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Mathematical models of cell phenotype regulation and reprogramming: Make cancer cells sensitive again!☆

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ABSTRACT

A cell's phenotype is the observable actualization of complex interactions between its genome, epigenome, and local environment. While traditional views in cancer have held that cellular and tumor phenotypes are largely functions of genomic instability, increasing attention has recently been given to epigenetic and microenvironmental influences. Such non-genetic factors allow cancer cells to experience intrinsic diversity and plasticity, and at the tumor level can result in phenotypic heterogeneity and treatment evasion. In 2006, Takahashi and Yamanaka exploited the epigenome's plasticity by "reprogramming" differentiated cells into a pluripotent state by inducing expression of a cocktail of four transcription factors. Recent advances in cancer biology have shown not only that cellular reprogramming is possible for malignant cells, but it may provide a foundation for future therapies. Nevertheless, cell reprogramming experiments are frequently plagued by low efficiency, activation of aberrant transcriptional programs, instability, and often rely on expertise gathered from systems which may not translate directly to cancer. Here, we review a theoretical framework tracing back to Waddington's epigenetic landscape which may be used to derive quantitative and qualitative understanding of cellular reprogramming. Implications for tumor heterogeneity, evolution and adaptation are discussed in the context of designing new treatments to re-sensitize recalcitrant tumors. This article is part of a Special Issue entitled: Evolutionary principles — heterogeneity in cancer?, edited by Dr. Robert A. Gatenby.

1. Introduction

Cancer is traditionally viewed as a genetic disease caused by the random accumulation of mutations in critical genes or pathways that control proliferation and other "hallmark" traits [1]. Heterogeneity within a tumor would then arise through classic Darwinian evolutionary processes of mutation and clonal selection [2]. Expansion of heterogeneous phenotypes can then limit the effectiveness of treatment which is inevitably directed to the majority (average) clones, as insensitive phenotypic variants emerge.

However, it is becoming increasingly clear that the phenotype of a cancer cell is not just determined by its genotype. Epigenetic [3] and microenvironmental [4] factors provide additional significant contributions, such that two cancer cells with identical genotype may actually exhibit distinct phenotypes (Fig. 1).

This establishes provocative parallels with embryonic development in which a single genome can give rise to widely diverging differentiated phenotypes. This review discusses key advances toward a systems-level understanding of cell identity and reprogramming, first in the context of normal development, then connecting it to cancer heterogeneity and evolution. We review the foundational theory of cellular reprogramming, and discuss quantitative methods to predict or improve reprogramming efficiency and outcomes. In the last section, we position these exciting recent cell biological breakthroughs in the context of cancer heterogeneity and tumor evolution.

2. Cellular reprogramming

Within developmental biology, the traditional dogma of cellular differentiation has been that an organism begins as a zygote which gives rise to pluripotent stem cells [5]. Upon division, environmental cues [6] or stochastic effects [7] can give rise to a hierarchy of cells with increasingly differentiated states. Differentiation was considered an irreversible process, in which histone modifications and DNA methylation controlled the accessibility of key DNA regions [5] through opening or closing of the chromatin structure. However, differentiated cells still maintain all the DNA required for pluripotency. Indeed, it was shown that implanting the nucleus of a somatic cell into a denucleated

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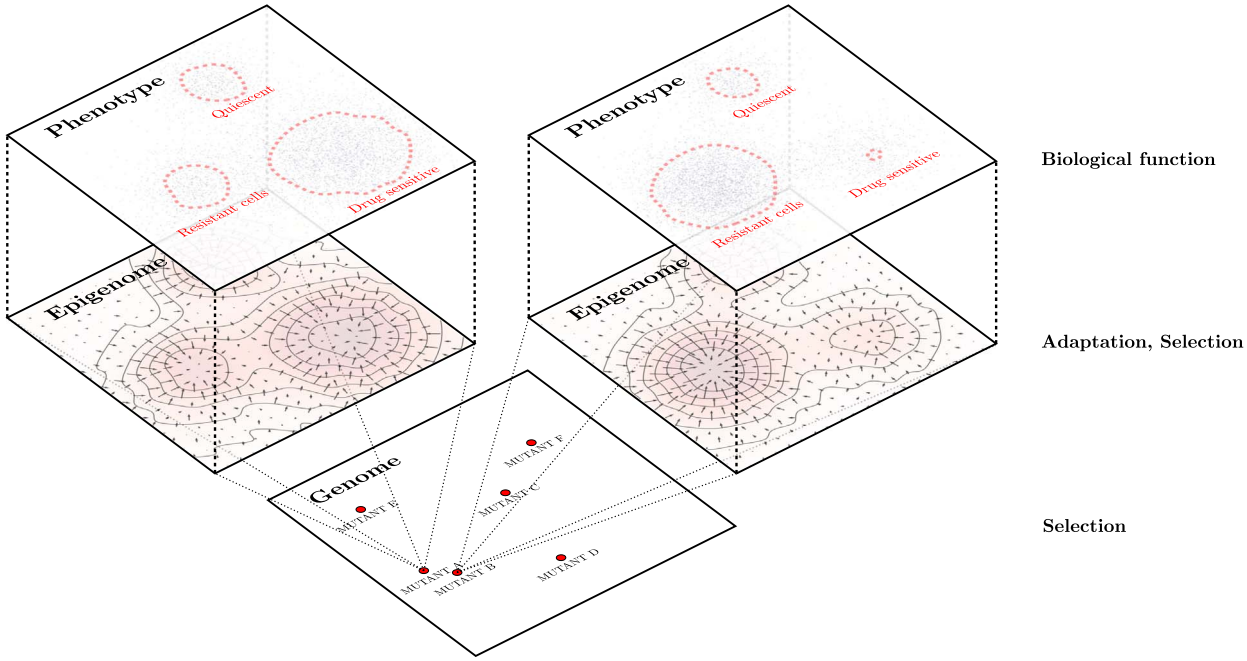

