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Oncometabolic Nuclear Reprogramming of Cancer Stemness

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SUMMARY

By impairing histone demethylation and locking cells into a reprogramming-prone state, oncometabolites can partially mimic the process of induced pluripotent stem cell generation. Using a systems biology approach, combining mathematical modeling, computation, and proof-of-concept studies with live cells, we found that an oncometabolite-driven pathological version of nuclear reprogramming increases the speed and efficiency of dedifferentiating committed epithelial cells into stem-like states with only a minimal core of stemness transcription factors. Our biomathematical model, which introduces nucleosome modification and epigenetic regulation of cell differentiation genes to account for the direct effects of oncometabolites on nuclear reprogramming, demonstrates that oncometabolites markedly lower the "energy barriers" separating non-stem and stem cell attractors, diminishes the average time of nuclear reprogramming, and increases the size of the basin of attraction of the macrostate occupied by stem cells. These findings establish the concept of oncometabolic nuclear reprogramming of stemness as a bona fide metabolo-epigenetic mechanism for generation of cancer stem-like cells.

INTRODUCTION

The correct functioning of the epigenome ensures fidelity in the establishment of gene-expression programs that are compatible with specific cell identities. The need for tightly controlled epigenetic landscapes is of critical importance for stem cells, which are able to both self-renew and generate differentiated progeny (Barrero et al., 2010; Chen and Dent, 2014; Papp and Plath, 2013; Spivakov and Fisher, 2007). The inability to stabilize stem cell states and functions by maintaining epigenome integrity, a process in which DNA methylation plays a major role, can trigger pathological self-renewal processes that ultimately lead to cancer (Ohnishi et al., 2014; Suva et al., 2013; Tung and Knoepfler, 2015). Interestingly, remodeling of DNA methylation is a cancer-initiating event manifesting in the presence of particular types of cancer-driving metabolites, termed oncometabolites, and in the nuclear reprogramming process of transcription factor-generated induced pluripotent stem cell (iPSC) derivation.

The shared mechanism by which abnormal accumulation of the oncometabolites 2-hydroxyglutarate (2HG), succinate, and fumarate causes potential transformation to malignancy is the ability to promote DNA hypermethylation through suppression of histone demethylation, which, in turn, results in the repression of genes involved in the epigenetic rewiring of lineage-specific differentiation and in the promotion of stem cell-like transcriptional signatures (Chowdhury et al., 2011; Killian et al., 2013; Letouzé et al., 2013; Lu et al., 2012; Terunuma et al., 2014; Saha et al., 2014; Xiao et al., 2012; Xu et al., 2011; Yang et al., 2013). The transient expression of stemness-associated transcription factors, i.e., *OCT4*, *SOX2*, *KLF4*, and *c-MYC*, in vivo generates tumors consisting of undifferentiated dysplastic cells exhibiting global changes in DNA methylation (Ohnishi et al., 2014), suggesting that the epigenetic regulatory machinery associated with iPSC derivation might initiate cancer development in a manner that does not require mutational changes in the genomic sequence (Ben-David and Benvenisty, 2011; Ohnishi et al., 2014; Knoepfler, 2009; Tung and Knoepfler, 2015).

