Journal of Cancer Biology

Afrasiabi, J Cancer Biol 2021; 2(3): 62-67.

Review Article

Entropy and cancer: The Future of cancer therapeutics

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Received date: June 15, 2021
Accepted date: July 15, 2021

Citation: Afrasiabi K. Entropy and cancer: The future of cancer Therapeutics. J Cancer Biol 2021; 2(3): 62-67.

Abstract

Evolution of our thinking and design of cancer therapeutics [1] has gone through a tortuous path in the last eighty or so years, since the first patient was treated with a chemical agent [2]. Introduction of nitrogen mustard in the treatment of cancer in 1940's was based on a serendipitous finding and observation during the second world war [3].

Design of multiagent chemotherapy protocols [4] which was the next step in the evolution of this path, was based on the thinking that killing cancer cells through interference with their life cycle in multiple directions and through multiple paths, would lead to a better outcome.

Through time, dissection of different intracellular pathways [5], related to cell survival and proliferation, has guided the design of newer agents interfering with and antagonizing those pathways [6]. The driving force of our thinking has all time been development of more sophisticated means to kill cancer cells [7].

Recurrence of cancer following complete response, as well as upfront resistance to chemo and targeted therapy has led to significant frustration and roadblock in clinical arena [8]. This has led to consideration of other kinds of approach to neoplastic disorders.

Meanwhile a better understanding of fundamental concepts, such as chromosomal instability [9] and intratumor heterogeneity [10], alongside developments, such as single cell sequencing [11] and nano-technology [12] have started to pave the road for future cancer therapeutics.

Keywords: Entropy, Master regulator complex, Cellular network entropy, Nano-machines, Cancer tumor evolutions, Future cancer therapeutics

Introduction

The second law of thermodynamics [13] has rightfully been recognized as the most fundamental law that prevails the known universe [14]. Interplay of living cell with this law is perhaps the most fascinating of all [15]. The most elegant part of this interplay is to maintain the network entropy [16] of numerous subcompartments of living cell at the lowest possible level, dictated by the limits of the second law. This inversely correlates with the maximum amount of free energy in different subcompartments of the living cell [17]. During the lifetime of living organisms, there is a constant tug of war, which at one end drags the cell towards higher level of entropy through the spontaneous increase in entropy of the surrounding universe, and a pullback by the constituents of living cell to lowest possible level, at the other end.

As such, since inception of life in primordial oceans [18], living organisms have armed themselves with sensors [19] in virtually every corner, angle and subcompartment, and executors which work in harmony to maximize free energy which inversely correlates with network entropy [20]. Indeed, this is the foundation of living organisms and the engine of their evolution in the last thirty-eight hundred million years or so.

One could see such footprints/sensors and executors across the board and without exception, ranging from telomeres [21] to epigenome [22], micro-RNA network [23], gene regulatory mechanisms [24] and protein-protein interactions [25]. Forward move of the thermodynamic arrow

of time gradually shifts the equation towards higher level of systems network entropy [26].

Among a multitude of DNA damaging agents [27], inflammation seems to be the strongest pro-entropy force carrying the most immediate destructive power [28]. That is why our cells at mid-life are loaded with diverse group of mutations, the goal of which is protection against this strong pro-entropy force [29]. However, during the latter part of our life, as a result of universal increase in systems network entropy, those protective mutations prove deleterious.

Consequently, it makes a lot of sense that our future cancer therapeutics would tackle this most fundamental issue.

Entropy and Living Cell

The second law of thermodynamics is sitting at the center of evolution of life on earth. By the virtue of this law, the index of instability or disorder of the known universe is incessantly on the rise. This correlates inversely with free energy of a closed thermodynamic system. It has long been recognized that the living cell is the most efficient machinery as far as capability to minimize the speed of rise in entropy is concerned. All the subcompartments of living cell have evolved and have been selected toward achievement of this goal. This ranges from quaternary structure of cellular proteins [30], to elasticity of cell membrane [31], regulatory gene mechanisms [32], RNA spliceosomes [33], micro-RNA network [34], and epigenome [35].

