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AUTHOR'S VIEW

Nuclear reprogramming of cancer stem cells: Corrupting the epigenetic code of cell identity with oncometabolites

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ABSTRACT

Generation of cancer stem cell (CSC)-like cells might occur through metabolic corruption of the epigenetic codes that govern cell identity. We recently identified how archetypal oncometabolites, without altering the baseline expression of endogenous stem cell maintenance genes but endowing cells with epigenetic states refractory to differentiation, considerably enhance the global kinetic efficiency of nuclear reprogramming processes that generate CSC-like states *de novo*. This study highlights that metabolo-epigenetic axes of communication can direct the development and maintenance of CSCs during the natural history of cancer diseases.

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The last 5 years have witnessed significant advances in our understanding of how altered tumor cell metabolism, identified almost a century ago by Otto Warburg, is actually a central contributor to the global process of carcinogenesis rather than being a passive player.¹ At the same time, we have quickly amassed in-depth knowledge of the striking “metabolic reprogramming” phenomena that occur in pluripotent embryonic stem cells (ESCs), tissue-specific adult stem cells (ASCs), and induced pluripotent stem cells (iPSCs).^{2–4} We are beginning to appreciate that “common” metabolites generated during bioenergetic and biosynthetic processes are actively employed in enzymatic reactions that lead to epigenetic modifications and transcriptional gene regulation, a metabolic contribution to global epi-transcriptional changes that ultimately impacts canonical stem cell features such as self-renewal and differentiation.⁵

The appreciation that metabolites that act as cofactors for histone deacetylation/acetylation and histone/DNA methylation (i.e., S-adenosyl methionine [SAM], acetyl-CoA, α -ketoglutarate [α -KG], flavin adenine dinucleotide [FAD], and nicotinamide adenine nucleotide [NAD^+]) can regulate many of the cell fate decisions made by stem cells has firmly established the notion that major metabolic pathways (i.e., one-carbon cycle, glycolysis, tricarboxylic acid cycle, and oxidative phosphorylation) can directly contribute to the chromatin state in stem cells through a metabolo-epigenetic axis of communication. Moreover, exploration of the early metabolic alterations that occur during establishment of pluripotency in iPSCs—without significant changes in gene expression—temptingly suggests that metabolic reprogramming *per se* may be a molecular pre-requisite for the successful acquisition of a stem cell

state. However, the possibility that a metabolically-driven *corrupted version* of the epigenome might also play a role in directing the so-called cancer stem cells (CSCs), which are thought to bear the majority of a cancer's tumor-initiating, metastatic, and treatment resistance ability, has remained largely unexplored.

We have recently proposed that, beyond the specific bioenergetic/biosynthetic demands of stage-specific cancer cell states such as CSCs, specific classes of elite metabolites and the relative spatio-temporal abundance of common interpreters of the metabolic state (i.e., SAM, acetyl-CoA, α -KG, NAD^+) can directly influence the 2 primary epigenetic codes (histone modification and DNA methylation) to causally redirect normal and non-CSC tumor cells toward a CSC-like cellular state. We have coined the term “metabostemness” to describe these metabolic parameters that causally control or functionally substitute the epi-transcriptional programs defining a CSC state.^{6,7} As such, metabostemness can be understood as the “physiological glue” that metabolically connects all the -omic layers with a self-autonomous but plastic CSC epigenetic quality and, therefore, as a function of observable phenotypes that predates systems biology and its subdisciplines (i.e., genomics, transcriptomics, proteomics, metabolomics) at the level of CSC cellular states. In a first attempt to update our current perception of the regulatory role of metabolic reprogramming in cancer cell fate decisions, we utilized specific metabolites that can be oncogenic by themselves, i.e., small-molecule components (or enantiomers) of normal metabolism termed oncometabolites whose accumulation is sufficient to establish a *milieu* that initiates and drives carcinogenesis. Because the malignant activity of most oncometabolites likely relies on their ability to epigenetically block differentiation markers,⁸ we tested the hypothesis that archetypal representatives

such as 2-hydroxyglutarate (2-HG) would considerably alter the global kinetic efficiency of nuclear reprogramming-like processes that generate CSC-like cells.

