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Review Article

Spatial entropyomics: The path to future cancer therapeutics

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Abstract

The hallmark of neoplastic transformation is a significant increase in master regulator complex network entropy of cancer cell. This happens as a result of breakdown of the fine interplay of the second law of thermodynamics with the living cell. The methodologies that have been employed towards elucidation of spatial genomics and polyomics of tumor mass, could be applied towards the generation of spatial master regulator complex network entropy, or spatial entropyomics of tumor mass. This would lead to the birth of a new blueprint for the development of future cancer therapeutics.

Introduction

Cancer and time have hand in hand [1], just like the passage of time along the thermodynamics arrow and aging. In case of aging of living cell, cellular network entropy increases smoothly for the most part [2]. In case of cancer, this increase happens at an aggressive, wild, and fast pace [3].

The control loops, such as apoptotic machinery [4], telomeres [5], and P53 [6], are mostly dysfunctional in cancer cell, and hence, not able to stop progression of neoplastic transformation. The evolution of cancer therapeutics in the last eighty years, from nitrogen mustard [7], to new generation of immunotherapy [8], and targeted therapeutic agents [9], and their limited success in metastatic neoplastic disorders, necessitates a new approach to this catastrophic disease.

Advancement of science including development of single cell sequencing [10] has made it possible to elucidate the evolutionary road map of tumor mass [11] along the axis of time. We have become able to identify genomics [12], epigenomics [13], micro-RNA diversity [14], and proteomics [15] of thousands of cells in neoplastic mass, as well as their dynamics of variation along the axis of time.

Based on available mathematical models [16] and published studies, we could measure master regulator complex network entropy of cells comprising the tumor mass [17] and develop models similar to spatial genomics, called spatial entropyomics. The main difference between spatial genomics and spatial entropyomics is that the latter lends itself to a much more practical and simpler therapeutic application. Here, we need to change one value, as compared with dealing with a complex genetic network. The simplicity and feasibility of this approach could potentially make it the main therapeutic strategy for neoplastic disorders in the future. One needs to keep in mind that the leading or driving zone of neoplastic mass, along the thermodynamic arrow of time [18], is the one with the highest cellular master regulator complex network entropy. As such, the driver zone is in constant flux and is persistently getting replaced with the one that has acquired a higher network entropy. (**Figure 1**). This value correlates with chromosomal or genetic instability (CIN) [19], which in turn shapes intra-tumor heterogeneity (ITH) (**Figure 2**) [20].

Consequently, the current notion of one driver zone is wrong, and targeting that zone would further promote the birth of a new driver zone with a higher master regulator network entropy. Spatial entropyomics model is expected to allow us to calculate the value of a yet unborn future driver zone, master regulator complex network entropy. So, in our future cancer therapeutics design, not only would we shift the calculated driver front network entropy toward normalcy, but also preemptively do the same thing to the future and as yet unborn values.

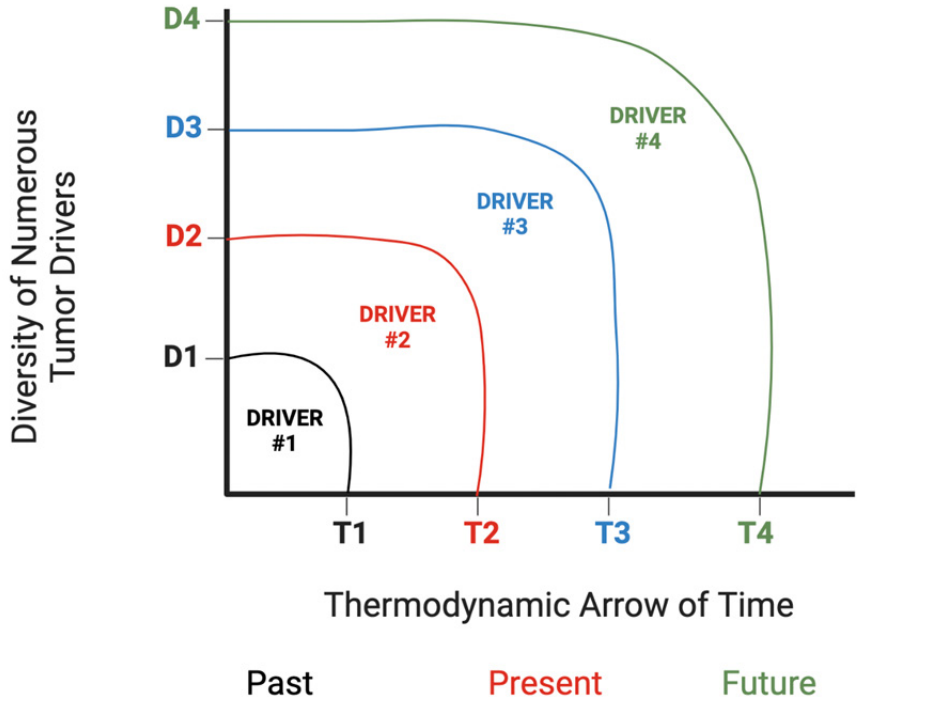

Figure 1. Different drivers come into existence to take over the forward evolutionary move of tumor mass, along the axis of time.

