



Review

Cancer signaling pathways with a therapeutic approach: An overview in epigenetic regulations of cancer stem cells



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ABSTRACT

One of the most important issues in cancer progression is cancer stem cells (CSCs) which have illustrated that the bulk tumors can arise from a special combination of cells. Remarkably, it has been proposed to be a notable and strong factor in carcinogenesis and tumorigenesis and also is a key parameter of therapeutic resistance. In this way, recent findings have shown the key roles of epigenetic regulations in cancer development. Considerably, epigenetic regulations of gene expression is an active and dynamic process including histone modification, DNA methylation and chromatin remodeling with a reversible trait. Meaningfully, recent and novel findings have described the significance of epigenetic regulatory proteins from diverse features comprising tumorigenesis, stem cell proliferation and carcinogenesis. Evidently, abnormal epigenetic regulations is directly related with many serious disorders particularly different cancers. We here review a discussion of how the deregulation of eclectic pathways containing *Sonic Hedgehog (SHH)*, *WNT*, *Beta catenin* and *NOTCH* can help to carcinogenesis specially focusing to survival and maintenance of CSCs in therapeutic approach.

1. Introduction

Many improvements and innovations in genetic and epigenetic researches have formed understanding of cancer biology recently [1,2]. In this account, besides the dysregulation of cells growing in an uncontrolled behavior, cancer mechanism is also illustrated by the hyperactive epigenetic and genetic modifications that help to carcinogenesis and tumorigenesis in many different cancers involving eclectic genes [3–8]. Conspicuously, epigenetic alterations including histone modifications and DNA methylation are the most vital factors in the programming process of stem cells tissue differentiation. Aberrant epigenetic modifications may cause transformation of the normal stem cells to CSCs with different cell fluctuations like loss of differentiation and the position of stem like features. Although, many recent studies have indicated that the epigenetic mechanisms can be used in therapeutic

involvements [9]. Anyway, the implications of CSCs with different cancer signaling pathways, is of high interest and importance. Relatively, diverse signaling pathways have different mechanism outcome and lead to a better understanding of epigenetic and genetic mechanisms in tumorigenesis and carcinogenesis [10] (Fig.1).

2. Cancer stem cells

Cancer stem cells (CSCs) describe a small unique population of different cells with self renewal potential in order to produce the eclectic cells that form the tumors [11]. These cellular combinations are called cancer stem cells because of their stem like properties in comparison with stem cells. Remarkable properties of these cells comprise extensive self renewal capacity including symmetrical and asymmetrical and differentiation ability [12,13]. Considerably, a general ability and

