The Cancer Principle-III: Evolution by Cancer

Asima Tripathy[1], Rajat Kumar Pradhan[2]

[1]Post Graduate Department of Zoology and Microbiology, [2]Post Graduate Department of Physics, Bhadrak Autonomous College (Departmentment of Higher Education, Govt. of Odisha), Bhadrak, Odisha, India

Abstract

Cancer evolves to make all else evolve along with it. Each cancer cell is the result of a huge number of mutations undergone till the point of activation of uncogenes by some kind of natural selection. The uncovirus evolved all along entering the primitive cellular life as an endosymbiont through the mitochondrial route and got itself thoroughly entrenched in the very life process of each living cell, waiting for the appropriate moment to trigger tumor genesis. We propose that multicellularism evolved to arrest cancerous proliferation i.e. overgrowth of single cell types. Afterwards specialized tumor suppression mechanisms, cancer suppressor proteins, lymphoid organs with immune cells evolved to protect the organism against carcinogenesis. It seems as if only to not fall into cancer's deadly trap, all creatures have evolved definite mechanisms and in the process have not only gotten their diversified morphologies, but also their specific physiological systems.

Key Words: *Cancer Principle, oncovirus, oncogenes, Cosmic ordering principle, Principle of Disorder, CSP, VEGF*

Introduction

Unrestrained proliferation of any one category is always opposed by the emergence of effective control mechanisms evolving alongside it to counter such canker. The unrestrained growth is a tendency towards disruption of order and organization in the system and thus the counteracting agency must be an ordering principle or agency that always works to restore or maintain order and organization by adopting as many means and methods as would be suitable to counteract the force of cancer. Evolution of cancer cells by mutation and selection are exactly like evolution of species by such processes[1].

Mutation risk increases with age and with number of cells of an organism. Correspondingly cancer risk too must increase, since carcinogenic mutations become more probable with increasing mass and age. It means that higher mass animals such as elephants and whales compared to humans (or humans compared to mice) should have more susceptibility to cancer, while it is not observed to be so. This is Peto's paradox[2]. There must have been selection for definite protection against cancer with evolution of new morphological and biological characteristics such as larger body size and longer life[3]. The killer capacity of cancer has been highlighted by Lichtenstein as an additional hallmark and this must have had its selection agency in the evolution of various species, their mutation rates, body sizes, longevity, susceptibility to mutagens and so on[4]. Evolution of malignant tissues has been seen to be similar to evolution of drug resistance in bacterial communities[5]. Evidences are there that skin acted as a selection agent in the evolution of black pigmentation in early hominin[6].

Species-specific and cell-specific requirements for malignancy has been studied all through, but there has also been corresponding evolution of resistance against the disease[7]. Klein has emphasized studying the genetics of cancer resistance rather than of cancer attack which is clearly an evolutionary perspective[8]. For example the P53 family of genes including P63 and P73 has its common ancestry in the P63/P73 genes found in fish and sea anemones. They have later diversified in their functions in higher vertebrates though their sole function is to protect the germ-line from genomic instability following from various stresses[9].

The contribution of cancer to evolution all along the history of life on earth is so deep that Greaves has echoed Dobjhansky's famous statement in regard to it-

Corresponding author:
Asima Tripathy
Email ID: asimatripathy09@gmail.com

"Nothing in cancer makes sense …"[10].

Multicellularism

Cancer has been branded as a disease of the multicellular organisms where multicellualrity has failed[11]. How cancer permeates the entire landscape of multicellular life forms has been reviewed by Aktipis *et al*[12]. Note that cancer, in this series of essays, is an evolutionary force of unrestrained proliferation and not just a disease.