To demonstrate the occurrence of CSC-generating epigenetic events manifesting in response to particular cancer-driving oncometabolites, we used a systems biology approach combining mathematical modeling, computation, and proof-of-concept studies with live cells.⁹ The oncometabolite 2-HG, without altering the baseline expression of endogenous stem cell maintenance genes but by endowing cells with an enhanced refractoriness to differentiation, rendered fully committed epithelial cells more receptive to the epigenetic rewiring required for the *de novo* acquisition of a CSC state.

Our biomathematical model, which introduced nucleosome modification and epigenetic regulation of cell differentiation genes to account for the direct effects of oncometabolites on nuclear reprogramming, revealed that 2-HG promoted higher efficiency and faster kinetics of the CSC nuclear reprogramming induced by a minimal core of stemness and oncogenic transcription factors (*OCT4* and *SOX2*). The fact that the oncometabolically-driven epigenetic modification of inactive/poised states of lineage-specific genes alone was sufficient to significantly alter the efficiency and speed of nuclear reprogramming strongly suggested that oncometabolite-driven pathologic versions of nuclear reprogramming might promote stemness in cancer tissues.⁹

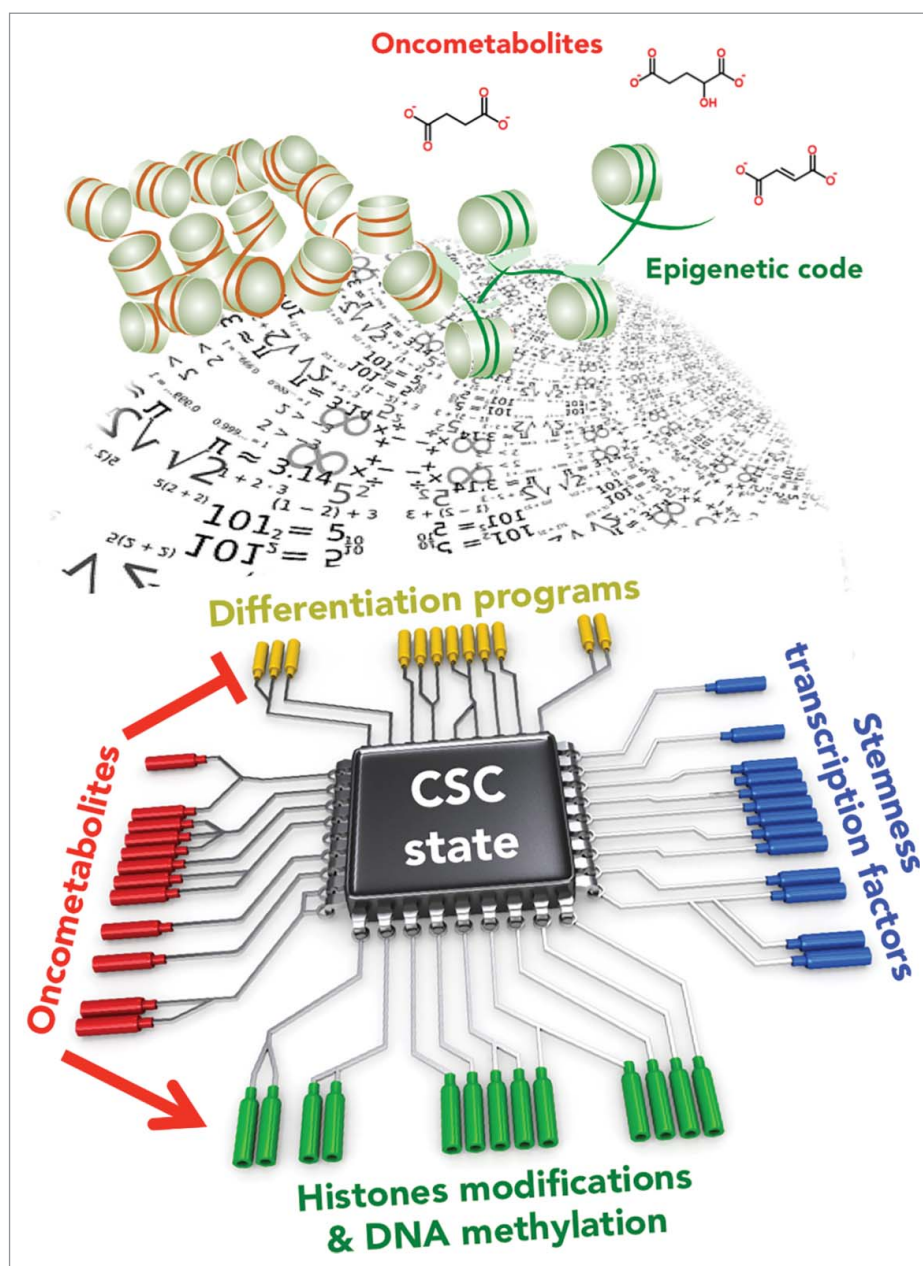


Figure 1. Oncometabolic reprogramming of cancer stem cells: Corrupting the epigenetic codes of cell identity. Figuratively speaking, oncometabolites operate as a corrupted version of the “operating system” (OS) that enables aberrant functioning of the epigenetic software of cancer stem cells (CSCs) and can be accessed by bypassing the usual “OS activation” requirements (i.e., hyperactivation of stemness genes). It might be possible to metabolically restore a corrupted version of the CSC OS to allow “tumor applications” and software “differentiation programs” to function properly. Indeed, the expected far-reaching epigenetic consequences of pharmacologic interventions aimed to target the oncometabolic reprogramming of CSCs are worthy of clinical exploration.

