the possibility that increasing transcriptional misregulation through a gradual loss of normal chromatin-dependent transcriptional regulation may be a general feature of organismal aging and that reversing this phenomenon could delay the onset of aging and age-related diseases (Figure 1). It may be the case for transcriptional regulation that, if it's too noisy, you're probably just too old.

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Epigenetic Networks and miRNAs in Stem Cells and Cancer

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Stem-like cells in human cancer (CSCs) have multiple properties of embryonic stem cells (ESCs). In this issue, Iliopoulos et al. (2010) identify molecular mechanisms that link miRNAs to epigenetic states and drive CSCs, contributing to tumor aggressiveness.

Cancers have many properties of embryonic-like cells. Increasingly, the link between the two is being seen at the level of genome-wide expression patterns, particularly in the most aggressive cancer states (Ben-Porath et al., 2008). Additionally, as the epigenetic determinants of ESCs and embryonic progenitor states are being dissected, it is recognized that increased expression of components of this regulatory network are a prominent feature of the cancer and embryonic stem cell signatures (Mikkelsen et al., 2007; Ben-Porath et al., 2008). In this issue, Iliopoulos and coworkers take these relationships a step further by functionally linking ESC-like determinants of epigenetic control, miRNA regulation, and generation of CSCs. Their findings have not only biologic relevance but implications for cancer biomarker derivation and cancer therapy.

In their study, Iliopoulos et al. demonstrate that interactions between the miRNA-200 family and Suz12, a subunit of the polycomb repressor complex 2 (PRC2), are required for CSC formation (Figure 1). The authors show that decreases in miR-200 lead to increased Suz12 expression, increased binding of Suz12 to the *CDH1* promoter, and increased H3-K27 trimethylation and polycomb-mediated repression of *e-cadherin* (*CDH1*) expression. Loss of CDH1 is important for tumorigenesis and metastasis and the actions of miR-200 appear to be as a tumor suppressor, to block CSC formation via inhibition of the PRC2 polycomb complex, which thereby prevents CDH1 repression. The loss of miR-200 appears to represent a progression step since the authors, in their model, show that the miR-200 family is downregulated in CSCs, but not in initial transformation. Finally, the role of miR-200 for CSCs also appears to include production of chemotherapeutic resistance.

The current findings highlight the central role of the polycomb group proteins (PcG) in cancer. Increased expression of key components of the system have all been shown by others to potentially play a role in cancer progression (Bracken and Helin, 2009). These components include EZH2 (a PRC2 constituent that catalyzes the transcriptionally repressive H3K27me3 histone modification), Bmi1 (a subunit of the PRC1 complex that recognizes the H3K27me3 mark), and the PRC2 constituent, SUZ12. While Iliopoulos et al. focus on E-cadherin as a key miRNA-influenced PcG target, their results define other potential targets as well because many genes are targeted by the PcG complexes during development (Boyer et al., 2006). Widespread PcG-mediated gene repression almost assuredly occurs in cancer, as suggested in Figure 1, and this has many ramifications. It may mean that a plethora of events that link ESCs, CSCs, and epithelial-to-mesenchymal transition (EMT) could be under the control of miR-200 and PcG. These events may variably come into play during tumor progression, thus acting as key determinants of cancer aggressiveness. Indeed, EMT can be considered a primitive state that is