The autonomous unicellular became multicellular only to resist cancer. Is that autonomy somehow stored in the highly complex and organized multicellular organisms? Are the individual cells incessantly endeavoring for selfish reproductive success resulting in this tug-of-war for reproductive success between the organism and its "would-be-cancer-cells"? Indeed, the reproductive success of the organism might be the explanation for the late-age appearance of cancer[13]. Nature in this manner gives a chance to the organism to propagate itself by struggling and maximizing its reproductive success against its individualistically endeavoring "would-be-cancer-cells". Success of cancer cells proves that nature favors them or they have molded nature successfully so that oncomutations get inherited thereby. Further, competition among cancer cells leads to the faster dividing cells overpowering and outcompeting the comparatively slower dividing cells. Nature thus favors the cellular over the organismic reproductive success! Cellular reproduction has overpowered natural selection[14] !

Evolution of sexual reproduction

Reproduction as a process of fulfilment of the instinct for perpetuation is the common characteristic of all life[14]. However, no life-form has been able to proliferate indefinitely. The emergence of multicellularism from unicellularism is one such stage where unrestrained growth of unicellular life was halted in favor of complexity. Indeed, phylostaratigraphic tracking of oncogenes suggests that multicellularism in metazoa emerged as a micro-evolutionary transition following a complex multi-level selection[15]. Further, divergence of species occurred at different epochs of evolution owing to various selection pressures. Such diversification effectively controlled unrestrained proliferation of any one species by competition. For this reason, cancer is seen to be a failure of multicellularity[16]. Similarly sexual reproduction evolved from the asexual mode to drastically reduce asexual proliferation of the particular type.

Differentiation of cells in an organism is similar to diversification of species in the sense that both can be seen as an effect of a regulatory force that restricts undifferentiated growth of a particular kind. A tumor in an organism is just such an undifferentiated growth, which may become cancerous. The cancer suppressor gene, apoptosis, autophagy and such other cellular mechanisms have evolved only to suppress or eliminate the possibility of such undifferentiated cell growth or tumor formation. The existence of the definite times for cell division in different tissues is also such an effective mechanism[17].

Cancer Suppression Mechanisms

Cancer suppressor proteins(CSP) are part of the defense system of the body against cancer cells. If there is any abnormality or deviation in the cell multiplication, then these CSPs cause the cell to die or lead to its senescence. Thus CSPs are the reason for normal growth and make us fittest for survival[17]. Then how does CSP fail to halt the success of normal cells and give in to the cancerous mode? Is it only to gain higher uncontrolled reproductive success or it has some other deeper meaning?

For example, among the CSPs, P^{16} is one which causes senescence of abnormally multiplying cells. Contrary to this, VEGF (Vascular Endothelial Growth Factor) stimulates blood vessels to supply the cancer cells with sufficient nutrients for successful growth and multiplication. Here which one competes with which? The P^{16} competes with VEGF or nature competes with the supreme conscious evolutionary force? While nature's objective is reproductive success, the evolutionary force has for itself the role of ultimately monitoring nature's forces and consequences and takes care of things by endowing the organism with P^{16} against VEGF. Or, do both operate simultaneously on both P^{16} and VEGF to compete among themselves and finally it is the achievement of the beneficial one (P^{16}) to win? It has been found that the tumors become refractory and then become resistant to any antibodies tried against the VEGFs[18]. Similarly Tumor suppressor protein P53 is pitted against MDMX and MDM2 (or HDM2 in case of humans) that inactivate them[19]. Cancer seems to be winning in this battle of evolutionary competition!

Similarly, the genes responsible for facilitating the human fetus to form placenta in to the womb, normally remain silent in adult tissues. In cancer cells these genes become active and trigger aggressive growth of blood vessels to ensure energy supply for their growth and multiplication. It seems as if a cancer cell were the knower of all advantageous set-ups of the body and specializes in employing them for its own purpose! Indeed recent studies indicate that ancient retroviruses had a significant contribution in the development of placental gene regulatory networks in mammals[20]. The huge variation in mammalian placental form and function across species as well as phenotypic plasticity may be linked to the evolutionary diversifications of the retroviruses themselves[21,20].

