International Journal of Research and Review
Vol. 9; Issue: 7; July 2022
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Cancer and Evolution: An Ancient Relation Explored Recently

Anirban Chatterjee

Department of Zoology, Bolpur College, Birbhum, WB, India

Corresponding Author: Dr. Anirban Chatterjee

DOI: https://doi.org/10.52403/ijrr.20220736

ABSTRACT

Cancer is a consequence of multi-cellularity and is a striking example of multilevel selection. The theory of cancer initiation and progression has its root deep within the evolutionary and ecological concepts. Cancer develops through somatic evolution, with genetic and epigenetic precariousness, generating fitness variation among the cells in the body. Epidemiological, genetic, and molecular biological research have cumulatively provided us with a brimming source of data that affirms our current understanding of the etiology and molecular pathogenesis of cancer. But this aspect only focuses on immediate mechanisms and does not competently explain the pervasiveness of tumors and cancer in animal species or what seems to be the exceptional vulnerability of *Homo sapiens*. At a practical level, analyses suggest that, for evolutionary reasons, as a species, we are inherently more likely to develop cancer (than we might like to admit). Though we cannot reverse our genetic legacies and predilection to cancer, emphasizing inherent vulnerability in an 'evolutionary' way strongly ratifies our current attempts to combat cancer. In actuality, neoplasms are microcosms of evolution. Within a neoplasm, a mosaic of mutant cells competes for space and resources, evades predation by the immune system, and can even cooperate to disperse and colonize new organs (metastasis). The evolution of neoplastic cells can explain both why we get cancer and why it has been so difficult to find a cure. Although the idea of cancer as an evolutionary problem is not new at least historically little attention has been delivered to applications of evolutionary biological principles in understanding and controlling neoplastic progression. Already, we have reached the high time when this should be changed. Ernst Mayr aptly said that "No biological problem is solved until both the proximate and the evolutionary causation has been elucidated"

Keywords: [Cancer, adaptation, evolution]

Cancer is a disease that affects us all, a global health problem that kills millions of people around the world every year. Recently, scientists have focussed to investigate cancer as a microcosm of evolution, a disorder of clonal evolution within the body itself, with cells picking up new mutations and spreading, analogous to Darwin's great tree of life. Cancer is a leading element of death worldwide and, regardless of an incredible amount of effort and monitory funding, the elimination or control of the disease especially during the advanced stage has not been realized. It is the very processes that have impelled the evolution of life on this planet that are inexorably at work within our bodies curating cancer development. We (both scientists and clinicians alike) crucially need a new way of thinking about how cancer originates, proceeds, advances, and how we might thwart and of course treat it based on evolutionary substantiality, and that too pretty soon [1-3].

Past half a century of scientific research has provided us with a much greater understanding of cancer biology and genetics. Still, the translation of our knowledge into clinical practice needs to

allow for the cellular convolutions of the disease and its dynamic, evolutionary characteristics. These countenances provide both impediments to, and opportunities for, successful treatment of the disease. The 'disease-ecosystem and adaptive landscape need to be focussed on. [4,5]. The scenario is now changing and showing promise toward further developments. Recent scientific evidence is pointing towards the intricate and indisputable involvement of 'Darwinian Evolution through Natural Selection' in the development and progress of cancer. On a microscopic scale, neoplastic cells meet the conditions for evolution by Darwinian selection: cell reproduction with heritable variability that affects cell survival and replication. This advocates that, like other areas of biological and biomedical research, Darwinian theory can produce a generic fabric for a logical Current and raw molecular data provide a promising opportunity that, this theory may guide in translating data into understanding and progress of the disease. Considerable conceptual and analytical tools from evolutionary biology can be applied successfully in interpreting cancer biology. At present two clinical problems may gain considerable betterment from the application of Darwinian theory: neoplastic progression and acquired therapeutic resistance. The Darwinian theory of cancer has especially (also) extensive significance in drug development, both in terms of interpreting past difficulties, and pointing the way toward new assuring and rational approaches. Since cancer engages complicated evolutionary processes, research should integrate both manageable experimental systems and also protensive observational studies of the evolutionary fluctuations of cancer in laboratory animals and human patients. Cancer biology demands contemporary and methodical tools to control the evolution of neoplastic cells. For ecologists and evolutionary biologists, natural selection and evolutionary theories are usually realized as the realm of peppered moths and finches, demonstrating adaptations in response to predation and competition owing to environmental changes. Indeed, few students of Darwin and Mayr would perceive that their role is far greater in the comprehensive understanding of the current paradigm of a so-called 'molecular disease'. Although molecular biologists, by disquisitive contrariety, have long perceived carcinogenesis as an evolutionary process involving natural selection among 'rebel' cells, the evolutionary forces that result in the development and progress of cancer have come under the intended investigation of evolutionary biologists (and ecologists) and this interdisciplinary interlacing is providing encouraging outcomes, in recent times [6-13]. We are indeed learning from the 'master'. The elemental principle of a Darwinian evolutionary system is the 'purposeless' and unbiased genetic variation of reproductive individuals of common descent, where natural selection favors the fittest variants. Cancer is an unmistakable illustration of such a system. It will not be 'over-saying' that, we humans are born with cancerous traits. Most mutational processes have a preference at the DNA sequence level. A particular mutational spectrum in a cancer cell is a rumination of error-prone repair processes or associated with various genotoxic stresses (for example, cigarette carcinogens/ mutagens, ultraviolet light, chemotherapeutic drugs, and other lifestyle pollutants) [14,15]. The dynamics of somatic evolution depend on the interaction of mutation rate and clonal expansion. The synergistic and complementary interactions among selectively advantageous 'driver' lesions, selectively neutral 'passenger' lesions and deleterious 'hitchhiker' lesions makes the cancer clones evolve just as life has evolved following the inevitable path of evolution. Supplementarily, 'mutator' lesions boost the rate of other genetic and microenvironmental changes that alter the fitness effects of those (previously mentioned) lesions [16-20]. The conventional model of clonal evolution advocates that a series of clonal expansions

