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New Concepts of Germline Gene – reactivated Cancer

Yue Zhang*

Department of Radiation Oncology, Beth Israel Deaconess Medical Center,Harvard Medical School, 99 Brookline Avenue, Boston, MA,USA

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The mechanism that ectopic expression of germline genes result in somatic tumors such as melanoma and brain tumors remains a big challenge [1,2]. A century of unproductive concentration on the cancer- is –a- cell-based –disease.Somatic Mutation Theory of carcinogenesis (SMT) [3-5], the paradigmatic instability is coming to eyes, for instance, the tissue level [e.g. the Tissue Organization Field Theory of carcinogenesis (TOFT)] has been repeatedly suggested as one competitive strategy. Most recently, at the genome regulatory network level(GRN), the cancer attractors hypothesis naturally explains tumorigenesis [6-8], but such a new network-based intellectual framework is still quite abstract [8] and also remains incompletely understood what its evolutionary origin is and what causes normal somatic cells be entrapped in [9].

The genetics and epigenetics mechanisms that orchestrate developmental programs, particularly through the chromatin remodeling systems (CRCs), such as the nucleosome remodelling and histone deacetylase(Mi-2/NuRD)complex [10,11], SWI/SNF [12] and Polycomb complexes[13], are integral to normal development, oncogenesis and cancer progression[11,14]. Such CRCs are key determinants of differentiation in embryonic stem cells and during development in various model systems [11]. The activities of CRCs, such as genetics, epigenetics and stochastic protein dynamics forming sources of heterogeneity, essentially providing the basis for the plasticity and robustness for normal and cancerous cells [15]. Unlike the genetics mutations, epigenetic alterations are much reversible, but they are mitotically heritable, and therefore available to natural selection and able to actively participate in normal and cancerous cell evolution [15].

According to cancer cell attractors theory, a phenotype is "determined" by a concerted, non-linear (i.e. "complex"), gene-network activity to represent an attractor in the epigenetic landscape. The cancerous cells is considered as one type of cells [6]. The "attractor" model is an alluring theoretical model providing a plausible alternative explanation for development of cancer. The mutations and/or oncogene activation can no longer be considered as the "proximate" cause of the carcinogenic process. Cancer might be considered a stable state, behaving according to the attractor's rules. Experts in attractor models argued that without any changes to the cell's logic, cancerous attractors exist within the reachable phase-space. Transition from a physiologic into a pathological attractor may not require mutations that lower the separating energy barrier. Instead, noise-induced attractor transition "across potential barriers" or other non-mutagenic signals may in principle suffice - at least to induce the pre-malignant state. Yet, the question how these attractors would attain sufficient stability against perturbations need more discussions. The stochastic perturbations of highly nonlinear systems may in part underlie the emergence and stability of biological patterns. CRCs offer a plausible mechanism through histone modifications to contribute to this stability, the plasticity and robustness. The GRN does not work in isolation or in a vacuum: its activity is likely to be considered permissive and must be integrated by biophysical influences, mediated by the microenvironment, so cell-to-cell and cell-to-stroma interactions are crucial.

To escape from the abstract, the cross-species compatible germline gene -reactivated cancer attractors was identified by using an intuitive global view on gene expression patterns (GEP) [16] in the model organisms *Caenorhabditis elegans, Drosophila melanogaster* and mammalian subjects [9] (Figure 1a). This result suggests that chromatin remodeling systems, including the nucleosome remodeling and histone deacetylase (NuRD)/dREAM/Myb-MuvB complex and the polycomb group (PcG) proteins, even its functional equivalent *RegA* in green algae *Volvox carteri* [17] could likely contribute to cell differentiation along evolution from unicellular to multicellular life. How CRCs are linked to the overall transition dynamics that is still a matter of investigation how to represent an attractor in the phase space, and this analysis is yet a proof of common attractors [9]. However, it could be predicted that the diseased multi-cellularity causes variable cancerous cell-fate states. The majority of abnormal cells may naturally recover and spontaneously return to healthy state without our attentions. The factors ,which are under the regulation of CRCs but ensure the robustness of multi-cellularity among the cell communities, such as extracellular matrix (ECM) contribution [18], the conflicts of germline-soma distinct [19], sex determination [20], cell proliferation [21], apoptosis [10,20], co-evolution [15], limiting of the hypoxic environments [15], the profit from experience of the Earth's primal organisms RNAs [22,23] (e.g. miRNAs for the stabilization of cellular phenotypes, the encoding gene with an alternative splicing route for a stressful state [15] will make the diversity of cancerous states further interpretable.