Lymphoid organs and immune cells

In both vertebrates and invertebrates antigen-specific immunity serves the purpose of defense against virus, bacteria and other pathogens and primarily they protect the organism against pre-cancerous and cancerous cells and thus they contribute towards tumor suppression[23]. Immune system is comparatively more developed and complex in vertebrates[24,25]. The design of the whole lymphoid system such as primary lymphoid organs (bone marrow, thymus), secondary lymphoid organs (lymph nodes, spleen, mucosa associated lymphoid tissue, skin associated lymphoid tissue and lymph cells) and immune cells such as B cells, T cells and NK cells; phagocytes i.e. monocyte-macrophage system and neutrophils; antigen presenting cells (APCs), granulocytes, mast cells, platelets is to defend the body[26]. The cell-mediated and humoral (antibody) responses of the immune system result from the coordinated activities of all the immune cells, organs and tissues found throughout the body and they combinedly function to defend the body against antigens.

The whole micro-system of the body is protected by a cascade of defense mechanisms including Tertiary Lymphoid organs (TLOs) and Ectopic Lymphatic Organs (ELOs), but still cancer can easily take its place successfully[27,28]. It seems as if cancer were already there and in response to it the body has tried to develop some successful mechanisms but finally could only develop these defense systems which are but too feeble to defend against cancer so much so that even if cancer is detected and treated at an early stage and in an early age, premature ageing of the survivors starts[29].

Enucleation of RBCs in mammals

RBCs are pivotal to the life of many higher organisms and in the mammals, they are bereft of nucleus and hence are devoid of DNA. The increased oxygen carrying capacity, the flexibility of having a biconcave shape after the ejection of the nucleus and mitochondria are definitely potent reasons for the enulcleation. But the more important reason seems to us to be to not have any genetic material which can possibly become cancerous, from which there would be no escape from certain death[30,31]. The greatest advantage of getting rid of mitochondria and nucleus on the part of the mature RBC is thus to avoid cancer by getting rid of all genetic material, since it is seen that (Nucleated RBC) NRBC appear in adult patients just 2 to 3 weeks before death.

We tabulate below the cancer inhibitory and the cancer supportive processes respectively brought about by the actions of the cosmic ordering principle(COP) and the principle of disorder(POD)[32]. Therapeutic approaches to counter cancer are merely the actions of COP acting through our intelligence to restore order in the system affected by cancer(POD). This lets us put them under COP, though it may be said to be artificial while the systemic defenses are natural. But the natural-artificial divide here is itself quite artificial since intelligence-based therapeutic approaches are only too natural for human beings to take recourse to!

Table 1: Action of COP in cancer inhibition and POD in Cancer progression:

Processes	**Cosmic Ordering Principle(COP)**	**Principle of Disorder(POD)**
A. Cellular Processes	1. Growth inihibition signals	Self-sufficiency in growth signals
	2. Limited Replicative potential	limitless replicative potential
	3. Apoptosis	Evasion of Apoptosis
	4. Autophagy	Inhibition of Autophagy
	5. Necroptosis	Inhibition of Necroptosis
	6. Anoikis	Anoikis resistance
	7. Oxydative Phosphorilation	Glycolysis (Warburg effect)
B. DNA related processes	1. Chromatin remodeling 2. Histone modification 3. Epigenetic Control 4. Transcription factors 5. RNAi 6. DNA damage sensors 7. Non-homogeneous end-joining path way (Repair mechanism)	DNA damage:- adducts and lesions Mutation accumulation. oncogenes Mutational inactivation of Tumor suppressor genes. DNA Repair failure. Intra tumor heterogeneity
	8. Antioxidant defense system	Over-production of oxyradicals and ROS.
	9. Telomere erosion	Telomere preservation/reactivation
C. Immune system	1. Immune cells of different kinds 2. Immune editing 3. Lymphoid organs	Immune suppression
	4. Cancer suppressor proteins	VEGF (Vascular Endothelial Growth factor), sustained angiogenesis, Lymphangiogenesis
	5. Macrophages	Anti-inflammatory immune suppressor
D. Extra-cellular processes	1. Cell-cell adhesion	Metastasis
	2. Tumor progression inhibitory microenvironment	Tumor progressive adaptations, Degradation of extra-cellular matrix to create new passages for metastasis
E. Therapeutic intervention	1. Surgical intervention 2. Ancillary clinical strategies such as anaesthetics, analgesics and anti-inflammatory drugs 3. Other therapeutic approaches	Post-operative accelerated metastasis and peri-operative immuno-suppression, All round Systemic dysfunction, multiple organ failure and the resultant appearance of host of other diseases

