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Cancers with Stem-Like Attractors and "Loss Of Differentiation" Novel Hallmark: Does the "Cyto-Education" with Stem Cell Therapy Help?

Yue Zhang

Division of Genetics and Development, The Toronto Western Research Institute, Toronto Western Hospital, University Health Network, Canada

Abstract

Cell fate determination includes the induction and execution of terminal differentiation. Studies of gene regulatory networks suggest that the correct fate is represented by stable dynamics. Gene expression dynamics inspectors assays show that cancer cell attractors converge to a stable stem-like state resulting from the aberrant expression of the masters involved in carcinogenesis and/ or metastasis, supporting "loss of differentiation" as a novel cancer hallmark. Cancer may be considered an aberrant reprogramming of normal cells by many factors. However, this fate could be reversed by differentiating cancerous cells into normal or terminally differentiated cells by cellular re-training ("cyto-education").

Main-Text

Currently, cancer, with its unrestricted cellular growth, remains as one most significant medical and socio-economic problem. Because of the chaos and dynamics of genome-wide gene expression, cells in multicellular organisms heavily rely on master regulators for chromatin remodelling and /or cell cycle to make different fate decisions, such as proliferation or differentiation into specialized cells which eventually lead to normal tissue specification and /or organ formation. Such cell fate determination should include cell fate induction and the proper execution of the terminally differentiated cell fates originated at stem-/ progenitor- /precursor cells. Previous theoretical studies of genome-wide gene regulatory networks (GRN) suggest that GRN needs to ensure cell fate trajectory on a right track with a manifestation of its ordered (stable) dynamics [1,2]. Having checked their genome-wide gene expression profiling data by gene expression dynamics inspector (GEDI), we can show that cell attractors converge to a common metastable stem-like state along with aberrant expression of such masters, which, including *Mi-2 β*, *Rb*, *EZH2*, *MTA1* and *l(3)mbt*, are involved in carcinogenesis and/or cancer metastasis [3-8]. This supports 'loss of differentiation" as a novel hallmark of cancer hereby via incorporating elements from systems biology.

Cancer may be considering as an aberrant reprogramming of normal cells due to intrinsic biologic and extrinsic environmental chemo-physical factors even likely socio/psychology stressors. Cell attractors theory also suggests that cancer cell fate could be reversed through the process of induction of differentiation of such cancer stem –like cells [9] into normal cells or terminally- differentiated cell by cellular re-training ("cyto-education") [2-5]. This has been in part validated with morphogenetic field experiments conducted using stem cell differentiation stage factors (SCDSFs) from different stages of development of Zebrafish embryos, oocyte extracts, or naive human umbilical cord matrix derived stem cells (hUMDSCs) on different tumor cell lines or cancers[reviewed in Ref.10 and references therein], as well as consistent with recent reprogramming of sarcoma cells with defined stemness factors and eventually its loss of their tumorigenicity and then dedifferentiation to mesenchymal stem cells (MSC) and hematopoietic stem cell (HSC)-like cells, which can be terminally induced and differentiated into mature tissues and cells [10,11]. SCDSFs significantly inhibit tumor cell growth because of increases in cell cycle master regulators, such as Rb [reviewed in Ref. 10].

Thus, cancer stem-like attractors, this concept would imply that proper stem cell -related therapy may be used as systematic cellular retraining (cyto-education/ cell reprogramming) onto lethal cancers. Such treatment may simply provide right reprogramming niche or fuel terminally –differentiation driving force for "immature" cancer cells [9] to exit from cancer stem-like attractors state and re-direct tumor cells to normal-like cellular development. In fact, stem cell therapy has demonstrated encouraging *in vivo* outcomes in pre-clinical trial studies and clinic trials in some aging-related complex diseases [7,12] having a layman-designated nickname as non–lethal "cancer', such as osteoarthritis [13], neuron/neurodegenerative diseases [14,15], heart diseases [16,17], etc. Further, a single passenger gene may be insufficient to switch cell attractors states, but a master or a cocktail of proper perturbing genes could likely achieve a successful reprogramming [18] so that the reprogrammed cancer cells could function in the same way as the normal cells. Finally, a well-designed longitudinal study with GEDI assays on certain cancer specimens from biobank may be expected to reveal early cancer prognosis of individual gene markers as well as cancer progression self-organisation pattern at a system level [19].

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***Corresponding author:** Yue Zhang, PhD, Division of Genetics and Development, The Toronto Western Research Institute, Toronto Western Hospital, University Health Network, 60 Leonard Avenue, Toronto, Ontario, Canada, Tel: +1-416-603-5800 Ext. 4797; E-mail: yuezhang@uhnres.utoronto.ca, zy1001@yahoo.com

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