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Engineering Cancer Resistance: A Novel Framework Inspired by Evolutionary Adaptations

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Abstract

Cancer remains a leading cause of mortality worldwide, characterized by cells that exhibit 'monster traits' such as uncontrolled proliferation, invasiveness, resistance to apoptosis, and immune evasion. Traditional therapies often target single hallmarks of cancer, leading to limited success and eventual resistance. This paper proposes a novel, integrative therapeutic framework inspired by evolutionary adaptations in species with remarkable cancer resistance, such as elephants (*Loxodonta Africana*). Elephants possess enhanced TP53-mediated cancer surveillance and DNA repair mechanisms, which contribute to their extremely low cancer incidence. We hypothesize that by synthetically recapitulating these 'anti-monster' factors—such as augmented p53 activity, enhanced DNA repair, and controlled inflammation—in human cells, we can reprogram malignant phenotypes towards benignity. Our proposed strategy combines synthetic biology, gene therapy (including CRISPR/Cas systems), and multi-targeted pharmacological approaches to simultaneously address multiple cancer hallmarks. By leveraging advanced *in vitro* organoid and *in vivo* models, this research aims to pioneer a new paradigm in oncology that moves beyond cytotoxic elimination towards cellular reprogramming and durable cancer prevention, potentially yielding a significant reduction in lifetime cancer risk.

Keywords: Cancer Hallmarks, TP53, Synthetic Biology, Cancer Resistance, Gene Therapy

Introduction

The war on cancer, now decades old, has seen significant advances in early detection and targeted therapies. Despite this, cancer persists as a formidable global health challenge, with conventional treatments like chemotherapy and radiotherapy often causing significant collateral damage to healthy tissues and fostering the selection of resistant clones [1]. The seminal "Hallmarks of Cancer" framework by Hanahan and Weinberg elegantly categorizes the acquired capabilities that enable tumor growth and metastatic dissemination [2, 3]. These hallmarks—sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, and others—can be conceptualized as a set of 'monster traits' that empower cancer cells to thrive at the host's expense.

A promising avenue for novel therapeutic development lies in the study of species that have evolved exceptional cancer resistance. Peto's paradox observes that, contrary to expectation, cancer risk does not scale with body size or lifespan across species [4]. The elephant is a prime example, possessing over 20 copies of the TP53 tumor suppressor gene, compared to a single diploid set in humans [5]. This genetic amplification results in a super-sensitive apoptosis response to DNA damage, providing a powerful mechanism for eliminating potentially malignant cells early. Similarly, other

long-lived species like the bowhead whale and certain tortoises exhibit enhanced DNA repair pathways and controlled inflammatory responses, which are crucial for maintaining genomic integrity over a long lifespan [6].

This paper synthesizes these concepts into a novel research proposal. We posit that the evolutionary solutions to cancer found in nature can be translated into a therapeutic strategy for humans. We outline a framework for engineering cancer resistance by integrating multi-targeted approaches designed to reverse the 'monster traits' of cancer cells. This involves a combination of gene editing to enhance intrinsic tumor suppression, pharmacological agents to target key vulnerabilities, and synthetic biology circuits for conditional, tumor-specific activation of anti-cancer programs.

Discussion and Conclusion

The proposed framework represents a paradigm shift from reactive cancer treatment to proactive cancer prevention and cellular reprogramming. By targeting the core 'monster traits' of cancer simultaneously, we aim to create a synergistic therapeutic effect that could prevent the emergence of resistance, a common failure mode of single-target therapies.

Our discussion revolves around several core strategies. First, the enhancement of TP53 activity, inspired by the elephant, could be achieved through CRISPR/Cas9-mediated insertion of additional TP53 retrogenes or the development of 'p53 booster' synthetic circuits. These circuits could be designed for conditional activation in response to oncogenic stress signals, thereby minimizing off-target effects in healthy tissues [7]. Second, this genetic approach can be combined with established targeted therapies—such as TGF- β inhibitors to block epithelial-to-mesenchymal transition (EMT), BCL-2 inhibitors to induce apoptosis, and anti-VEGF agents to inhibit angiogenesis—to create a multi-pronged attack on the tumor's supportive infrastructure [8, 9].

