The Cancer Principle-I: Introducing Cancer as a Fundamental Principle of Nature

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Abstract

In a series of five articles we put forth and establish a new principle, namely the cancer principle which we propose as a fundamental principle of nature. Cancer is an agent of the principle of disorder and is at the root of origin of life, evolution of species and may be, is also the determinant of the ultimate fate of all life. We introduce and motivate this principle and provide arguments in favor of its being at the origin of all evolution. Cancer is defined as the tendency for unrestrained proliferation that is operative in both inanimate and animate worlds and that has given rise to the phenomenon of life from the nonliving background.

Keywords: *cancer, disorder, order, evolution, self-replication*

Introduction

Cancer is unrestrained proliferation. The unicellular organisms evolved as the primary life-forms on earth at least around 3 to 3.5 billion years ago[1,2]. The multiplication rate in them is no doubt high, but the average time taken for each division is typical of the species and is constant. In multicellular organisms, the cells stop dividing when the respective organs reach their appropriate size, but in case of cancer, the cells go on dividing indefinitely. The cancerous cells are having remarkable adaptive ability for survival. They work on the surrounding cells and destroy them and create space for their own accelerated multiplication and growth[3,4].

Hippocrates (460-370BC) used the ancient Greek name *carcinos* (meaning crab), pronounced *karkinos*, which has its origin in the proto-indo-european word *korkros*, or may be, even pre-dated by the corresponding original Sanskrit word *karkata* (also meaning crab), possibly due to the finger-like projecting spiculations from the sore which make a crab-like appearance[5] and it may also be related to angiogenesis[6]. This most ancient name also surprisingly indicates that cancer is a living organism and not just a disease[7]. Perhaps, no other disease has such a name. Interestingly, the analogy with crab also catches the other prominent characteristics of cancer: the crab makes several holes for its residence by digging out lumps of mud which dry up to harden, and which do look like tumors on earth (Tumorigenesis)! If its hole is closed in one place, it digs out a lump at another place, exactly as does cancer in post-operative metastasis[8].

The increased virulence of harmful pathogens is because of their adaptive evolution in course of time. The drug resistance in the pathogens is part of the mechanism of survival fitness in terms of evolutionary advantage[9]. Insecticide resistance in a vector is an adaptation for the evolutionary advantage of the vector species for its survival and reproductive success[9,10,11]. In the chain of vigorous competition, cancer-causing pathogens have gone much ahead. In recent works, carcinogenesis has been proposed to be a form of speciation and cancer development as an evolutionary process in which nature selects some cells that can develop new metabolic pathways of aggression and resistance[12,13].

Cosmic origins of molecular Self-replication

Each elementary particle (*e.g*. an electron or a proton or even a photon) has the ability to store information and to interact in specific ways with other particles depending on their quantum numbers. When such particles come together to form larger aggregates such as nuclei in stellar

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interiors and atoms in relatively colder regions such as planets, the information-storing ability increases and gets encoded in the quantum states of such composite systems[14]. In course of time and in suitable conditions such as the earth's, long chains of carbon atoms with different functional groups forming biomolecules can come up with their definite information and interaction capacities. The possibility of self-replication is inherent in long chains of carbon atoms because of the self-similarity of the chain over long segments, the reason for self-similarity being the availability of particular kind of radicals in a particular environment. Fragments of such chains of carbon atoms can become ligand as well as receptor for the formation of larger biomolecules that can replicate themselves. A chain of carbon atoms thus holds within itself the most important possibility of self-replication[15]. Too long a carbon chain may easily break into similar and smaller fragments which is the basis of self-replication of complex biomolecules such as nucleic acids and proteins[16].

Evolution and Cancer

As per the Darwinian evolution paradigm, the mutations are random and nature selects the fittest under the circumstances to survive and therefore, the individual organism seems to have very limited personal, willful choice in its evolution because it is nothing but a colony of its genes which gets propagated down the generations, presumably with naturally selected mutations[17]. Natural selection is often credited with the power to bring up complex adaptations in nature[12]. We may ask: What is the urgency in the cells to divide so rapidly as to become cancer cells? What is the origin of oncogenes? What is the active principle of natural selection of these cancer cells here? What is the purpose of the complex adaptations of a cell to be cancerous? Why natural selection is unable to drive out or kill these cancer cells from the body in order to ensure survival of the organism? Or, is there some other more powerful natural process which, in its own course, will be able to wipe out the cancer cells from the body of the organism, or is it the contrary: *Is all life going to merge in Cancer*?

Existing theories of cancer such as the SMT (Somatic Mutation Theory) and TOFT (Tissue Organization Field Theory) are partial in their success since most of the cancers remain untraceable to their underlying causes[18]. SMT holds that cancer is a disease of cell proliferation while TOFT holds that it is a disease of tissue organization. The SMT, TOFT and other such approaches are mere plausible mechanisms of cancer and don't completely address the fundamental causes thereof[19,20]. In the integrative approach, metabolic imbalance and immunologic response in the host are taken along with genetic causes as determining cancer formation as well as growth lading to eventual mortality[21]. Analysis of bioenergetics of cells lends further support to such an integrative theory of cancer as to its molecular basis in living cells, though it is yet unclear how driver mutations and passenger mutations are related and why such huge numbers of driver mutations are there in the uncogenic landscape[22,23] of the same type of cancer even.