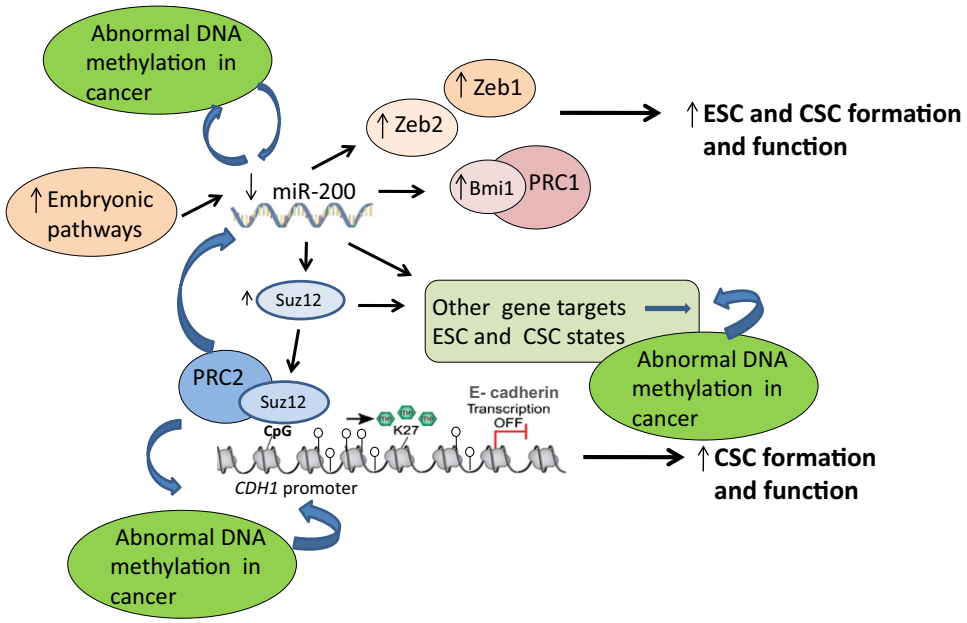

Figure 1. An Epigenetic Regulatory Network in Normal and Neoplastic Stem Cells

The core of the network is depicted to include the miR-200 regulation of PcG and CDH1 as defined by Iliopoulos et al. (2010). These events have many other gene targets in ESC and CSCs as shown. Finally, feedback loops are suggested where, in ESCs and CSCs, miR-200 regulates PcG constituents; in turn, miR-200 might be regulated by PcG and DNA methylation. White lollipop symbols, non-DNA-methylated CpG sites.

important in development—and that evolves in cancer, and of which repression of E-cadherin expression is but one event for this full state to be present (Ben-Porath et al., 2008).

Considering the potentially numerous gene-silencing targets of the pathway outlined in the Iliopoulos et al. paper, a network with potential feedback loops can be envisioned that richly informs our view of epigenetic abnormalities central to tumorigenesis (Figure 1). First, the final outcome of pathway events leading to cancer can be viewed as a molecular progression in which the depth of abnormal gene silencing can become more and more stable. Normally, many genes are regulated by PcG regulation in ESCs. The large majority of these genes have promoter CpG islands and are maintained in a low but poised transcription state (Boyer et al., 2006; Chi and Bernstein, 2009). This is likely achieved by a balance in promoter chromatin organization, termed "bivalent chromatin," wherein the repressive, PcG-induced, H3K27me3 mark is balanced by simultaneous presence of the active marks, H3K4 me2 and me3 (Chi and Bernstein, 2009). This state helps maintain stemness by keeping expression of lineage commitment genes low until ESC enter more differentiated stages of development (Chi and Bernstein, 2009). Thus, the poised state of involved genes has a plasticity that facilitates dynamic regulation during embryogenesis, and presumably helps CSCs maintain degrees of stemness. Normally, these PcG-targeted ESC genes do not have the more stably repressive modification of DNA methylation (Chi and Bernstein, 2009). However, in cancer, there are many genes, some important tumor suppressors, that are abnormally silenced in association with aberrant promoter CpG island DNA methylation. An inordinate number of such genes are among those discussed above that are PcG marked in ESC (Ohm and Baylin, 2007). It may be that more stable silencing of these genes in cancer might help select for stemness. This silencing likely involves quantitative replacement of PcG marks with DNA methylation. This switch, in turn, may arise through the ability of the PcG complexes to recruit the DNA methyltransferases during all phases of tumor progression (Ohm and Baylin, 2007). While Iliopoulos et al. found that the target gene, CDH1, was not DNA methylated, this is not the case in many breast cancers (Graff et al., 2000). It will then be of great interest to determine the DNA methylation of this and other targets in both CSC and non-CSC cancers with reduced levels of miR-200.