It might be argued that, *in vivo*, the number and complexity of the molecular events required for *de novo* generation of new stem-like cell types (e.g., chromatin decondensation, loss of differentiation marks, transcriptional activation of stemness genes, suppression of competing cell lineages) should intrinsically prevent the initiation of pathologic versions of nuclear reprogramming phenomena in differentiated tissues, including those of tumors. However, we have learned that premature termination of *in vivo* nuclear reprogramming upon transient induction of stemness factors may be sufficient to induce a stably transformed state through epigenetic, rather than genetic, mechanisms.¹⁰ It therefore seems plausible that the speed and efficiency of pathologic nuclear reprogramming phenomena might be increased in the presence of certain physiologically-biased molecular scenarios that pre-lock cells into more easily reprogrammable cell states *in vivo*. Indeed, if our assumption that metabolically-driven installation of CSC-like faulty epigenetic programs is a *bona fide* cancer-promoting event (Fig. 1) is correct, a testable prediction is that those carcinomas in which oncometabolically-driven epigenome rewiring suffices to establish a *milieu* that initiates carcinogenesis but requires additional cooperating mutations for complete transformation and disease progression must behave as accelerated forms of the oncometabolite-independent versions of the same tumors. Accordingly, 2-HG-overproducing *IDH1/2*-mutated gliomas, acute myeloid leukemia, and central cartilaginous tumors or succinate-overproducing *SDH*-mutated paragangliomas tend to present at a younger age than 2-HG- and succinate-negative forms of the same tumors.

It might be relevant to evaluate whether organ-, tissue-, or cell-specific aberrant forms of nuclear reprogramming-like epigenetic reorganizations, which appear to drive certain forms of pediatric embryonal tumors, can also be described in terms of an aberrant installation of histone/DNA epigenetic software driven by the yet-to-be discovered oncometabolic facet of well-known hereditary cancer syndromes (e.g., *BRCA1/2*). Perhaps, and unexpectedly, early-onset cancers driven by mutations in metabolic genes and embryonal tumors driven by epigenetically disorganized developmental signaling cascades might become invaluable models to explore alternative mechanisms of tumor formation and evolution in which, unlike the traditional view solely based on the acquisition of mutations that drive multistage cancer development, metabolic reprogramming of the epigenome might operate to increase both cancer susceptibility and clinical aggressiveness.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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