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Shared Epigenetic Mechanisms in Stemness and Cancer

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Editorial Note

Monotremes notwithstanding, eutherian mammalian embryos develop from the embryoblast, an inner cell mass within the blastocyst composed of embryonic stem cells. Under optimal conditions, these cells are defined by their unlimited capacity of self-renewal and by their potential to differentiate into all cell lineages (pluripotency). Adult mammalian tissues also harbor stem cells, with similar self-renewal properties and broad cell lineage determination propensities (multipotency). These cells support diverse biological processes including tissue renewal and repair, underlying their potential in reparative cell therapies for ailments raging from neurodegenerative and myocardial disorders to cancer. Though the existence of stem cells was formulated as early as the 19th century by zoologist Ernst Haeckel in his treatise on the Natural history of creation [1], stem cells were isolated and stably cultured only in the early 1980s [2,3]. Similarly to stem cells, cancer cells, and perhaps more so cancer stem cells, are also characterized by perpetual self-renewal under optimal growth conditions. Contrary to stem cells, however, most cancer cells fail to undergo cellular differentiation when subjected to tissue-specific signaling cues, leading to uncontrolled growth. Understanding the commonalities and divergences between stem cells and cancer cells would not only bring about a better understanding of the mechanisms of stemness and cancer pathogenesis, it may also yield molecular therapeutic targets to impede tumor growth and/or promote tumor cell differentiation.

Mounting evidence supports a role for epigenetic mechanisms in the biology of stem and cancer cells, including those that are most likely to be transgenerational, rendering their involvement in tumor growth, progression, and dissemination a distinct possibility. Such mechanisms include those responsible for the establishment and/or maintenance of three heritable repressive chromatin states represented by CpG DNA methylation (effected by DNMT3A, DNMT3B, and DNMT1; [4-6]), trimethylated histone H3 lysine 27 (H3K27me3; catalyzed by EZH2 [7]), and removal by LSD1 of methyl groups from mono- (H3K4me1) and di-methylated histone H3 lysine 4 (H3K4me2) [8-11]. The fate and biological outcome of these three epigenetic marks appears to be tightly knitted in several biological systems, as for example recently shown in leukemic stem cells [12]. H3K4me3, an activating epigenetic modification, and H3K27me3, a repressing histone mark, form together a combinatorial code known as "bivalent domains". Such epigenetic domains silence the expression of genes that drive cellular differentiation in embryonic stem cells [13], as well as tumor suppressor genes in cancer stem cells [14], while maintaining them poised for transcriptional activation. Similarly, loci harboring the H3K27me3 mark can recruit *de novo* DNMTs in stem cells, leading to CpG methylation, and possibly, to a lasting silencing of cell differentiation and cell cycle inhibitor genes, providing a permissive setting for tumorigenesis [14,15]. Thus, while epigenetic mechanisms allow for a plastic response to environmental signaling cues to regulating the opposing forces of cell growth and differentiation, their dysregulation can lead to uncontrolled growth and presents with the possibility of epigenetic therapeutic intervention in cancer.

In addition to the well established roles of DNMTs and EZH2 in cancer (e.g. [14-18]), a recent analysis of some 500 tumors showed LSD1 overexpression to associate with several different mesenchymal stem cell-derived tumors, and pharmacological inhibition of LSD1 blocks cell growth of all LSD1-overexpressing tumors tested, highlighting the therapeutic potential of LSD1 in cancer [19]. Other tumor-specific epigenetic alterations, including some that are shared by several different mesenchymal tumors, may also represent viable therapeutic targets and warrant further investigation [20]. Based on these and other considerations, it can be surmised that several other epigenetic mechanisms underlying stemness are likely to be implicated in tumor pathogenesis or maintenance and may also serve as drug targets. In my capacity of Editor, I call on researchers investigating the epigenetic bases of stemness and cancer to submit their work to us for consideration.

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