Cellular networks, ranging from G-protein coupled receptors [36] which act as the radar of cellular energetics, modulating fair and balanced distribution of cellular energy, to proteasomes [37] and ubiquitination machinery [38] which eliminate old proteins characterized by their distorted quaternary structures which portend significant decrease in their plasticity or free energy, follow the same law. This further extends to fine harmony and alignment of constituents of Krebs cycle [39] and ATP generating machinery of mitochondrion [40].

Mitotic spindles [41], microtubules [42], kinetochores [43], centromere geometry [44] and centrosomes [45], as well as telomeres [46] are not exceptions to this rule. Indeed, the fine orchestration and spontaneity of sequence of complex events are all different notes of this fascinating symphony of life.

I have alluded to this process as law of spontaneity in the book that I published in 2018 [47]. The two major components of this fascinating harmony are sensors [48], which exist at virtually any subcompartment of the cell and executors [49], which have evolved to adopt the task of keeping cellular networks entropy at the lowest level, as per the limits of the second law of thermodynamics. Perhaps the most important of these sensors are the ones that sense thermodynamics arrow of time [50], which directly lead to aging [51] and increase in cellular network entropy.

Telomeres could be considered the masterpiece built into the genome in this regard [52]. Their shortening following consecutive rounds of mitosis reflects the passage of time [53], which at a critical threshold activates apoptotic machinery to prevent catastrophic cellular events [54].

As perfect a machinery as living cell is, clearly it cannot escape minimal increase in network entropy [55], the accrual of which through time, leads to aging [56], disease [57], and demise [58]. In this regard, neoplastic transformation [59] could be considered a process in which increase in cellular networks entropy happens at a massively fast pace [17], such that the built-in cellular machineries cannot catch up with its repair, even if they have remained functional. Clearly sensors, executors, or a combination of both could have become dysfunctional in different scenarios and to different degrees.

Methodology

By employing single cell sequencing technology, we could derive and decipher DNA, RNA, micro-RNA, epigenome, and protein signatures of master regulator clusters of cells in game changing compartments of tumor mass [60]. In this regard, glioblastoma multiforme could serve as a reasonable example [61] (Figure 1).

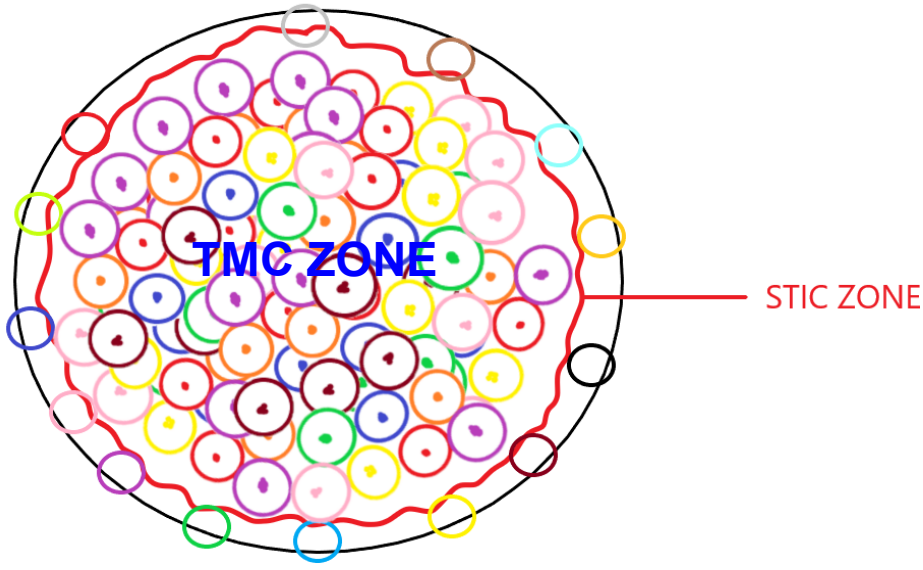

Figure 1: General schema of glioblastoma multiforme tumor mass with TMC and STIC zone representations.

TMC zone (Tumor Mass cell zone) generates tumor bulk, by replication and generation of pre-existing and new gene signatures. STIC zone (Stem-like tumor initiating cell zone) homes the stem like initiating cancer cells. Cells in this zone could reprogram tumor mass following surgical resection, by a multitude of mechanisms, including conversion to tumor mass zone cells.

