



Mini-Review

Stem Cell Surface Markers and Their Role in Cancer Progression

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ABSTRACT

Cancer progression and metastasis is rarely or less studied phenomenon. It has been known that cancer stem cells are the significant agents playing critical in metastasis and advanced tumorigenesis because of their heterogeneous nature. Their changed molecular expression with the passage of time and induction of normal cells into cancerous cells are correlated and determining these stem cell markers expression on CSCs can help to understand the progression of cancer and resistance to chemotherapy approaches. Identification of these signaling pathways and their modulation role are the key necessities for precise diagnosis and targeted therapeutic approaches development.

Keywords: Signalling pathways, Stem cells, Cancer progression, Tumorigenesis

In early 1875, Julius Cohnheim raised the theory that stem cells may be derived from residues left over from embryonic development (1). The concept of stem cells was reported in 1994 (2). The first time in 1977, blood stem cells were isolated by John Dick et al, and in 2003, Michael Clarke managed to find the stem cells of solid tumors such as breast cancer (3). Cancer stem cells are tumorigenesis and produce tumor by differentiation into several types of cells and because of their heterogeneous nature, these cells remain in the tumor as a distinct population and cause relapse and metastasis and producing new tumors (4, 5). Breast cancer is the most common type of cancer in women (6). Due to the characteristics of stem cells, breast cancer stem cells play an important role in the progress of cancer through a process of self-renewal and inducing a relapse of tumors, and by resistance to

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chemotherapy and radiotherapy (7, 8, 9, 10, 11). CD29, CD24, CD44, CD49f are considered as some of the important surface markers in BCSCs (12). Breast cancer stem cells have expressed some of the markers including CD44 and mutually, are negative in some markers including CD24 (3, 13). CD44 is a family of transmembrane glycoproteins in the cell that lead to progression of malignancy and metastasis of breast cancer (14) and CD49f is required to growth and survival of tumor cells (15) and also, the activity of the specific enzyme, aldehyde dehydrogenase isoform 1 (ALDH1) of the group iso-enzyme is considered as the other marker of BCSCs (12).

Literature Review

Given that the cancer stem cells are used in diagnosis, invasion, metastasis, and recurrence of the tumor (16) and CSCs play an important role in resistance to chemotherapy and radiotherapy, so identifying the

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signaling pathways including Hedgehog Notch and Wnt, that are involved in BCSC, is so important (17). Wnt family is of secreted proteins and in mammals, there are 19 members of the Wnt. The Wnt signaling pathway activity is associated with the expansion of stem cells. In human cancer, it is often deregulated (18). The first time, the important role of The Wnt signaling pathway was identified in tumorigenesis of mammary glands, associated with the MMTV virus in the position of Int-1 (Wnt1) and overexpressing of Wnt1 induces tumorigenesis of mammary glands (19, 20). The key role of B-catenin in regulating the differentiation of stem cells and dysregulation of this pathway and its relation to resistance to radiotherapy and also, in 18% of mutations in the APC gene, in the progression of breast cancer, has been studied (21, 22, 23). When the ligand of Wnt is connected to the protein receptor of Frizzled attached to the membrane, the Frizzled receptor activates the protein in the cytoplasm, thereby inhibits glycogen synthase kinase 3, and this makes separation of β -catenin from APC and β -catenin accumulates in the nucleus and induces expression of target genes of WNT1 by cooperation of transcription factors (24, 25, 26, 27, 28). The Hedgehog signaling pathway, as a catalyst, involves in the embryonic development, proliferation, and tumorigenesis and plays an important role in breast cancer mammary glands development and recurrence of breast cancer stem cells (29). In mammals, there are 3 Hh members including Desere, Sonic, and Indian (Dhh, Shh, Ihh) all of which are of the secreted proteins (30). In breast cancer, activation of the pathway in the stem cells takes place using the ligand Shh and expression of transcription factors GLI1 and GLI2 (31). In this way, after SHH binds to the Patched receptor, PATCH naturally inhibits a transmembrane protein called SMO. When Shh is connected to patch, the inhibitor of the protein smo is removed and with the removal of this inhibitor, an intracellular signaling cascade is waged and form the expression of transcription factors (30). The Notch signaling pathway controls the renewal process of the epithelial cells in mammary glands and breast cancer stem cells (32, 33, 34). The Notch signaling pathway relies on a cell-cell interaction. The Notch receptors involve in the bio-functions such as cell proliferation, differentiation, survival, and tumorigenesis of the cells (35). There are 4 types of receptors Notch 1-

4 and 5 ligands Jagged 1-2 and DLL 1, 2, 4 in mammalian (36). After connection of protein Notch to the ligand and activation of Notch in the extracellular field, a part of Notch intracellular domain (NICD) is cut by a protease called presenilin 1 and leads to release of NICD from plasma membrane and then, NICD is introduced into nucleus and together with the transcription factor CSL influences on the expression of its target genes (37).

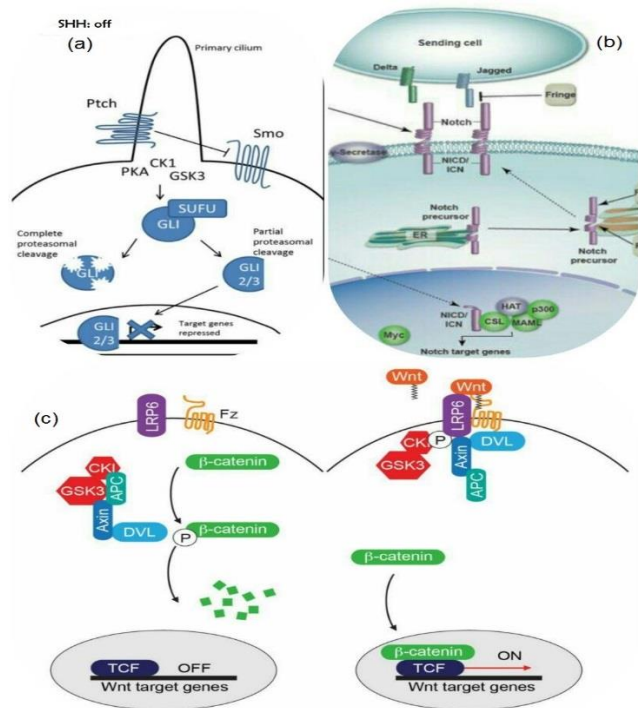


Figure 1. Hedgehog signaling pathway (a), Notch signaling pathway (b), Wnt signaling pathway (c)

Conclusion

Considering the characteristics of the stem cells, one of the existing challenges is to identify the cancer stem cells among the tumor cells. In this regard, identifying the signaling pathways are considered as the important agents in the progress of cancer stem cells that can be considered as a means to diagnosis as well as the therapeutic practices.

Conflict of Interest

Authors declare no conflict of interest.

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