their cancer rates are not correspondingly high. This phenomenon is known as Peto's Paradox; it reveals that better suppression mechanisms are being developed (Tollis et al. 2017). This happens because the bigger species have found different strategies to survive long enough to reproduce offspring.

Elephants, for example, possess numerous copies of the TP53 gene, which triggers apoptosis in response to DNA damage (Tollis et al. 2017). Whales have a prolonged cell cycle and superior DNA repair systems (Jacqueline et al. 2016). Another strategy is having a high-molecular-weight hyaluronan, which is produced by the naked mole rat, which is renowned for their rare tumor development. The high-molecular-weight hyaluronan prevents tumor formation and inhibits cellular transformation and overpopulation of cells (Harris et al. 2017). This strategy is effective because it prevents the accumulation of cells together, which prevents the formation of colonies that could turn into malignant cells.

These instances demonstrate how ecological and life-history circumstances influence the development of cancer suppression strategies. However, there are costs and trade-offs associated with these adjustments and strategies as portrayed in *Figure 1*. Elephants give birth infrequently, and they also have long gestation periods. Naked mole rats have a slow metabolic rate, and they live in low-oxygen environments. Reproduction, survival, and energy consumption compromise impacts evolutionary approaches to cancer (Jacqueline et al. 2016).

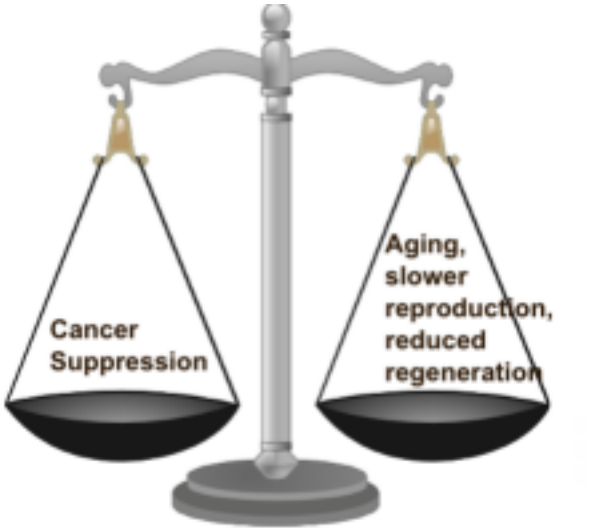

Figure 1: Evolutionary Trade-Off in Cancer Suppression

Natural selection favors certain traits and mechanisms that suppress cancer, such as senescence, apoptosis, and surveillance. However, these defenses incur other biological costs like aging and slower reproduction. *Figure 1* illustrates how if one side increases, the other will decrease.

Concluding Remarks

Natural selection has influenced the complex interplay of genetic, cellular, and immunological strategies that have evolved to inhibit cancer. At the same time, cancer persists because of evolutionary constraints: the necessity of having to balance against essential biological functions (DeGregori 2011). By recognizing cancer as a Darwinian phenomenon, researchers could use that perspective to build and improve new inventive and flexible therapies that anticipate the growth of tumors and the resistance that could form (Guo et al. 2024). As we study evolution within and across organisms, we conclude that although evolution has produced many cancer defenses, it remains an imperfect process shaped by trade-offs. Evolution prioritizes survival and reproduction, and as the body reaches a certain age where fertility becomes compromised, the body's ability to suppress tumor formation declines.

Future research should also concentrate on improving immunotherapies to better use the existing immune responses and to strengthen them further (Guo et al. 2024). Another aspect that research should focus on is comparative oncology to get inspiration and identify new suppression strategies across species (Tollis et al. 2017). In the end, the challenge and design for cancer resistance are presented by nature. Gaining knowledge of how organisms evolved to prevent or delay cancer can assist us in creating new, innovative therapies that mimic the tried-and-true methods found around us in nature.

Glossary Box

Clonal evolution	The process by which tumor cells develop into unique subpopulations under selective pressure after accumulating mutations.
Senescence	A permanent state of cell cycle arrest that prevents the replication of damaged cells.
Apoptosis	Programmed cell death is used by the body to eliminate potentially harmful cells.
Peto's Paradox	The observation that large-bodied, long-lived animals do not get more cancer than smaller animals, despite having more cells.
mmune Surveillance	The process by which the immune system detects and eliminates potentially cancerous cells.

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