Fig. 1. Due to genetic instability, cancer cells in a tumor may have several distinct genomes (bottom). Each distinct genome underlies a unique epigenetic landscape (middle), which defines what cell phenotypes are possible (top). This allows both for cells with identical genomes to adopt distinct phenotypes, and also for cells with distinct genomes to identify identical phenotypes (left VS right). This opens up powerful possibilities for reprogramming cancer cells with diverse genetic backgrounds into more treatable or less malignant phenotypes.

oocyte could produce a stem cell [8], demonstrating the existence of unknown regulatory mechanisms in the oocyte cytoplasm which were able to re-activate the "locked" pluripotency state.

In 2006, Takahashi and Yamanaka found a set of 4 transcription factors (TFs): Oct3/4, Sox2, Klf4, and c-Myc (collectively "OSKM"), that could cause dedifferentiation of mouse embryonic fibroblasts to induced pluripotent stem cells (iPSCs) [9]. On average, though, only about 0.05% of transduced cells underwent transformation, and upon relaxation of the TF cocktail, the cells fell back into their previous, differentiated state [10]. Other studies have extended the gamut of reprogrammable cell types [11], and while in many cases efficiency has been greatly improved [12,13], deciphering the regulatory programs controlling cell identity promises to enable many biomedical applications [14,15], and may have future impacts on cancer therapy.

The OSKM TFs have been classified as "pioneer transcription factors," able to bind enhancers in a closed chromatin state [16]. These factors were also found to promiscuously activate multiple off-target genes, such that final establishment of the pluripotent state very likely requires a system-wide rebalancing of the gene regulatory network (GRN) [16].

Mathematical modeling is appropriate for understanding the GRN dynamics underlying this rebalancing, and could accelerate discovery of key TFs to reprogram cells to a target phenotype. This may be especially true in cancer cells, in which phenotypes are often not clearly classifiable, especially with respect to treatment sensitivity. In the next sections, we will discuss theoretical frameworks which aim to clarify the topology of "epigenetic landscapes" in mathematical terms, and could help resolve the nature of cancer cell phenotypes and their drivers.

3. The epigenetic landscape and theory of attractors

In 1957, CH Waddington proposed the concept of an epigenetic landscape [17] (Fig. 2a), in which cells roll downhill through bifurcating channels representing differentiation pathways. As cells progress down these metaphorical slopes, they become increasingly committed to a terminal phenotype at the bottom. Distinct pathways are separated by ridges, confining cells to their differentiated identity. While this framework was intended purely as a conceptual tool to obtain a "rough and ready picture" that "cannot be interpreted rigorously" [17], it was nonetheless developed within the mathematical context of dynamical systems theory.

This was reasonable since, within this theory, stable states (named attractors) commonly arise from dissipative systems which must exchange energy and matter with their environment to sustain function [18], a seemingly realistic and necessary behavior for cells. Thus, biologically, an attractor describes a state in which a cell identity can stably persist.

Over the past 50 years, several researchers have taken on the task of formalizing this attractor framework in the context of biology, in order to understand how signaling pathways and GRNs may robustly coordinate cell behavior [19–32]. The next section highlights these efforts and their potential relevance to cell reprogramming.

4. Gene regulatory dynamics and attractors

Stuart Kauffman proposed the idea of Boolean network models, in which genes can either be ON or OFF [20], in order to simulate the dynamics of GRNs. His models revealed that networks with certain structural properties did indeed settle into a small number of stable attractors, providing the first evidence that cell types may correlate with GRN attractors [20,21]. A few decades later, Huang et al. [22] provided an experimental justification for this intriguing idea. In mathematics, attractors by definition have an associated region called the "basin of attraction" (Fig. 2b) corresponding to all states that will eventually approach the attractor [33]. Huang et al. exploited the fact that HL60 human promyelocytic leukemia cells can be induced to differentiate into neutrophils via treatment with either DMSO or ATRA. Tracking the trajectory of a 2773-gene expression panel, they showed that HL60 cells respond divergently to treatment with these agents. However, the trajectories eventually converged to an identical neutrophil state. They reasoned that the divergent trajectories must both have been within the basin of attraction of the neutrophil state, which must then be an attractor [22].

This basin of attraction is ultimately responsible for the stability of an attractor, as small deviations from the attractor will remain confined