flourishes to overshadow the neoplasm (‘selective sweeps’) [21,22]. The altercation of gradualism versus punctuated equilibrium (an enduring debate in species evolution) has emerged in the scrutinizing and contemplation of the clonal evolution of neoplasms in recent times. It is to be scientifically discerned, whether malignant clones, with their considerably altered genomes, evolve gradually through a sequence of genetic alterations and clonal expansions accumulating many lesions over time in subtle and uncommon situations, resulting in undetected subclones that finally appear and progress through clonal expansion; or have a few, considerable punctuated modifications, possibly prompted by contemporary but severe insults or a single, calamitous mitotic event that generates multiple lesions pan-genome (or on a single chromosome, known as chromothripsis) [23-26]. Cancer-cell habitats are not closed systems. The site and elements for fitness selection (the adaptive landscape) for the cancer cells are provided by the tissue ecosystems. The interaction between cancer cells and their tissue habitats is complementary. Reconditioning of the tissue microenvironment and establishing ‘tailored’/ specific niches where they can thrive well with a greater competitive advantage by the cancer cells has been well established. In addition to regulation by several intrinsic and fundamental factors (such as nutrients and hormones) or invasion by inflammatory or endothelial cells, the tissue ecosystem is altered by various external factors too such as radical chemotherapy or radiotherapy. On many occasions, the stroma or ‘specialized habitat niches’ may protect cancer cells against therapies, however, these therapies successfully exterminate most of the growing tumor cells, but the reconstructed landscape generates new selective pressures, resources, and opportunities that may allow pre-existing variant cancer cells that survived treatment to emerge; mostly the ‘cancer stem-cells’ which lie hidden and dormant deep within a tumor mass with a plethora of adaptive characteristics. [27-32]. Natural Selection is driven by several ecological interactions, such as competition, predation, and cooperation. These same selective forces and other factors encourage the somatic evolution of cancer systems in living tissue. [33–36]. Predators successfully regulate the population sizes of prey and select for antipredator adaptations, in ecological interactions, limiting their foraging abilities too. The cellular cognate of predation is an immune system attack on cells recognized as unfamiliar, abnormal, or ‘rogue’, which has recently been established as imperative in suppressing and eliminating cancer in the early stages/ premalignant stages. [33, 34, 37, 38].