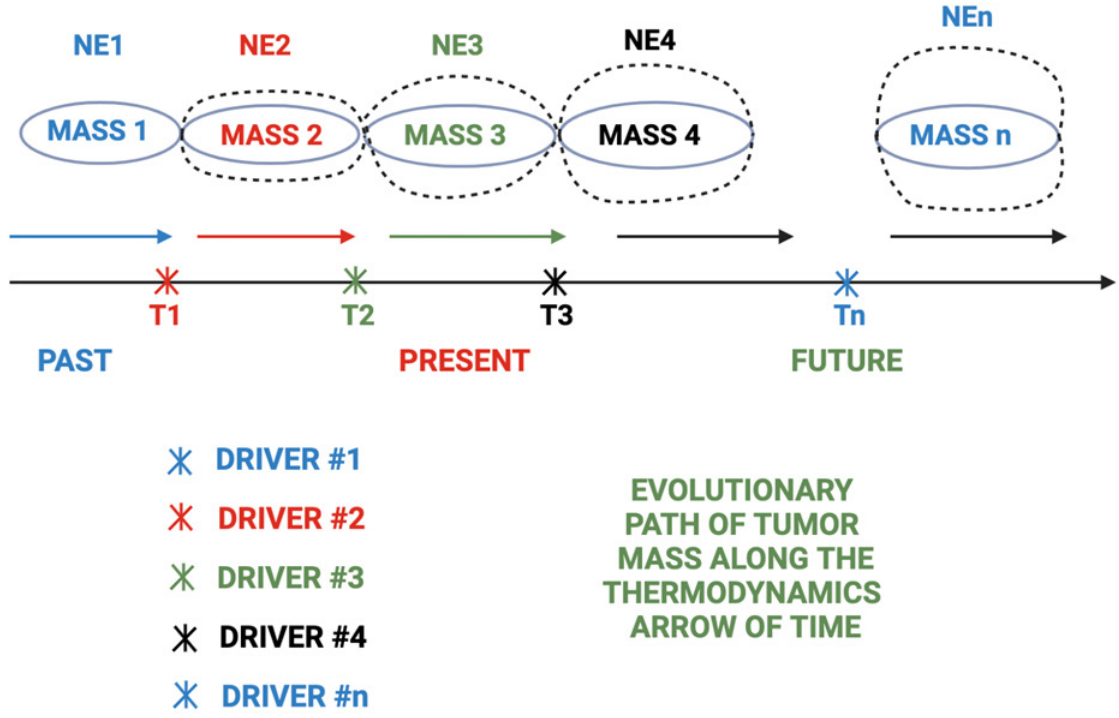

Figure 2. Cellular network entropy [NE] constantly increases, and the forward evolutionary move of tumor mass, along the thermodynamic arrow of time, is managed by new born drivers at more advanced stages of cancer evolution shown by bigger size. NE: Network Entropy; Mass: Tumor Mass.

Design of Programmable Nano-Machines [21]

Cancer can be treated based on spatial entropyomics concept. **Figures 3 and 4**, depict the basic principles and concepts that govern homeostasis and evolution of tumor mass. These concepts and principles build the foundation on which the design of future cancer therapeutics by employing nano-machines. **Figure 5** depicts conversion of curve A to curve B. Curve A, shows an increase in genomic diversity [22] and net tumor network entropy, along the axis of time. Curve B, shows a decrease in genomic diversity and net tumor network entropy through the therapeutic effect of programmable nano-machines.

Programmable nano-machines, could have one of the many possible designs, including vibrating nano-beads [23], non-pathogenic viruses [24], loaded with crispr-cas9 editing machinery [25], or micro-RNA of interest [26], all the way to smart molecules [27] capable of executing the task of interest.

The common denominator among a diverse group of programmable nano-machines, is their capability to decrease the leading or driving front network entropy as close to normal as possible. By doing so, the driver front loses its capability of evolutionary forward move of tumor mass into a higher level of genomic complexity, CIN, ITH, and cellular network entropy.

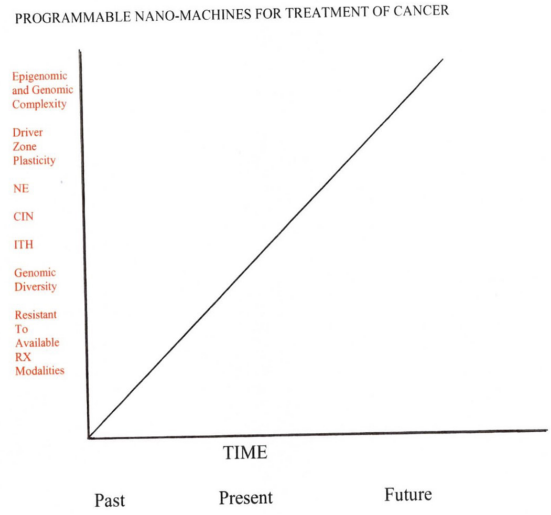

Figure 3. The value of epigenomic and genomic complexity, as well as driver zone plasticity and its network entropy constantly increase along the thermodynamic arrow of time. These changes get reflected into a higher CIN, ITH and resistance to available treatment measures. CIN: Chromosomal Instability; ITH: Intratumor Heterogeneity.