The "wild type" epigenetic landscape has been carefully shaped over evolutionary time to establish distinct cell fate lineages, and that the tumor has maintained some of this developmental architecture [9,15]. Importantly, the CRCS and its leashed GRN, tightly together with it microenvironment could be one unit under natural selection. Among the range of tolerance, their robustness gives them the stability; otherwise, a sufficiently strong stress causes the organism's frailty and catastrophe. Like all other systems, the cancer is hence inevitable. As above mentioned, deregulated chromatin structure is a source of genetic and epigenetic expression heterogeneity. The GRN, esp. epigenomic profile is extensively distorted in cancers. Such "epimutations" [15] or "quasi-mutations" [9] can silence tumor-suppressing genes and

***Corresponding author:** Yue Zhang, Department of Radiation Oncology, Beth Israel Deaconess Medical Center,Harvard Medical School, 99 Brookline Avenue, Boston, MA 02215, USA, E-mail: yzhang1@bidmc.harvard.edu

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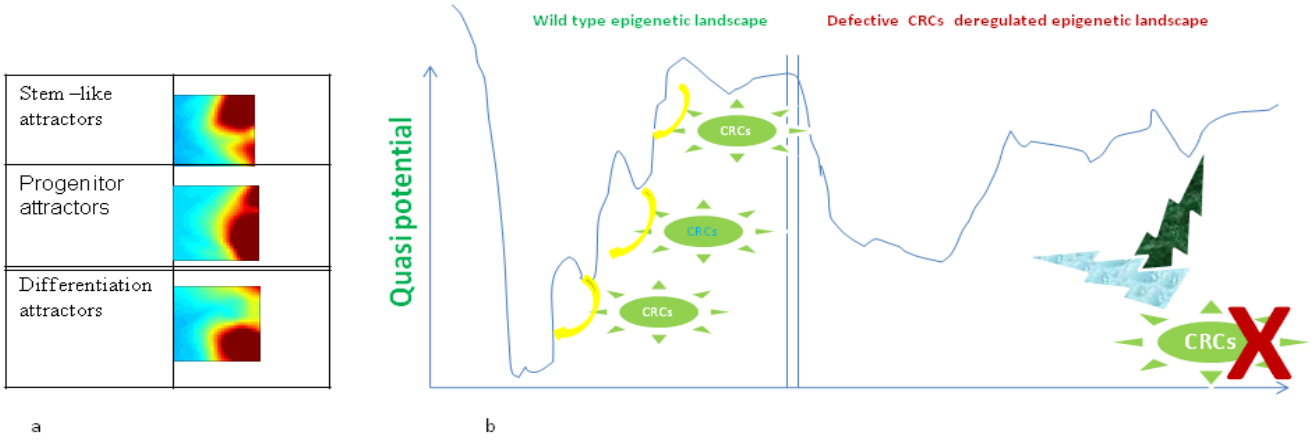

Figure 1: The cancer "avalanche" model of CRCs regulated epigenetic land scape.
a. Representative GEDI maps of stem-like attractos, progenitor/intermediate attractors and differentiation attractions.
b. (Left panel) An illustration of hierarchy within an epigenetic landscape for a single transition pathway frow stem cell (top) to final cell type (bottom). (Right panel) Deregulation and modification of the epigenetic landscape as a consequence of defective CRCs regulated epigenetic landscape.

re-activate oncogenes, and are likely to be functionally equivalent to genomic cancer mutations [9,15]. Like normal cells, cancers with a stable epigenetic landscape have correspondingly stable attractors, leashed cancer cells into defined states. However, very aggressive tumors with high levels of genetic and epigenetic instability would be expected to display a progressive deregulation of the epigenetic landscape, resulting in attractors that become increasingly less stable and that no longer maintains the same clear hierarchical architecture (Figure 1b). Because cancer cells are able to move more freely between different attractor states, including transitions to what might have once been a cancer stem cell phenotype, making its previously-emphasized "drivers" role in this disease faint. Recent experimental evidence from Roesch et al. [24] argue that melanoma tumor-initiating cells are generated spontaneously or induced by environmental cues within the melanoma tumor bulk, consistent with the idea of meta /pseudo-stable attractor states driving tumor growth in aggressive cancers.

The regulation of such chromatin remodeling systems is largely reversible [10]. This empowers them to not only buffer the challenge of internal and external changes as robustness but also provide the basis of cellular reprogramming [10, 25]. Such contribution to robustness could also maintain the evolvability of multicelluarity [26] and thus act as the organismal constraint of cancer attractors [10]. The GEDIs analysis [16] also shows that chromatin remodeling systems contribute to plasticity and dynamics during cell differentiation, which could be assumed to partner with chaperones like HSP90[27], or nuclear receptors like DAF-12/ liver X receptor alpha [25] within distinct system components (e.g. proteins, pathways, cells, organisms), so its robustness ensures the evolvability during evolution of multicellularity. Its failure may cause cancerous diseased multicellularity, its heterogeneity and degeneracy ,which characterizes with the necessity of more resource, suboptimal performance in "wild type" health , and new layer of robustness at such degenerated state, like drug resistance. New evolution could also start at this point. The robustness for "wild type" health comes with a cost, like ageing [28], cancer is hence at tradeoff with population survival but reprogrammable through modifications of CRCs" regulation.

Finally, we enter an accelerated artificial -interference era rather than natural selection alone. New concepts are also for the reversals of cancer with cellular reprogramming [29], which is suitable for a systems biology approach to attack robust and evolvable tumors by screening the chemicals [30,31]. Another focus is to divert tumor evolvability to normal track with an effort to mitigate therapy resistance in the hope of preventing or delaying the emergence of therapy resistance [15,32]. For the anti-cancer drug –resistance, several platforms could be referred to develop a strategy for research based on the similarity of the evolution of drug resistance in bacterial communities (i.e. biofilm) and malignant tissues [33] and the organsimal constraint of the distinct of germline and soma between the green algae and other more advanced organisms [17].

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