Alike individual animals living in an ecosystem, cells exist in a complex interactive environment too, and the cellular niche or habitat is defined by intercommunication with the extracellular matrix as well as with other cells, and such contacts are indeed essential in controlling the cell growth. Thus, stem cell proliferation can be disciplined by the cellular microenvironment, and an insult to this environment can institute carcinogenesis. A fresh clone of cancer cells competes with nearby cells for food and other vital services, such as waste removal, initially within its indigenous environment. Scientists have incorporated tumor heterogeneity and have developed an evolutionary ecological model that demonstrated that interactions in such cellular associations could lead to competitive exclusion of cell lineages, on a few occasions giving rise to ‘hypertumors’ that capitalize on/ abuse the developed vasculature to grow more rapidly than do other cancer cell clones, but eventually disappear because unable to support further angiogenesis. Ancillary histological evidence supports the existence of hypertumors in some cancers and the evolution of the balance between cooperation and competition in tumor cells has crucial clinical implications for the successful development and delivery of

various cancer therapies. The preservation of diversity and cellular heterogeneity in tumors might also be influenced by competition between genetically different cancer cell populations, just as competition cultivates diversity in ecological communities at the population and species levels creating dimensions of adaptive fitness and circumstances of evolution. [35, 39-42]. In recent times, genomic instability has been viewed as a process that greatly increases levels of genetic variations and accelerates the rate of somatic evolution in carcinogenesis and these genetic variations provide the fundamental raw material for somatic and population-level evolution of cancers. Genomic instability is essentially important to the development and thriving of malignancy for many types of cancer. Selection for increased mutation rate in cancers has decisive significance for various cancer therapy because many chemotherapeutic agents are themselves selective mutagens that might encourage cellular variations through positive selection resulting in adaptive fitness and rendering such therapeutic interventions seemingly ineffective in the long run[43-45].

An accelerated evolution is expected to engender evolutionary disequilibrium that gets revised over time, but antagonistic coevolution might drive continuing changes that generate some degree of maladaptation in patients, which becomes supposedly difficult to treat using conventional practices[46]. Phenomenon aptly described as 'tugs-of-war' over resources as observed during gestation mediated by the invasiveness of placentation and other physiological processes of pregnancy, translates into evolutionary facets such as 'Parent-offspring conflict' which also promote the evolution of increased cancer risk [47-49]. Recently, several epigenetic factors (in addition to accepted genetic and environmental components) have been established to play key roles in promoting carcinogenesis through 'genomic imprinting. Even effective therapeutic interventions are notably dependent upon such epigenetic aspects (such as protein modifications, gene-switching, etc.). These epigenetic factors greatly influence the adaptive landscape of tumors and their eventual evolution [50,51]. Considerable contemporary studies have provided evidence that natural selection brings about diverse macroevolutionary constraints on morphology and development while reducing cancer risks. Anticancer selection actively selects against morphogenetic variants and induces evolutionary conservatism in morphology and physiology those in turn somehow are 'pre-cancerous' [52-55].

Although undoubtedly genes and mutations are essential –at the same time, it has been well established that's the fuel by which cancer evolves. So maybe one can gain improved acumen in understanding, preventing, and treating cancer if one relocates into the mindset of ecologists and evolutionary biologists, thinking about tumors as populations of genetically diverse individuals roving around in the habitats of the body, subject to the rules and impulse of natural selection. And to successfully appreciate the evolutionary expedition that each of them took to get there and enumerate where they might be heading in the future, not only do we need to know about their genes, but we also need to map the adaptive landscapes in which they thrive and progress. An evolutionary and ecological understanding of cancer development will allow scientists, clinicians, and policymakers to better associate cancer incidence with its causes. Carcinogenesis, a form of 'somatic evolution' follows similar evolutionary principles known from organismal biology. Its impact on our lives makes our understanding of this process direly pivotal. Beyond simply therapeutically targeting cancer phenotypes, one has to learn how to exploit and influence the fitness value of oncogenic genotypes by regulating the tissue microenvironment. An evolutionary understanding of cancer, superintended by adaptive oncogenesis and other

contemporary theories, should determine how we prevent, diagnose, and treat cancers. To maneuver tissue fitness landscapes, one needs to better contemplate how the conditions of tissue landscapes can either preclude or promote oncogenesis. Recognition, realization, and clinical acceptance that the fitness effects of oncogenic mutations are highly dependent on the tissue microenvironment can allow us to devise procedures that not only cripple cancer cells but also diminish precancerous scenarios. It is high time we admit that cancer risk has been shaped by evolution at the organismal level and cancers evolve within us, molded by many of the same evolutionary forces throughout the evolution of life itself. A deep understanding of both of these frameworks will allow us to better control this dreaded disease.