The atavistic theory of cancer proposed by Davies and Lineweaver views it to be a return to the preferential expression of ancient genes that were present during the transition from unicellular to multicellular species[24]. This pre-dates the origin of cancer to about a billion years back when metazoan life was present which acted as an intermediate stage between unicellulars and more complex multicellulars.

All the characteristics of cancer were nicely paraphrased as the six hallmarks by Hanahan and Weinberg as: (1) self-sufficiency in growth signals, (2) insensitivity to growth-inhibitory (antigrowth) signals, (3) evasion of programmed cell death (apoptosis), (4) limitless replicative potential, (5) sustained angiogenesis, and (6) tissue invasion & metastasis[25]. There are, no doubt, natural defense mechanisms in the individual organism to fight against cancer[26]. Then what evolutionary advantage do the cancer cells gain by overpowering the defense mechanisms of the individual *i.e.* by working against the survival of the organism itself, whose constituents they actually are? Is it not the intense urge for unrestrained proliferation ingrained somehow in each cell to acquire the greatest reproductive success since the time when it was but a unicellular organism? And, since that time, it has been the organism's continuous effort to gain the ability to multiply as rapidly as possible to establish its maximum potentiality to gain reproductive and survival fitness but, only that it took its time to come to the multicellular organism? Or, is the root of cancer somewhere else?

On the other hand, there is increasing realization among biologists that cancer has played a major role in the evolution of multicellularism, cellular defenses, apoptosis, cancer suppressor genes, tumor suppressor mechanisms and epigenetic mechanisms, all in the

direction of naturally combating cancer only[27]. In the process, diversifications of many species as well as of the many viral strains of the oncovirus have all occurred and are still continuing. Thus, susceptibility to cancer seems to be a possible key selection pressure on organisms, thereby determining their evolution. Therefore, what are stated to be the causes of cancer are actually its effects[19]. We therefore envisage cancer as a fundamental principle of nature, namely the principle of unrestrained proliferation following from the principle of disorder (POD), rather than as a mere disease.

The cancer principle

We thus propose:

Cancer is at the origin of life; the incessant struggle against it is the evolution of species and finally, succumbing to it is the ultimate fate of all life.

Hugely surprising it may seem, but which fact about cancer is not surprising! Defined as *unrestrained proliferation*, it is indeed what perfectly captures the phenomenon of life. Cancer, as the tendency for unrestrained proliferation, has taken the form of life. This is the proposal of "origin of life in cancer". In fact, the astrobiological theory of cancer proposes on certain evidences that it must have been a universal phenomenon in all life in the cosmos, including alien life and those in exoplanets, because any star that supports such life must have UV radiation predominant in its spectrum against which in case of life on the earth there evolved the tumor suppressor genes P53/P63/P73, whose primary function in those early times was to protect the DNA against damage due to UV radiation[28].

The next three essays in this series will deal with the role of cancer in evolution and evolution of cancer itself since the beginning. There are many factors that try to limit the propensity of life for unrestrained proliferation, and hence comes evolution[29]. In the last decade or so, it has been increasingly realized that cancer itself has an independent evolutionary path through the expert adaptation of the oncoviruses to outcompete all others in the fray. On the other hand, tools of evolutionary biology have also been increasingly getting used for studying cancer and dealing effectively with it[30,31].

Finally, in the last two articles we deal with the last part of the principle i.e. the inevitability, invincibility and immortality of cancer, which sounds like doom-saying. But going by the rampaging trend of unstoppable march of cancer as a phenomenon (about 70% to 80% of all cancer is of unknown etiology), we feel that it can be amply justified. Davies opines, "In that sense, cancer is an accident waiting to happen"[32]. It is as certain as that! The cancer principle thus seeks to invert the argument that cancer is the product of evolutionary processes[33]; rather it is cancer that causes all evolution! What concerns us in this series is the ontology of cancer rather than its epistemology as a multistage process[34,35] or as an effect of evolution.

Conclusion

Different points of view on cancer that we have outlined here only point to its multi-facetedness and we have not exhausted all the views that have so far been proposed by way of theorizing. Cancer as a fundamental principle determining all evolution, from the origin of life itself to the dissolution, is of course a startling proposition. What we have motivated in this first article is that, if we define it as the urge for unrestrained proliferation instead of being just a disease, then it does indeed turn out to be an all-potent determining agency which, by its collusion and conformity with the principle of disorder(POD) that is universally operative, has led to all evolution by opposing the cosmic ordering principle(COP). This continuous see-saw between the ordering principle and the disorder agent (cancer) is at the root of all evolution, and even, of the origin of life itself. From the low entropy initial pre-big-bang state to the expanding universe, from structure formation to radiating stars, from abiogenesis to tumorigenesis – all are processes brought about by the principle of disorder against the cosmic ordering principle that ever acts to organize, regulate and systematize.

In trying to counteract the tendency to move towards the maximally disordered state of thermodynamic equilibrium of non-living components of the universe, the compromise obtained by COP is what we call "life". But it too is not free from the operations of the disorder principle, as it is inherent and inbuilt into the very fabric of the universe, and hence is present in all the constituents of living organisms. The living organisms are far-from-equilibrium systems which are complex dissipative structures. They maintain homeostasis, order and organization by continuous exchange of matter, energy and entropy with the surroundings, ever striving for an organized steady-state rather than sliding down to maximally disordered thermodynamic equilibrium, which is nothing but death of the organism. The COP

strives to bring forth and maintain order and organization in all systems in opposition to the POD.

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