Conclusion

We focused on how cancer has shaped up evolution in crucial stages and in decisive ways, out of which we explicitly dealt with evolution of multicellularism, reproduction, immune system and a few other aspects. Multicellularism arrests unicellular proliferation but, the organization of tissues and decentralization of responsibilities by their spatially limiting the urge for proliferation of the cells create a pressure on the somatic cells to react and become cancerous. Cancer is thus a fundamental factor in evolution of multicellulars with all kinds of tumor-suppression mechanisms. In the extracellular niche, the cells proliferate and are continuously under competition pressure for nutrition, survival and space. Thus, the cell may reach a competing state to acquire high ability to grow, divide and gain strength to attain immortality, by acquiring an oncomutation. Though tumor-suppression mechanisms are in place, cancer has its ways to wade around them and metastasize. Indeed, nothing in evolution makes sense except in the light of cancer.

Ethical Clearance- Not needed for this kind of study

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References

1. Casás-Selves M, DeGregori J. How Cancer Shapes Evolution and How Evolution Shapes Cancer. Evolution: Education and Outreach. 2011;4(4):624–634
2. Peto R. *et al*. Cancer and ageing in mice and men, Brit. J. Cancer. 1975;32:411-426.
3. Leroi A. *et al*. Cancer selection. Nature reviews. Cancer. 2003;3:226–231
4. Lichtenstein AV. On evolutionary origin of cancer. Cancer Cell International. 2005;5(1):5-13.
5. Lambert G, Estevez-Salmeron L, Oh S, Liao D, Emerson BM, Tlsty TD, Austin RH. An analogy between the evolution of drug resistance in bacterial communities and malignant tissues. Nat Rev Cancer. 2011;11(5):375–82.
6. Greaves M. Was skin cancer a selective force for black pigmentation in early hominin evolution? Proc Biol Sci B. 2014;281(1781):20132955.
7. ***Rangarajan A,*** *et al*. Species- and cell type-specific requirements for cellular transformation. Cancer Cell. 2004;6:171–183
8. Klein G. Toward a genetics of cancer resistance. Proceedings of the National Academy of Sciences of the United States of America. 2009;106:859–863
9. Belyi VA *et al*. The origins and evolution of the p53 family of genes. Cold Spring Harb Perspect Biol. 2010 ;2(6):a001198
10. Greaves M. Nothing in cancer makes sense except… BMC Biology 2018**;**16:22. https://bmcbiol.biomedcentral.com/articles/10.1186/s12915-018-0493-8
11. Trigos AS, Pearson RB, Papenfuss AT, Goode DL. How the evolution of multicellularity set the stage for cancer. British Journal of Cancer (2018) 118, 145–152.DOI: 10.1038/bjc.2017.398.
12. Aktipis CA *et al*, Cancer across the tree of life: Cooperation and cheating in multicellularity, Phil Trans R Soc B. 2015; 370: 20140219. http://dx.doi.org/10.1098/rstb.2014.0219
13. Rozhok AI, DeGregori J. The evolution of lifespan and age-dependent cancer risk. Trends Cancer. 2016;2(10):552–560.DOI:10.1016/j.trecan.2016.09.004
14. Tripathy A, Pradhan R. The Indomitable Force of Instinctive Urge in Competitive Success, Stress Response and Evolution, IJSRR Apr-Jun 2019a; 8(2):2286-2300.
15. Domazet-Loso T, Tautz D. Phylostratigraphic tracking of cancer genes suggests a link to the emergence of multicellularity in metazoa, *BMC Biology* 2010,**8**:66. http://www.biomedcentral.com/1741-7007/8/66
16. Pennisi E. Is cancer a breakdown of multicellularity? *Science* 29 Jun 2018;360(6396):1391,DOI:10.1126/science.360.6396.1391
17. Jakobisiak M, Lasek W, Golab J. Natural mechanisms protecting against cancer, Immunol Lett. 2003 Dec 15;90(2-3):103-22.
18. Shibuya M. Vascular Endothelial Growth Factor (VEGF) and Its Receptor (VEGFR) Signaling in Angiogenesis: A Crucial Target for Anti- and Pro-Angiogenic Therapies. Genes & Cancer 2011;2(12):1097–1105.DOI: 10.1177/1947601911423031.
19. Sherr CJ. Principles of Tumor Suppression. Cell