The novelty of this approach lies in its integrative nature. It does not merely seek to kill cancer cells but to reprogram them by reinstating natural defense mechanisms that have been perfected by evolution. The concept of 'elephantizing' human cellular defenses, while futuristic, is grounded in observable biology. The potential human outcomes are profound, suggesting a path toward a dramatic reduction in lifetime cancer risk, potentially to less than 1%, alongside increased healthy lifespan due to enhanced genomic stability [10].

However, this vision is not without significant challenges and risks. The practical delivery of genetic material or specific activators, such as Piezo1 agonists, requires innovative solutions, potentially involving focused ultrasound or nanoparticle-based systems [11]. From a safety perspective, the risks of regulatory failure are non-trivial; over-activation of apoptosis could lead to catastrophic tissue loss, while under-activation could allow cancer to escape. Furthermore, the ethical implications of 'human genetic engineering' for enhanced traits, even for therapeutic purposes, demand careful and early consideration, including public dialogue and robust regulatory oversight [12].

In conclusion, the evidence from evolutionary biology provides a compelling blueprint for engineering superior cancer resistance in humans. By learning from nature's champions of longevity and cancer suppression, we can develop a new generation of therapies that target the very essence of malignancy. The next steps involve rigorous 'in vitro' validation using engineered organoid systems that recapitulate the tumor microenvironment, followed by studies in genetically modified mouse models. If successful, this research could fundamentally alter humanity's relationship with cancer, transforming it from a common deadly disease into a rare and manageable condition.

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References

- [1] Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71(3):209-49.
- [2] Hanahan D, Weinberg RA. The Hallmarks of Cancer. *Cell.* 2000;100(1):57-70.
- [3] Hanahan D, Weinberg RA. Hallmarks of Cancer: The Next Generation. *Cell.* 2011;144(5):646-74.
- [4] Peto R. Epidemiology, multistage models, and short-term mutagenicity tests. In: Hiatt HH, Watson JD, Winsten JA, editors. *The Origins of Human Cancer.* Cold Spring Harbor Laboratory Press; 1977. p. 1403-28.
- [5] Abegglen LM, Caulin AF, Chan A, Lee K, Robinson R, Campbell MS, et al. Potential Mechanisms for Cancer Resistance in Elephants and Comparative Cellular Response to DNA Damage in Humans. *JAMA.* 2015;314(17):1850-60.
- [6] Keane M, Semeiks J, Webb AE, Li YI, Quesada V, Craig T, et al. Insights into the evolution of longevity from the bowhead whale genome. *Cell Rep.* 2015;10(1):112-22.
- [7] Lim WA, June CH. The Principles of Engineering Immune Cells to Treat Cancer. *Cell.* 2017;168(4):724-40.
- [8] Albini A, Sporn MB. The tumour microenvironment as a target for chemoprevention. *Nat Rev Cancer.* 2007;7(2):139-47.
- [9] Fulda S, Debatin KM. Targeting apoptosis pathways in cancer therapy. *Curr Cancer Drug Targets.* 2004;4(7):569-76.
- [10] Gorbunova V, Seluanov A, Zhang Z, Gladyshev VN, Vijg J. Comparative genetics of longevity and cancer: insights from long-lived rodents. *Nat Rev Genet.* 2014;15(8):531-40.
- [11] Ibsen S, Tong A, Schutt C, Esener S. Sonogenetics: A New Frontier for the Control of Cellular Activity. *Proc SPIE Int Soc Opt Eng.* 2015; 9540:95400L.
- [12] National Academies of Sciences, Engineering, and Medicine. *Human Genome Editing: Science, Ethics, and Governance.* Washington, DC: The National Academies Press; 2017.

Declarations:

Author's Contribution:

- Conceptualization, and intellectual revisions, Data collection, interpretation, and drafting of manuscript
- The author agrees to take responsibility for every facet of the work, making sure that any concerns about its integrity or veracity are thoroughly examined and addressed

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