The Cancer Principle-IV: The Inevitability and Invincibility of Cancer

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Abstract

The inevitability and invincibility of cancer despite the evolution of various systemic strategies such as apoptosis, senescence and autophagy etc. over millennia in all species, point to its fundamental ingrainment in all existence as the principle of unrestrained proliferation. Cancer is in real command of all cellular and organismic processes and can reorient and modulate them all to its advantage. It seems reasonably clear that all life, whether unicellular or multicellular, individual or species, is destined to end in a cancerous boom. It has found ways to evade all suppression mechanisms and strategies and can stem from many sources and causes such as external chemical and viral carcinogens and also internal genetic reasons.

Key words: *apoptosis, oncovirus, oxyradicals, immortality*

Introduction

Cancer has defeated all our attempts to control any of its hallmarks precisely because neither its pathology nor its biology completes its etiology[1,2]. It seems that it has some inbuilt strategy to counteract any attempt from outside for prevention, intervention, treatment and eradication by multipronged therapeutic approaches. This strong never-say-die character of cancer hints at the deepest principle of immortality which is operative in all organisms as the struggle for survival.

Continuously occurring mutations in a cell lineage over a length of time increase the chances of hitting upon an oncomutation provided mutations are truly random. In contrast metaevolutionary transencoding of urges and instincts into the genes through epigenetic channels may suffice to give more definite routes for oncomutations to occur. In particular long term impact of stress and repercussions of acute shock induced by accidents and bereavements may be sufficient to produce oncomutations in the DNA by over-production of ROS. Inevitable exposure to environmental carcinogens (UV radiation, chemical mutagens etc.) leads to a faster rate of cellular proliferation which leaves little scope for the DNA repair mechanisms to heal the damages caused. Our approach to cancer prevention has to be modified by a suitable shift of attitude since cancer is not a disease but a living force that has proved its mettle for survival since times immemorial.

Cancer as a late age phenomenon

Generally, cancer is the disease in late ages[3,4]. The delay is possibly because the cells should gain multiple variations before they become cancerous as if the cancerous cells know and remember that multiple variations are required for being selected to survive to the next generation unfailingly. The multicellular organisms are equipped with efficient tumor suppressive mechanisms, otherwise it would have been impossible for them to develop into a well coordinated organized organism[5]. Recently, by Monte Carlo simulation of the effect of key somatic evolutionary parameters on carcinogenesis, ageing-dependent somatic selection and evolution of species-specific tumor suppression mechanisms have been demonstrated to have played significant roles in cancer incidence across tissues as well as species[4]. Similarly Xu and Taylor studied epigenetic changes by DNA methylation that lead to a lowering of threshold for malignant transformation that partly explains the increased incidence of cancer with age[6]. In our view, all these fundamentally imply that in

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addition to the urge for reproduction, the urge to avoid becoming a tumor cell was also a primary objective for the unicellular in the primordial stages of evolution.

Cell senescence and apoptosis

Cell suicide (Apoptosis) and cell senescence and autophagy are mechanisms in the cells to get rid of carcinogenic mutations[7]. These mechanisms can also be seen as having developed to achieve tumor suppression[8]. Suppression of rogue cell growth was thus a primary objective of the primordial living cell. It implies that though unrestrained cancerous proliferation is at the origin of life, the whole process of origin and evolution of complexity of life can be seen as a continuous struggle only to enhance the tumor suppressive mechanisms to limit cancer. In fact, cancer treatment by exploiting cell senescence mechanisms have long been proposed since by the early onset and acceleration of senescence in the tumor cells, they can be made to die before proliferating too much[9]. Similarly, if massive autophagy can somehow be triggered in the cancer cells in a targeted manner, tumors can be effectively eradicated.

Apoptosis is the natural design for the cell for its death in fixed time. Apoptotic mechanisms are highly regulated to ensure such programmed cell death[10]. It is the process of elimination of unnecessary and unwanted cells. The information for apoptosis is encoded in every gene but the process gets activated, if there is DNA damage or uncontrolled proliferation[11]. There is loss of apoptotic regulation in cancer[12]. The apoptotic pathway is regulated by intracellular (mostly mitochondrial) and extracellular (death receptor) mechanisms. The signals generated at intracellular level are DNA damage, deprivation of growth factors and deprivation of cytokine. The signals which are generated from extracellular level are by toxic T cells for the damaged cells for death of infected or impaired cells[13].