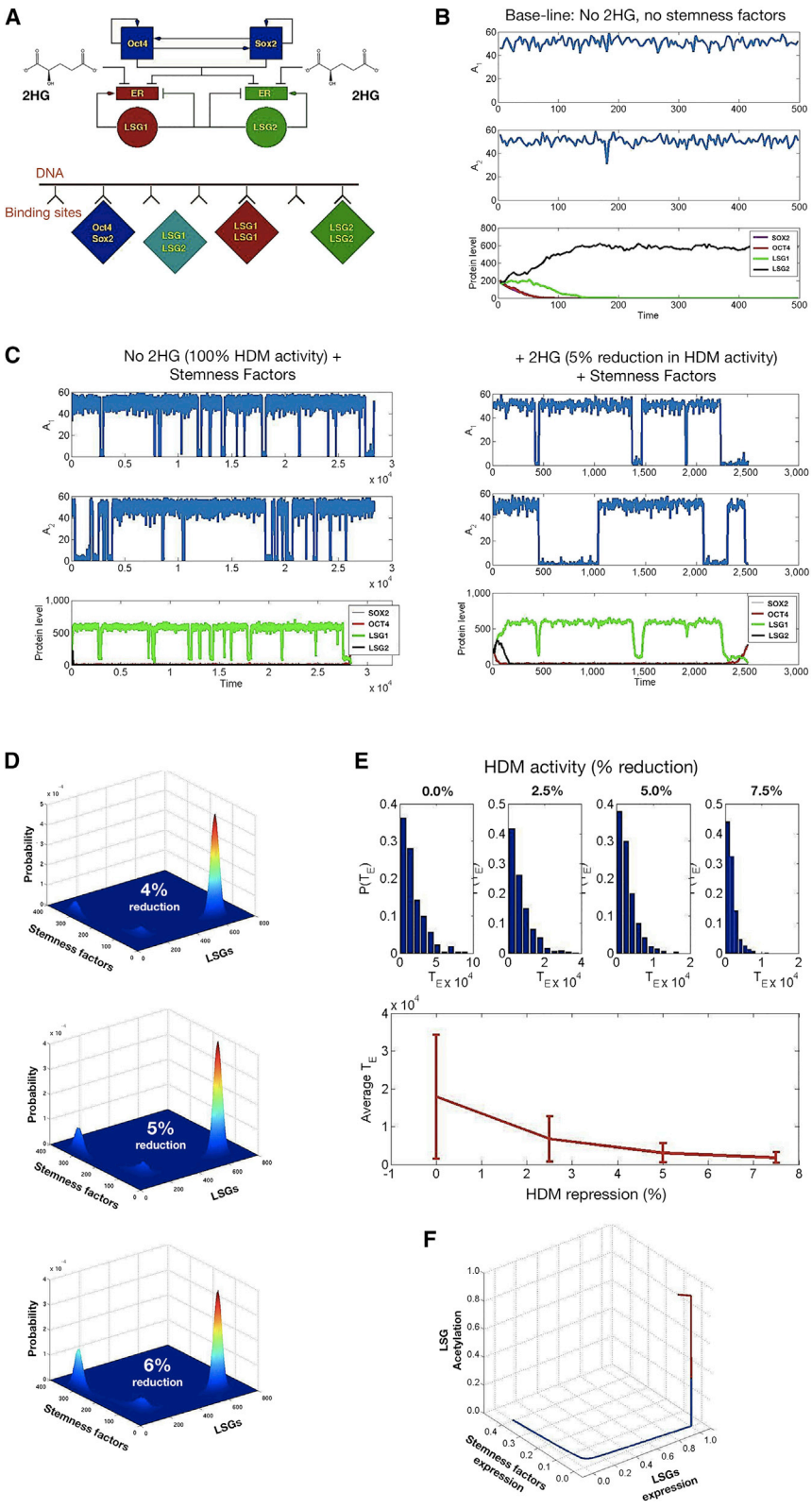

Figure 1. Computation Simulation of Oncometabolic Nuclear Reprogramming Phenomena

(A–C) A stochastic model of oncometabolic nuclear reprogramming. (A) Top: Schematic representation of the minimal gene regulatory network considered in our stochastic model, consisting of a coupled pluripotency module (self-activation of *Oct4* and *Sox2*) and a differentiation module (mutual antagonism between *LSGs*). Arrows denote activation and blunt-ended lines denote inhibitory interactions. Bottom: Schematic representation of the competitive binding model for activation/repression in the minimal gene regulatory network. (B) A realization path in which our stochastic model was run under baseline conditions (baseline HDM activity and lack of induction of stemness-related transcription factors, i.e., h_i-values as per values given in Table S7 [Supplemental Appendix E] and $\rho_1 = \rho_2 = 0$). Since the system is symmetric with respect to LSG1 and LSG2, a state where $O = 0$, $S = 0$, and $L_2 = 0$, whereas $L_1 > 0$, is also an absorbing state. (C) A realization path in which our stochastic model was run under induction of stemness-related transcription factors (parameter values $\rho_1 = \rho_2 = 1.85 \times 10^7$). At the onset of stemness factor induction, i.e., we let $\rho_1 > 0$ and $\rho_2 > 0$, the absorbing states observed in the simulations shown in (B) are not absorbing any longer and, therefore, there is a positive probability for the system to go from the differentiated cell state to the stem cell state. Left: Normal-like metabolism, baseline HDM activity; right: 2HG-induced reduction of HDM activity by 5% with respect to the baseline scenario.

(D–F) Epigenetic landscapes and reprogramming performance in response to 2HG. (D) 2HG-induced inhibition of HDM activity affects the depth of the stem cell attractors by lowering the barriers of the epigenetic landscape. Figures show the joint probability of the random variables $O + S$ (stemness factors) and $L_1 + L_2$ (LSGs) for different values of the relative oncometabolic-induced reduction of HDM activity with respect to the baseline scenario. To obtain the epigenetic landscapes for different degrees of 2HG-induced reduction of HDM activity in shorter computational time, we considered the following parameter values: $\rho_1 = \rho_2 = 5.55 \times 10^{-7}$ and $\vartheta_o = \vartheta_s = 0.2$. We have also considered that the expression of the LSGs is induced at certain rates given by the following parameter values $\rho_{L1} = \rho_{L2} = 2.78 \times 10^{-7}$. The landscapes with 4%, 5%, and 6% reduced HDM activity correspond to $h_2 = 0.96$, $h_2 = 0.95$, and $h_2 = 0.94$, respectively. The

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