miRNAs themselves may be regulated in CSCs (Figure 1). PcG could mediate the downregulation of miR-200, and it is known that, in cancer, aberrant promoter DNA methylation can be associated with miRNA silencing (Saito et al., 2006). Such silencing of miRNAs has been shown to help stabilize increases in the DNA methyltransferases (Fabbri et al., 2007). Thus, the findings of Iliopoulos et al. provide further impetus for dissecting the epigenetic regulation of both normal and neoplastic stem cells.

If the epigenetic circuits above provide insight into the biology of cancer, the Iliopoulos et al. paper also highlights important translational implications. First, many of the parameters studied provide potential biomarkers for assessing tumor prognosis and behavior such as levels of SUZ12 and the numbers of CSC present with the properties outlined. The association shown in the present paper of such cells with metastatic capacity and drug resistance illustrates this point. Further, epigenetic drive for expansion, or creation, of such cells as a mechanism of drug resistance and tumor expansion

has recently been an exciting focus of others (Roesch et al., 2010; Sharma et al., 2010) . Inherent to these concepts is the possibility that ''epigenetic therapy'' with drugs that target steps like histone deacetylation, PcG complexes, and abnormal DNA methylation might reverse an entire program of events to blunt tumor growth and/or reverse and delay drug resistance. The future will bring many basic and clinical studies to explore all of these exciting possibilities.

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Evolution of Central Carbon Metabolism

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Organisms share a common core to their metabolic networks. But what determined this: chance, chemical necessity, or evolutionary optimization? In this issue of *Molecular Cell*, Noor et al. (2010) provide new evidence for selection of a network with optimal features from a broader set of possibilities.

If we found extraterrestrial life on Mars, how similar would its metabolic network be to those of organisms on Earth? That is a difficult question, since the relative importance of chemical constraints, selection pressure, and chance in the evolution of terrestrial metabolism is unknown. Even for a carbon-based metabolism that can process small organic molecules to produce the known precursors for proteins, nucleic acids, and lipids, are there other feasible solutions for a viable network? If so, would selective pressure inevitably lead to convergence to metabolism like that on Earth?

An original approach to this problem was developed by Meléndez-Hevia and Isidoro (1985) for the pentose phosphate cycle interconverting hexose and pentose sugars. They assumed that the substrate specificities of transketolase and transaldolase could be relaxed to allow them to transfer two carbon and three carbon units, respectively, between a wider range of sugar molecules than is currently involved. That is, the existence of transaldolase and transketolase implies there are no intrinsic chemical constraints preventing the evolution of enzymes carrying out the other reactions. They also ignored isomerizations between aldoses and ketoses since these do not necessarily need enzymes to take place. They then determined the shortest path needed to convert six pentoses to five hexoses and showed that it corresponded to the sequence of reactions in the known pathway. There were other feasible solutions, but these were longer, suggesting that for the pentose phosphate pathway at least, there had been selection for the shortest route. Why the shortest pathway should be optimal is another question, but it reduces the number of intermediates in the cell contributing to osmotic potential and maximizes the metabolic rate by maximizing the thermodynamic driving force per step.

The connectivity structure of metabolic networks has also been examined for signs of selection pressure during evolution. It has been proposed that metabolism is not randomly connected but has a ''small world'' structure (Jeong et al., 2000, Wagner and Fell, 2001), which could point to selection for robustness, and evolution of the network by gene duplication of existing enzymes so that new metabolic reactions are more likely to involve existing highly connected metabolites. However, most of the steps in this chain of reasoning have been contested (e.g., Arita, 2004). Again, the difficulty in attributing significance to the graph properties is the lack of appropriate comparisons; the usual technique in