We observe that apoptosis is designed specifically for the prevention of cancer[14]. Because of loss of apoptotic regulation the tumor cells survive longer, as a result of which mutations get accumulated, thereby increasing invasiveness and virulence and thus angiogenesis is stimulated which enhances cell proliferation and negatively affects cell differentiation[15]. The mitochondrial pathway of apoptosis may be seen as the initial action of the COP to make mitochondria endosymbiotic in bacteria for multicellularism to come up and restrict the unrestrained proliferation of unicellulars, but afterwards resistance mechanisms to it developed leading to apoptotic deregulation by which cancer thrives. Now researchers are focusing to effect apoptosis by targeting such pathways so that cancer cells will become apoptotic to eradicate cancer cells[16]. But who can guarantee that cancer is not already in the know of such attempts and can easily find its way out?

Stem cells and Telomeres

As per Darwinian view, cancer might be the attempt of a cell to adapt to a changing and unsuitable environment. Thus it supports our hypothesis of primal role of cancer in the first emergence of life since during that time the environment was changing and not suitable. This answers the question: Why cancer targets stem cells for initiation and why are stem cells situated in highly shielded locations[17-19]? It seems that only to evade cancer only stem cells have a highly shielded niche. Stem cell mechanism is in place in the organism in such a way that it must prevent somatic cell division through divergence, as if it were suspected pretty prior to the multiplication of somatic cells that they will definitely grow cancerous if left differentiated! All the stem cells of the respective tissues are positioned in well planned locations which guarantee protective niches for them, but almost all cancers with more than two mutagens have been observed to have some link to mutations at the level of corresponding stem cells, though the transit cells are more prone to replication errors than the average stem cell[17].

The chromosomes are capped by telomeres to maintain the DNA codons which thus act as part of the tumor suppressive mechanisms. In unicellular organisms and the germ cells, telomeres are maintained to ensure exact propagation of the original genetic code. But in case of adult tissue, the somatic cells cannot maintain telomeres since they get reduced in length by repeated cell division. The shortened telomere causes cell death and this might be the reason for decline of tissues during aging[20]. The cancerous urge of the somatic cells to acquire immortality in spite of telomere erosion by possible reactivation mechanisms leads to tumors[21].

Invincibility of oncovirus

Cancer occurs through mutations and these mutations make them grow faster, survive better and reproduce faster[25]. As the organisms grow in complexity and organization, this particular instinct in each individual cell is suppressed by the corresponding evolution of

the cancer suppressor genes whose only function is to control the rate of multiplication in specific manner. On the contrary, the viral strains continue to increase their virulence by becoming more and more specific to their hosts and were always looking for infecting any organism which would guarantee their fastest rate of multiplication. This they achieve by disabling the cancer suppressor gene in a particular infected cell. The most dominant factor of evolution has been the instinct for multiplication right from the stage of the peptides and nucleotides. When mitotic cell division became the prominent mode of multiplication, this particular instinct drove organisms towards the fastest possible multiplication in their existing environments but when multicellularism evolved, this particular instinct in every cell for the fastest rate of multiplication could not be fulfilled because of specificity of their functions for ensuring survival of the multicellular organism. Cancer cells acquire immortality by gaining the ability to divide for ever (Infinite reproduction fitness). This is how tumors arise as a consequence of the most dominant instinct for fastest multiplication in every cell.

Biotic interactions may be having their role in the evolution of the individual to divide faster than others, which is responsible for origin of cancer. This is similar to the competition occurring between somatic and germ cells. As per ecological theory, species extinctions may have a role in preventing cancer. Along with species extinction cancer elimination occurs either by their habitat destruction[26] or competition or resource limiting factors that disrupt their life. So, this unavailability of resource may be one reason for metastasis of the cancer cells exactly as in case of organisms, resource unavailability leads to diversification of the population (dispersal). So it seems nature selected cancer cells first and cancer suppression mechanisms came in after such selection.

Stress, Oxyradicals and the inevitability of cancer

The eventual expression of the oncogenes is so inevitable that so far only unsuccessful suppressor mechanisms of different kinds have evolved against it through the entire course of evolution of life on earth. Therefore, no single cancer suppressor mechanism has proved itself effective enough to eradicate cancer as if the cosmic ordering agent acting against it were certain about the invincibility of cancer and hence the suppression mechanisms are only to continuously improve in an unending succession.

One of the reasons for the inevitability of cancer is its relation to mental and physical shock and stress, both of which can lead to tumors. The mechanism has to do with stress induced oxy-radicals in the cellular level which damage DNA and thereby increase chances of carcinogenesis[27,28]. Overproduction of ROS leads to mitochondrial malignancy[29]. For example, bereavement of a loved one can cause such a melancholic vacuity in the mind that it can act in a psycho-somatic way on the physical body and form tumor in a specific organ[30,31]. Similarly, an accidental physical injury (Such as a burn injury) suffered in any organ leading to a fibrosis (Scarring) may turn malignant in course of time[32]. And, who on earth can be completely free from shocks, stress and accidents in life!

