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Review Article

Overview: Epigenetic Regulation in Cancer Stem Cells by Methylation

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Abstract

Epigenetic regulation mechanisms in stem cells are crucial for self-renewal and differentiation capacities, however these abilities are deregulated in cancer stem cells (CSCs), which are able to induce and maintain the tumor growth. Due to cancer stem cells share physiologic properties with their normal counterparts, there is a rationale to evaluate epigenetic regulation mechanisms that drive the unpaired self-renewal and differentiation abilities resulting in cancer. DNA and histone methylation plays a relevant role in the gene expression regulation of components belong to cell signaling pathways involved in self-renewal CSCs such as Wnt, Notch and Hg. In this review, we make an overview of epigenetic mechanisms to regulate the highly CSCs tumorigenicity methylation-mediated.

Keywords: Cancer stem cells, methylation, tumorigenicity.

Cancer stem cells

Cancer still be a significant human public disease in whole world. Into the tumor, there are highly heterogenic cell populations that shown different cancer hallmarks such as resisting cell death, epithelial-mesenchymal transition (EMT), mutations in tumor suppressor proteins and oncoprotiens [1]. Furthermore, epigenetic mechanisms also have relevant impact to drive the carcinogenesis and contribute to get cells with unlike level of differentiation resulting cells with different properties and capabilities including their tumorigenic potential. Taken together, these hallmarks sustained the cancer stem cells (CSC) or "Tumor Initiation Cells (TIC)" model, which in addition to have highly potential to induce and maintain tumor growth, these cells are able to rinse cells with different level of differentiation and also with high cell proliferation rate to form the tumor mass. Self-renewal, potential of differentiation and quiescent state are some representative capabilities of CSC that share with their normal counterparts[2]. The origin of CSCs remain unknown, however there are some theories including niche environment, accumulation of mutations in crucial genes as tumor suppressor and oncogenes, which are related with apoptosis evasion, drug resistance, drug exclusion mechanisms mediated by ABC bomb [3], active DNA repair system and key proteins involved in signal transduction pathways promoting self-renewal and cell proliferation such as Wnt, Notch and Hg pathways [4]. Pluripotent associated transcription factors such as OCT-4, SOX-2, NANOG, MYC regulate the embryonic stemness including their pluripotency to differentiation, however these factors have been expressed in adult CSC from several tumors [5] such as pancreatic intraepithelial neoplasia [6], lung cancer [7], breast cancer [8], brain cancers [9], hepatocellular carcinoma [10]. The expression of pluripotent markers into tumors could explain the presence of undifferentiated cancer cells which are related with poor prognosis.

In contrast, there are some studies that show the presence of non-leukemogenic cancer cells with rarely ability to induce tumor generation in specific conditions [11-14]. Under clonal evolution theory, all cancer cells have the capacity to induce tumor growth. Thus, there is the possibility that cancer cells could be reprogrammed to become TICs by epigenetic and genetic changes which are related with the heterogenicity among cancer cells [15].

In a specific manner, in melanoma the tumorigenic ability is not restricted to small population of this neoplaisa, but interestingly these cells are widely shared among phenotypically diverse cells. Also, these distinct melanoma cells form tumors that recapitulated the phenotypic diversity of the tumor which they derived, suggesting that these tumorigenic melanoma cells undergo reversible changes in markers expression *in vivo* [15]. Studies in melanomas obtained from patients, can be observed and a broad range of markers turn on and turn off into lineages of tumorigenic cells, phenomenon named "phenotypic plasticity" [15,16]. However, there are several groups that still evaluating the presence of CSCs in different cancers including hematopoietic malignances and solid tumors [17].

These characteristics and functions of CSC and/or TIC including their thinning differences could be related with the resting time of quiescent stem cells increasing the rate of mutation in key genes, but also epigenetic mechanisms which can regulate gene expression related with stemness and tumorigenicity.

Epigenetic of CSC

The CSC and their normal counterparts share some characteristics including some epigenetic gene expression regulation such as chromatin remodeling factors, DNA methylation, microRNAs and post-translational modifications such as phosphorylation, acetylation, ubiquitination, and SUMOylation [18]. We will take up the methylation epigenetic regulations in cancer stem cells.

Self-renewal, cell differentiation and proliferation are crucial activities that are deregulated in CSCs. In addition to understand the mechanisms related with the high tumorigenic capacity of CSCs, it is necessary knowing the cellular and molecular rules that drive uncontrolled self-renewal and aberrant differentiation to design new and accurate therapeutics strategies to help patients with cancer.