Cluster of master regulator and driver cells reside in TMC (tumor mass cell) zone, and regenerator cells exist in STIC (stem-like initiating cell) zone [62]. Master regulator and driver cluster of cells in TMC (tumor mass cell) zone act as a driving force for repopulating the tumor mass. Regenerator cells could replenish the whole glioblastoma multiforme tumor mass with their diverse group of DNA, RNA, protein, and epigenome signatures following surgical resection [63] (Figure 2).

Following single cell sequencing and measurement of master regulator complex network entropy and genetic signature of malignant cells in these two key areas of tumor mass and deciphering their evolutionary roadmap, programmable nano-machines would get deployed to execute appropriate modifications of their cellular and master regulator complex network entropy and distorted signatures [64] (Figure 3).

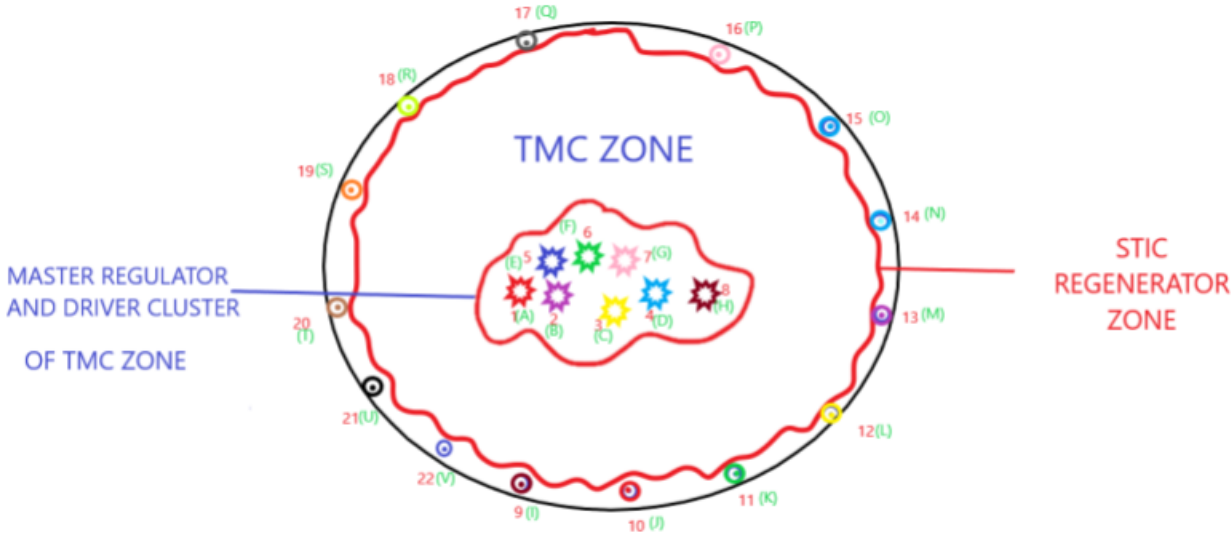

Figure 2: Master regulator complex network entropy. A-H: different values of master regulator complex network entropy and single cell sequenced DNA & RNA signatures; 1-8: hold master regulator network entropy values and their signatures of A-H; 9-22: STIC (stem-like initiating cell) regenerator cells, hold master regulator network entropy values and their signatures of I-V.