Mitochondrial DNA as the Uncogenome

The role of mtDNA mutagenesis in cancer initiation and progression has recently been in focus[33,34]. Oxidative damage is one of the primary causes of such mutagenesis though replicative polymerase error is also proposed to be the next possible reason. Free oxy-radicals in the mitochondria are abundant as it is the site of cellular respiration and these free radicals can cause oxidative damage to the mtDNA. About 60% of all solid tumors have more than or equal to one mtDNA mutation, though not all are caused by oxidative damage[35,36]. Still, the fact that the damaged mtDNA lead to cancer, only shows its inevitability since respiration is an unavoidable cellular process and this happens in the mitochondria and is associated with oxidative damage to mtDNA. Further, it could be surmised that it might be cancer that drove the mitochondrion in the first place to become endosymbiont in the process of evolution of the eukaryotes.

Conclusion

Each cell in an organism has a different history, and hence a different life, specific to itself. For this reason oncogene expression in a particular cellular lineage is specific to that lineage having its own evolutionary time scale to become manifest. This is the reason why successful treatment of cancer of one affected tissue does not protect the organism against cancer of other tissues. Continuous exposure to organic and inorganic carcinogens increases the stress and thus pro-tumorigenically alters the cellular processes such as redox homeostasis and makes the oncogenes expression more probable and hastened.

Faster growing populations are thus more favored by the cancer principle to survive as species and indeed the lower organisms such as viruses and bacteria, having faster growth rates are the ones that are seen to be vastly outnumbering the higher organisms in nature. They, like cancer cells, not only multiply faster but also adapt at a faster pace to changing selection pressures in the biotic and abiotic environments. Faster multiplication and expert adaptation are key characteristics of the cancer cells as well as of the favored species in nature. Somatic cells try to become immortal by outcompeting the reproductive cells which have conditional immortality (if they take part in reproduction) and thus become cancer cells. Immortality seems to be a fundamental feature of life and all life is striving for immortality only. "Survival of the fittest" cannot mean survival till a certain death occurs, even for that fittest of organisms or species. Cancer points to this fundamental fact of immortality beyond the death of the organism.

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Conflict of Interest- NIL

References

1. Hanahan D, Weinberg RA. Hallmarks of cancer, Cell 2000;100:57-70.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144: 646–674.
3. Harding C, Pompei F, Lee EE, and Wilson R. Cancer Suppression at Old Age. Cancer Res. 2008;68(11). DOI:10.1158/0008-5472.CAN-07-1670
4. 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
5. Rozhok AI and DeGregori J. Toward an evolutionary model of cancer: Considering the mechanisms that govern the fate of somatic mutations. Proc Natl Acad Sci U S A.2015;112(29):8914-21. DOI:10.1073/pnas.1501713112.PMID:26195756. PMCID: PMC4517250.
6. Xu Z, Taylor JA. Genome-wide age-related DNA methylation changes in blood and other tissues relate to histone modification, expression, and cancer. Carcinogenesis 2014;35(2): 356-64. DOI:10.1093/carcin/bgt391.
7. Childs BG, Baker DJ, Kirkland JL, Campisi J, van Deursen JM. Senescence and apoptosis: dueling or complementary cell fates? EMBO reports 2014;15(11):1139
8. Cerella C, Grandjenette C, Dicato M, Diederich M Roles of Apoptosis and Cellular Senescence in Cancer and Aging. Curr Drug Targets. 2016;17(4):405-15.
9. Lee S, Lee JS. Cellular senescence: a promising strategy for cancer therapy. BMB Rep. 2019;52(1):35-41.PMID:30526771,PMCID:PMC6386234.
10. Wong RSY. Apoptosis in cancer: from pathogenesis to treatment, Journal of Experimental & Clinical Cancer Research 2011;30:87. http://www.jeccr.com/content/30/1/87
11. Danial NN. Korsmeyer SJ. Cell death: Critical control points. Cell 2004;116:205–219.
12. Fernald K, Kurokawa M. Evading apoptosis in cancer. Trends Cell Biol.2013;23(12): 620–633. DOI:10.1016/j.tcb.2013.07.006
13. Ouyang L. et al, Programmed cell death pathways in cancer: a review of apoptosis, autophagy and programmed necrosis. Cell Proliferation 2012;45:487–498.DOI:10.1111/j.1365-2184.2012.00845.
14. Sellers RW and Fisher DE. Apoptosis and cancer drug targeting. J Clin Invest. 1999;104(12):1655-1661.https://doi.org/10.1172/JCI9053.
15. Lowe SW, and Lin AW, Apoptosis in cancer. *Carcinogenesis 2000;*21(3):485–495, https://doi.org/10.1093/carcin/21.3.485
16. Nguyen C, Pandey S. Exploiting Mitochondrial Vulnerabilities to Trigger Apoptosis Selectively in Cancer Cells.Cancers 2019;*11*(7):916. https://doi.org/10.3390/cancers11070916
17. Cairns J. Somatic stem cells and the kinetics of mutagenesis and carcinogenesis. Proc Natl Acad Sci U S A. 2002;99(16): 10567–70. PMCID:PMCPMC124976. pmid:12149477
18. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. Nature 2001; 414(6859):105–11.[PubMed: 11689955]
19. Gatenby RA, Gillies RJ, Brown JS. Evolutionary dynamics of cancer prevention. Nat Rev Cancer. 2010; 10(8):526–7.[PubMed: 21137109]
20. Shay JW, Wright WE. Senescence and immortalization: role of telomeres and telomerase.