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In humans, DNA methylation is generated by DNA methyltransferase 1 (DNMT1) and maintained by DNMT3A and DNMT3B [19, 20]. In mice leukemia model, using knockout of Dntm1, further pre-leukemia development is blocked compare to Dnmt1wild type. This role could be explained in part for possible hypomethylation of tumor suppressor genes. Trough ChIP assay using H3K27me3 antibodies, Trowbridge and collaborators found that the Enhancer Zeste Homologue 2 (EZH2)-regulated target genes are depressed in Dntm1 haplo-insufficient mice model, suggesting that Polycomb gene (PcG) complex might cooperate with DNA methylation to regulate leukemia stem cell functions such as to induce tumor growth [21].

PcG, it has been considered as a relevant complex for gene expression regulation including cancer. Upregulation of EZH2 promotes several cancer progression such as prostate, ovarian and breast cancer [22,23]. In ovarian cancer, there is a direct relationship by the EZH2 expression in the side population (SP) tested, a subset enriched in CSCs [24]. In breast cancer, a high level of EZH2 expression induces a spreading out of TICs demonstrated by the mammosphere formation assay. This effect is mediated in part or the aberrant accumulation of β-catenin mediated by RAF1-ERK activation upon EZH2 overexpression. It is known that canonic Wnt- β-catenin pathway is close related with self-renewal capacity of stem cells. Additionally, RAD51 a component of DNA damage repair system, is downregulted in response of an increase of EZH2 leading specific genomic instability and tumor progression [25].

Components of PcG complex, including EZH2, are decreased in pancreatic cancer cells treated with difluorinated-curcimin (CDF). This event is related with a decrease of pancreactic CSC markers such as CD44, EpCAM and also the transcription factor OCT-4. Furthermore, falling EZH2 expression is associated with reducing of Notch. Interesting, also under CDF treatment, there is an increase of the micro RNA-101 (miR-101), which belong to panel of tumor-suppressors miRNAs. Taken together, these findings demonstrate that these epigenetic molecular CDF-effects result in ablation of pancreatic CSCs *in vitro* and *in vivo* assays [26]. Similar results are obtained by 3-Dezaneplanocin A (DZNeP), which it has been used for the treatment of several cancers. Under the treatment of DZNeP, like CDF as EZH2 inhibitor, a depression in sphere formation of LNCaP and DU145 prostate cancer cell lines is observed. It means that DZNeP has a cytotoxic effect on CSCs [27].

Both hypoxia-inducible factor-1α (HIF-1α) and HIF-2α are expressed in gliomastoma cells where they have an effect on CSC activities including the sphere formation and promote CD133, OCT-4, NANOG and MYC expression [28,29]. The hypoxia CSC microenvironment factors the expression and activity of the histone methyltransferase mixed-lineage leukemia (MLL1) and it enhance hypoxia responses. Using a shRNA MML-1 in glioma cells, a diminishing if HIF-2α expression and ablation of glioma sphere formation was observed, and also a decreasing of glioma stem cells represented by the measure of CD133-positive cells was observed. Actually MLL-1 and the marker CD133 co-localized in glioma sphere cells [30]. These observations suggest the relevant role of MLL-1 in the tumorigenic of CSCs.

In addition of EZH2 effect on CSCs, it also be relevant the opposite effect of histone demethylases as LSD1/KMD1 that suppress gene expression by converting di-methylated to mono and un-methylated H3K4. However, the expression of LSD1 is related with pluripotent markers OCT-4, SOX-2 and NANOG expression which are also expressed in most of CSCs. Transient knockdown of LSD1 decrease expression of these pluripotent stem markers followed by the growth inhibition of pluripotent cancer cells such as teratocarcinoma, embryonic carcinoma and seminoma [31].

Conclusion

For better understanding CSCs biology, it is necessary to know must of mechanism that regulate their stemness and tumorigenicity. In this overview about epigenetic gene expression regulation focused in DNA and histone methylation, we remark the crucial role of these mechanisms to favor the CSCs deregulated self-renewal capacity and their highly tumorigenicity. However, it is clear that not only DNA and histone methylation, which are close related, are relevant epigenetic mechanisms; other histone modifications and miRNAs are also implicated. Finally, in addition to several researchers, we are convinced that epigenetic factors related with CSCs have to be considered as therapeutic targets to prevent and eradicate cancer in patients.

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