2004; 116(2): 235-246. https://doi.org/10.1016/S0092-8674(03)01075-4

20. Chuong EB, Rumi MA, Soares MJ, Baker JC. Endogenous retroviruses function as species-specific enhancer elements in the placenta. Nat Genet. 2013;45(3):325–329. DOI:10.1038/ng.2553
21. Sharif J, Shinkai Y, Koseki H. Is there a role for endogenous retroviruses to mediate long-term adaptive phenotypic response upon environmental inputs? Phil Trans Roy Soc. B 2013;368(1609):20110340. http://dx.doi.org/10.1098/rstb.2011.0340
22. Chuong EB. The placenta goes viral: Retroviruses control gene expression in pregnancy. PLoS Biol. 2018;16(10):e3000028 .doi:10.1371/journal.pbio.3000028
23. Buchmann K. Evolution of innate immunity: clues from invertebrates via fish to mammal 2014; 5 Article 459 : 1
24. Cooper MD, Alder MN. The Evolution of Adaptive Immune Systems. Cell 2006 Feb; 124(4):815-822. DOI:https://doi.org/10.1016/j.cell.2006.02.001
25. Hirano M. Evolution of vertebrate adaptive immunity: immune cells and tissues, and AID/APOBEC cytidine deaminases. Bioessays. 2015 Aug; 37(8):877-87.doi: 10.1002/bies.201400178. Epub 2015 Jun 17.
26. Engelhard VH, Rodriguez AB, Mauldin IS, Woods AN, Peske JD, Slingluff Jr. CL. Immune Cell Infiltration and Tertiary Lymphoid Structures as Determinants of Antitumor Immunity J Immunol. 2018; 200 (2): 432-442.DOI: https://doi.org/10.4049/jimmunol.1701269
27. Colbeck EJ, Ager A, Gallimore A, Jones GW. Tertiary Lymphoid Structures in Cancer: Drivers of Antitumor Immunity, Immunosuppression, or Bystander Sentinels in Disease? Front. Immunol. 2017; 8:1830.DOI:10.3389/fimmu.2017.01830
28. Lin L, Hu X, Zhang H, Hu H. Tertiary Lymphoid Organs in Cancer Immunology: Mechanisms and the New Strategy for Immunotherapy. Front Immunol. 2019; 10:1398.DOI:10.3389/fimmu.2019.01398
29. Cupit-Link MC, Kirkland JL, Ness KK, et al. Biology of premature ageing in survivors of cancer. ESMO Open 2017; 2:e000250.DOI:10.1136/esmoopen-2017-000250
30. Schering JL, Munoz J, Raybon E, Hegab S, Hanbali AS, and Kuriakose P. The diagnostic and prognostic implications of nucleated red blood cells in myelophthisis. Journal of Clinical Oncology 2011; 29(15): 6576-6576
31. Danise P, Maconi M, Barrella F, et al. Evaluation of nucleated red blood cells in the peripheral blood of hematological diseases. Clinical Chemistry and Laboratory Medicine (CCLM) 2011; 50(2): 357-360.DOI:10.1515/cclm.2011.766
32. Tripathy A, Pradhan RK. Consciousness as the cosmic ordering principle and the interplay of order and disorder in the physical and biological systems, IJSRR 2019 b; 8(1):859-73