Carcinogenesis 2005;26(5):867-74.

21. Bernal A, Tusell L. Telomeres: Implications for Cancer Development, Int J Mol Sci. 2018; 19: 294;DOI:10.3390/ijms19010294
22. Alizon S, Bravo IG, Farrell PJ, Roberts S. 2019 Towards a multi-level and a multi-disciplinary approach to DNA oncovirus virulence. Phil. Trans. R. Soc. B 374: 20190041. http://dx.doi.org/10.1098/rstb.2019.0041
23. Kareva, I. What can ecology teach us about cancer? Translational oncology 2011;4:266–270.
24. Vaiko M, Izakovic M, Mazur M, Rhodes CJ, Telser J. Role of oxygen radicals in DNA damage and cancer incidence. Mol Cell Biochem. 2004;266(1-2):37-56
25. da Fonseca RR, Johnson WE, O'Brien SJ, Vasconcelos V, Antunes A.. Molecular evolution and the role of oxidative stress in the expansion and functional diversification of cytosolic glutathione transferases. BMC Evol Biol.2010;15(10): 281. DOI:10.1186/1471-2148-10-281.
26. Ralph SJ et al. The causes of cancer revisited: "Mitochondrial malignancy" and ROS-induced oncogenic transformation – Why mitochondria are targets for cancer therapy. Molecular Aspects of Medicine 2010;31(2):145-170. https://doi.org/10.1016/j.mam.2010.02.008
27. Soung, NK, Kim, BY. J Anal Sci Technol.2015;6:30. https://doi.org/10.1186/s40543-015-0070-5
28. Braem MG, Onland-Moret NC, Schouten LJ *et al*. Multiple miscarriages are associated with the risk of ovarian cancer: results from the European Prospective Investigation into Cancer and Nutrition. PLoSOne.2012;7(5):e37141. DOI:10.1371/journal.pone.0037141
29. Wallingford SC, Olsen CM, Plasmeijer E, Green AC. Skin cancer arising in scars: a systematic review. Dermatol Surg.2011;37(9):1239–1244. DOI:10.1111/j.1524-4725.2011.02060.x
30. Song S, Gong S. *et al*. The interaction between mitochondria and oncoviruses, BBA - Molecular Basis of Disease, 2018;1864 (2):481–487
31. Gammage PA, Frezza C. Mitochondrial DNA: the overlooked oncogenom**e?** BMC Biology Aug 2019;17: 53.
32. Stewart JB, Alaei-Mahabadi B, Sabarinathan R, Samuelsson T, Gorodkin J, Gustafsson CM, Larsson E. Simultaneous DNA and RNA mapping of somatic mitochondrial mutations across diverse human cancers. PLoS Genet. 2015;11(6):e1005333.
33. Yuan Y. *et al*. Comprehensive molecular characterization of mitochondrial genomes in human cancers. bioRxiv.2017:161356.
34. Strakova A, Murchison EP. The cancer which survived: insights from the genome of an 11000 year-old cancer. Curr Opin Genet Dev.2015;30:49-55. DOI:10.1016/j.gde.2015.03.005.
35. Lotka AJ. Contribution to the Theory of Periodic Reaction, *J Phys Chem.*1910.14
36. Lotka AJ. Analytical Note on Certain Rhythmic Relations in Organic Systems. Proc Nat Acad Sci USA.1920;6:410.