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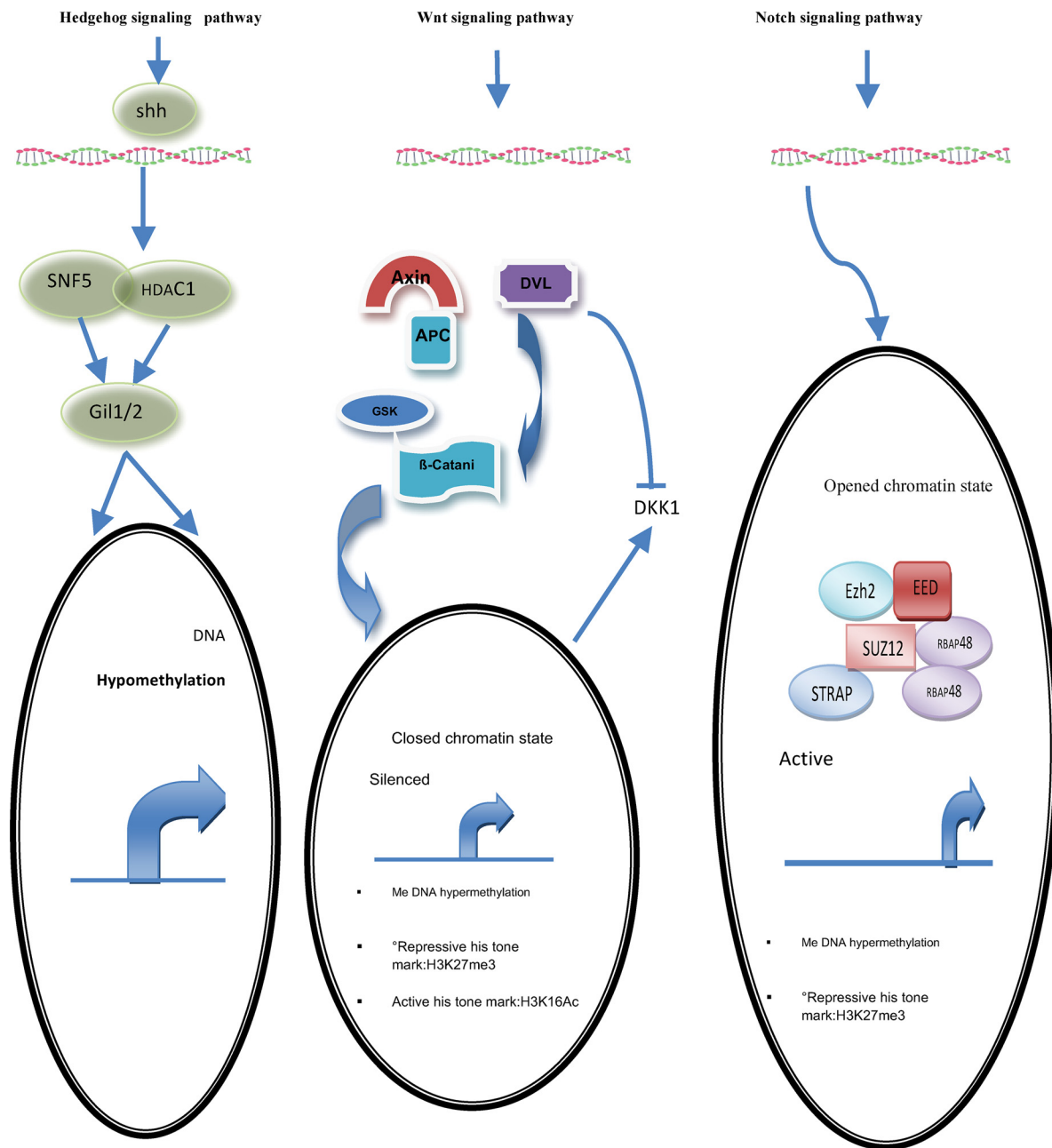


Fig. 1. An overall relationship of Wnt, Notch and Hedgehog signaling pathways. The main important regulation mechanism of key cancer stem cell molecular signaling pathways which is involved by epigenetic mechanism. Importantly, Wnt/ β -catenin signaling can be increased by reduced expression of the DKK1 inhibitor through promoter hypermethylation and enhanced H3K27 ME3 and also reduced H3k16 acetylation marks. Correspondingly, Notch signaling certain genes including *hes1* and *hes5* can have an active function by inhibition of H3K27 inhibitory methylation. Hedgehog molecular signaling pathway can have an active function in cancer stem cells epigenetically by *shh* promoter hypomethylation.

potentiality to differentiate is not an essential characteristic of cancer stem cells and also the potential of these special cells repopulate the different cells in the tumor and differentiation of these cells is of great importance. Notably, cancer stem cells must illustrate their remarkable potent in tumor initiation ability [14] (Fig. 2).

3. Role of CSCs in carcinogenesis and tumorigenesis

According to the hierarchic organization of the tumor structure or cancer stem cell pattern, CSCs are at the germline core of tumor development which is similar to a normal adult stem cell, containing the ability of the differentiation and also self renewal capacity [15,16]. In this account, recent evidence and studies have supported the hierarchic

cancer pattern for initiation many solid tumors comprising cancers of digestive system [17,18]. Conspicuously, the cancer stem cells have a main responsibility for generation of distant metastasis except their notable roles in tumor initiation. These particular traits of CSCs are specially responsible for a multi resistant tumor structure in many different malignancies importantly in cancers of digestive system [19]. Transparently, there are two common models in this way: The first one is stochastic and the second one is hierarchic models. Accordingly, the basic clonal evolution model confirms that the tumor formation and creation is the result of accumulating genetic occurrence randomly in all differentiated cell whereas the CSCs pattern suggests that a single cancer stem cell give arises to hierarchic structure in tumorigenesis process [20]. Correspondingly, the stochastic and hierarchic patterns of

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