More than forty years ago, Philadelphia-born scientist Peter Nowell wrote a short article in the prestigious journal 'Science', with unnerving prescience, the last two lines of the paper's summary read: "Hence, each patient's cancer may require individual specific therapy, and even this may be thwarted by emergence of a genetically variant subline resistant treatment. More research should be directed toward understanding and controlling the evolutionary process in tumors before it reaches the late stage usually seen in clinical cancer" [4]

REFERENCES

1. Greaves, M. Cancer: The Evolutionary Legacy, Oxford University Press, 2000
2. Graham, J. Cancer Selection: A New Theory of Evolution, Aculeus, 1992
3. Gatenby, R.A. and Vincent, T.L. An evolutionary model of carcinogenesis. Cancer Res. 2000; 63, 6212–6220
4. Nowell, P. C. The clonal evolution of tumor cell populations. Science. 1976; 194, 23–28
5. Crespi, B. & Summers, K. Evolutionary Biology of Cancer. Trends Ecol. Evol. 2005; 20, 545–552
6. Heppner, G. & Miller, F. The cellular basis of tumor progression. Int. Rev. Cytol. 1998; 177, 1–56
7. Cairns, J. Mutation selection and the natural history of cancer. Nature. 1975; 255, 197–200
8. Tsao, J. L. *et al*. Genetic reconstruction of individual colorectal tumor histories. Proc.Natl Acad. Sci. USA. 2000; 97, 1236–1241
9. Tsao, J. L. et al. Colorectal adenoma and cancer divergence. Evidence of multi-lineage progression. Am. J. Pathol. 1999; 154, 1815–1824
10. Michor, F., Iwasa, Y. & Nowak, M. A. Dynamics of cancer progression. Nature Rev. Cancer. 2004; 4, 197–205
11. Maley, C.C. and Forrest, S. Exploring the relationship between neutral and selective mutations in cancer. Artif. Life. 2000; 6, 325–345
12. Galis, F. and Metz, J.A.J. Anti-cancer selection as a source of developmental and evolutionary constraints. Bioassays. 2003; 25, 1035–1039
13. Leroi, A.M. *et al*. Cancer selection. Nat.Rev. Cancer. 2003; 3,226–231
14. Stratton, M. R. Exploring the genomes of cancer cells: progress and promise. Science. 2011; 331, 1553–1558
15. Bardelli, A. etal. Carcinogen-specific induction of genetic in stability. Proc. Natl. Acad. Sci. USA. 2001; 98, 5770–5775
16. Maley, C. C. et al. Selectively advantageous mutations and hitchhikers in neoplasms: p16 lesions are selected in Barrett's esophagus. Cancer Res. 2004; 64, 3414–3427
17. Bignell, G. R. *et al*. Signatures of mutation and selection in the cancer genome. Nature. 2010; 463, 893–898
18. Greenman, C., Wooster, R., Futreal, P. A., Stratton, M. R. & Easton, D. F. Statistical analysis of pathogenicity of somatic mutations in cancer. Genetics. 2006; 173, 2187-2198
19. Youn, A. & Simon, R. Identifying cancer driver genes in tumor genome sequencing studies. Bioinformatics. 2011; 27, 175–181
20. Bozic, I. et al. Accumulation of driver and passenger mutations during tumor progression. Proc. Natl Acad. Sci. USA. 2010; 107, 18545–18550
21. Schwartz, M., Zlotorynski, E. & Kerem, B. The molecular basis of common and rare fragile sites. Cancer Lett. 2006; 232, 13–26
22. Loeb, L. A. Human cancers express mutator phenotypes: origin, consequences, and