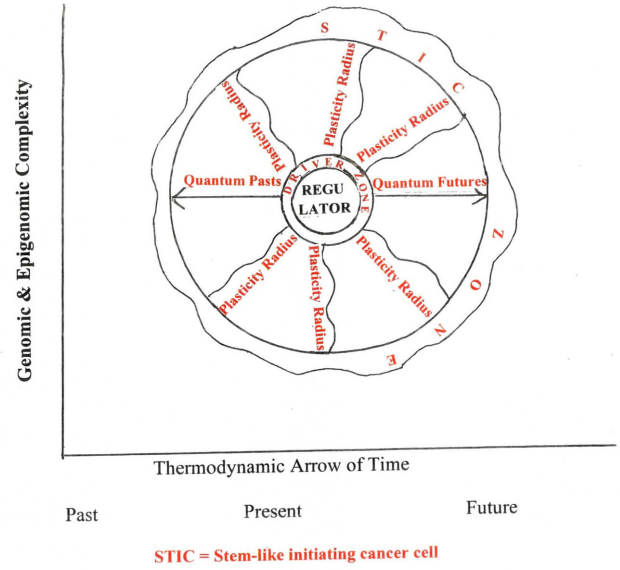

Figure 4. Regulator of the driver zone is the most ideal target for programmable nano-machines. By using artificial intelligence [32] and machine learning technology [33], we could identify RDZ. This zone is expected to have the highest master regulator network entropy, which correlates with CIN and ITH, and inversely correlates with the transmembrane electrostatic force [33]. RDZ: Regulator of Driver Zone; CIN: Chromosomal Instability; ITH: Intratumor Heterogeneity.

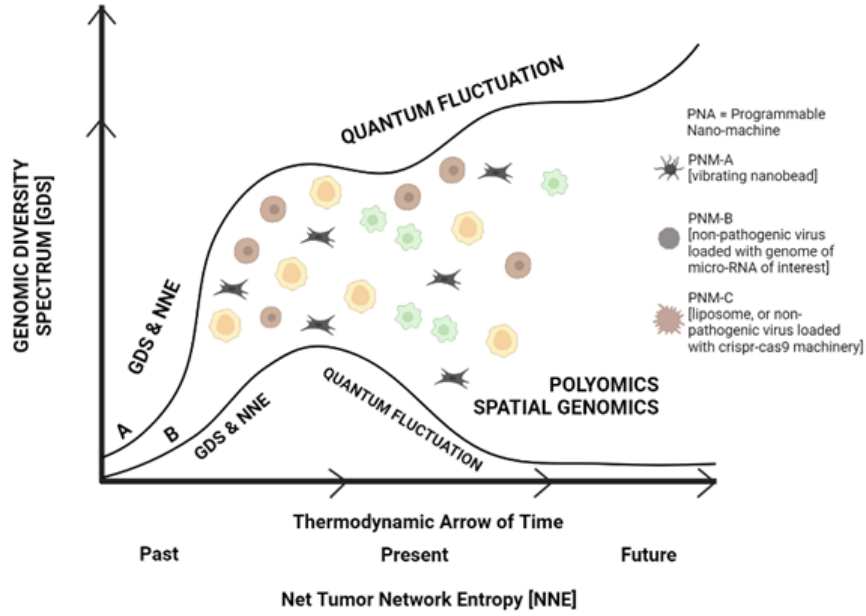

Figure 5. Programmable nano-machines would convert curve A, a tumor with higher genomic diversity and net tumor network entropy, to curve B, a tumor with lower genomic diversity and net tumor network entropy.

Consequently, neoplastic disorder [28] loses its progression capability and it shifts toward a chronic disease [29]. Such treatment could get repeated at predetermined time intervals, calculated for migration of spatial entropyomics to a lower level of cellular master regulator complex network entropy.

Conclusion

Spatial entropyomics, is expected to give birth to a new blueprint and path to future cancer therapeutics. As compared with other members of polyomics, such as spatial genomics and epigenomics, which represent complex genomic and epigenomic signatures making their modification very difficult or impractical, spatial entropyomics represents a single value, the highest of which sits at the driver forefront of tumor mass.

This simplicity lends itself to modification and reversal towards the normal range by one of the many designs of programmable nano-machines. As such, a new era of cancer therapeutics, which started eighty years ago with nitrogen mustard, will be led by programmable nano-machines which would modify the master regulator network entropy of driver zone of tumor mass, so that the forward evolutionary move of tumor mass [30] would cease or slow down significantly and consequently turn cancer into one of the many manageable chronic diseases [31].

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