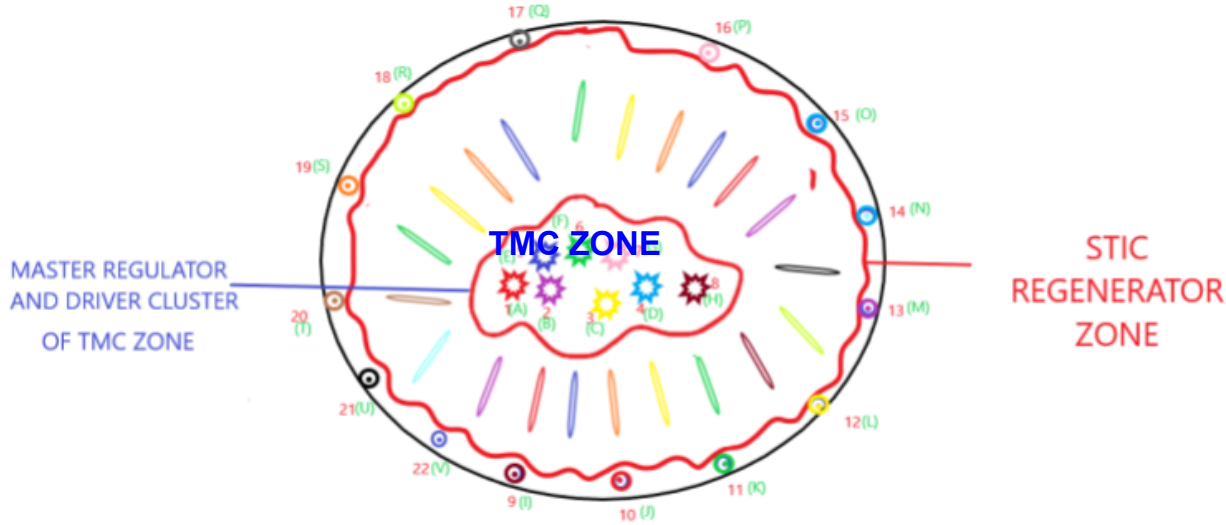

Figure 3: Master regulator complex network entropy and distorted signatures. TMC zone: Tumor Mass Cell Zone; STIC zone: Stem-like Initiating Cell Zone.

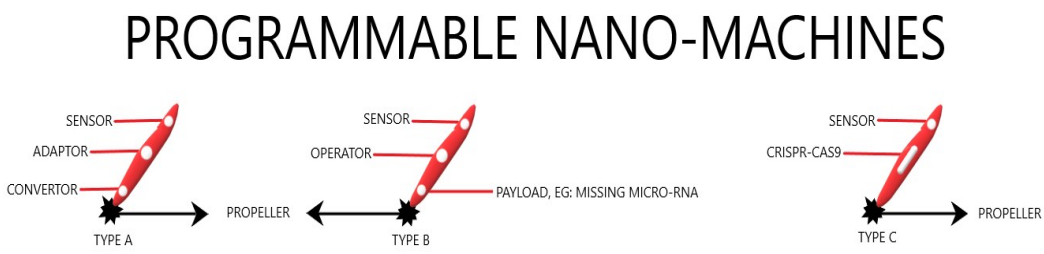

Figure 4: Programmable nano-machines.

Depiction of programmable nano-machines deployed into tumor mass to execute the task of appropriate modification of master regulator network entropy and gene signatures. There are so many different ways to achieve this goal and this needs to get tailored and customized for different malignancies, in different ways. In case of glioblastoma multiforme, programmable nano-machines could get delivered intraoperatively or following surgical resection by painting the resection margins with a liquid containing the programmable nano machines. Generally speaking, programmable nano-machines, which are capable of modifying the master regulator complex network entropy and other distortions, could either get delivered intralesionally or systemically.

Such conversion could be done either by delivering the calculated electrostatic forces into the cells in the areas of interest [65], or by delivering the necessary modifications in genome, epigenome, protein, RNA, or micro-RNA compartments [66] (Figure 4).

As such, we would be tackling the heart of the matter, namely distorted cellular and master regulator complex network entropy, which is sitting at the center of neoplastic transformation. Consequently, evolutionary road of tumor mass would get blocked or slowed down. This eventually leads to significant prolongation of patient's life, and on occasion could potentially translate into cure.

Conclusion

The last eighty or so years has been quite a fascinating journey in the history of cancer therapeutics. We started with nitrogen mustard and evolved into multi-agent chemotherapy, targeted [67] and immunotherapy [68]. We have developed multimodality treatment strategies, combining surgical resection, chemo and radiation therapy.

As technology and knowledge in cancer biology have evolved, we also have continued to evolve our cancer therapeutics. However, our metastatic cancer patients for the most part have remained incurable.

The time has come for addressing the most fundamental principle that is sitting at the heart of neoplastic transformation, namely distorted cellular and master regulator complex network entropy of malignant cell, and push these abnormal states towards normalcy. We need to change our path of thinking and cancer treatment strategy. As Albert Einstein once said, stupidity is best defined as going the same path and expecting to reach a different destination.

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