targeting. Nature Rev. Cancer. 2011; 11, 450–457
23. Siegmund, K. D., Marjoram, P., Woo, Y. J., Tavare, S. & Shibata, D. Inferring clonal expansion and cancer stem cell dynamics from DNA methylation patterns in colorectal cancers. Proc. Natl Acad. Sci. USA. 2009; 106, 4828–4833
24. Aktipis, C. A., Kwan, V. S. Y., Johnson, K. A., *et. al*. Overlooking evolution: a systematic analysis of cancer relapse and therapeutic resistance research. PLoS ONE. 2011; 6, e261000
25. Beerenwinkel, N. et al. Genetic progression and the waiting time to cancer. PLoS Comput. Biol. 2007; 3, e225
26. Stephens, P. J. et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. Cell. 2011; 144, 27–40
27. Aguirre-Ghiso, J. A. Models, mechanisms and clinical evidence for cancer dormancy. Nature Rev. Cancer. 2007; 7, 834–846
28. Cairns, J. Mutation selection and the natural history of cancer. Nature. 1975; 255, 197–200
29. Anderson, A. R., Weaver, A. M., Cummings, P. T. *et. al.* Tumor morphology and phenotypic evolution driven by selective pressure from the microenvironment. Cell. 2006; 127, 905–915
30. Chen, J., Sprouffske, K., Huang, Q. & Maley, C. C. Solving the puzzle of metastasis: the evolution of cell migration in neoplasms. PLoS ONE. 2011; 6, e17933
31. Gilbert, L. A. & Hemann, M. T. DNA damage-mediated induction of a chemoresistant niche. Cell. 2010; 143, 355–366
32. Jones, S. et al. Comparative lesion sequencing provide insights into tumor evolution. Proc. Natl Acad. Sci. USA. 2008; 105, 4283–4288
33. Breivik, J. The evolutionary origin of genetic instability in cancer development. Semin. Cancer Biol. 2005; 15, 51–60
34. Summers, K. et al. Intragenomic conflict and cancer. Med. Hypotheses. 2002; 59,170–179
35. Gonzalez-Garcıa, I. et al. Metapopulation dynamics and spatial heterogeneity in cancer. Proc. Natl. Acad. Sci. U. S. A. 2002; 99, 13085–13089
36. Nagy, J.D. Competition and natural selection in a mathematical model of cancer. Bull. Math. Biol. 2004; 66, 663–668
37. Jako´bisiak, M. *et al*. Natural mechanisms protecting against cancer. Immunol. Lett.2003; 90, 103–122
38. Maley, C.C. and Reid, B.J. Barrett esophagus. In Nature Encyclopaedia of the human genome (eds), 2003; pp. 253–257
39. Khong, H.T. and Restifo, N.P. Natural selection of tumor variants in the generation of "tumor escape" phenotypes. Nat. Immunol. 2002; 3, 999–1005
40. Michor, F. et al. Dynamics of cancer progression. Nat. Rev. Cancer. 2004; 4, 197–205
41. Klein, C.A. The systemic progression of human cancer: a focus on the individual disseminated cancer cell - the unit of selection. Adv. Cancer Res. 2003; 89, 35–66
42. Nagy, J.D. Competition and natural selection in a mathematical model of cancer. Bull. Math. Biol. 2004; 66, 663–668
43. Breivik, J. and Gaudernack, G. Resolving the evolutionary paradox of genetic instability: a cost-benefit analysis of DNA repair in changing environments. FEBS Lett. 2004; 563, 7–12
44. Komarova, N.L., and Wodarz, D. The optimal rate of chromosome loss for the inactivation of tumor suppressor genes in cancer. Proc. Natl. Acad. Sci. U. S. A. 2004; 101, 7017–7021
45. Gatenby, R.A. and Freiden, B.R. Information dynamics in carcinogenesis and tumor growth. Mutat. Res. 2004; 568, 259–273
46. Thaler, D.S. Hereditary stability and variation in evolution and development. Evol. Dev. 1999; 1, 113–122
47. Kavanagh, K.D. Embedded molecular switches, anticancer selection, and effects on ontogenetic rates: a hypothesis of developmental constraint on morphogenesis and evolution. Evolution. 2003; 57, 939–948
48. Kleene, K.C. Sexual selection, genetic conflict, selfish genes and the atypical patterns of gene expression in spermatogenic cells. Dev. Biol. 2005; 277, 16–26
49. Crespi, B. and Semeniuk, C. Parent-offspring conflict in the evolution of the vertebrate reproductive mode. Am. Nat. 2004; 163, 635–653

50. Ohlsson, R. et al. Epigenetic variability and the evolution of human cancer. Adv. Cancer Res. 2003; 88, 145–168
51. Nunney, L. The population genetics of multistage carcinogenesis. Proc. R. Soc. Lond. B Biol. Sci. 2003; 270, 1183–1191
52. Weinstein, B.S. and Ciszek, D. The reserve-capacity hypothesis: evolutionary origins and modern implications of the trade-off between tumor-suppression and tissue-repair. Exp. Gerontol. 2002; 37, 615–627
53. Frank, S.A. *et al*. Patterns of cell division and the risk of cancer. Genetics. 2003; 163, 1527–1532
54. Heppner, G. H., Miller, B. E. & Miller, F. R. Tumor subpopulation interactions in neoplasms. Biochim. Biophys. Acta. 1983; 695, 215–226
55. Crespi, B. J. & Summers, K. Positive selection in the evolution of cancer. Biol. Rev. Camb. Philos. Soc. 2006; 81, 407–424

How to cite this article: Anirban Chatterjee. Cancer and evolution: an ancient relation explored recently. *International Journal of Research and Review*. 2022; 9(7):320-326. DOI: *https://doi.org/10.52403/ijrr.20220736*

******