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Differentiation of Cancer Stem Cells

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1. Introduction

Tumors originally develop from normal cells that acquire the ability to grow aberrantly and metastasize to distant organs (Hanahan and Weinberg, 2000). These malignant transformations are considered to be induced by the accumulation of multiple genetic/epigenetic changes (Yamashita et al., 2008b). Although considered monoclonal in origin, cancer is composed of heterogeneous cell populations. This heterogeneity is traditionally explained by the clonal evolution of cancer cells through a series of stochastic genetic events (clonal evolution model) (Fialkow, 1976; Nowell, 1976). In contrast, cancer cells and stem cells have similar capabilities with respect to self-renewal, limitless division, and the generation of heterogeneous cell populations. Recent evidence suggests that tumor cells possess stem cell features (cancer stem cells) to self-renew and give rise to relatively differentiated cells through asymmetric division, thereby forming heterogeneous populations (cancer stem cell model) (Clarke et al., 2006; Jordan et al., 2006). Accumulating evidence supports the notion that cancer stem cells can generate tumors more efficiently in immunodeficient mice than non-cancer stem cells in hematological malignancies and in various solid tumors (Al-Hajj et al., 2003; Bonnet and Dick, 1997; O'Brien et al., 2007; Ricci-Vitiani et al., 2007; Singh et al., 2004).

Cancer stem cells are considered to be resistant to chemotherapy and radiotherapy, which might be associated with the recurrence of the tumor after treatment (Boman and Huang, 2008; Dean et al., 2005; Diehn et al., 2009; Zou, 2008). These findings have led to the proposal of “destemming” cancer stem cells (Hill and Perris, 2007) in order to induce their differentiation into non-cancer stem cells or to eradicate cancer stem cells by inhibiting the signaling pathways responsible for their self-renewal. Recent studies have supported this proposal and suggest the utility of several factors to induce the differentiation of cancer stem cells and facilitate tumor eradication; however, it is still debatable whether the simple differentiation of cancer stem cells effectively eradicates tumors. Here, we summarize current knowledge on the differentiation of cancer stem cells and discuss the utility and limitation of differentiation therapy to eliminate cancer.

2. Cancer stem cell system

The consensus definition of a cancer stem cell is a cell within a tumor that possesses the capacity to self-renew and to generate the heterogeneous lineages of cancer cells that

comprise the tumor, as proposed by the AACR workshop in 2006 (Clarke et al., 2006). Thus, cancer stem cells can only be defined experimentally and their self-renewal ability is generally evaluated by the capacity of serially transplanted cells in immunodeficient mice. A cancer stem cell may give rise to one or two daughter cells that have essentially the same ability to replicate and generate differentiated non-cancer stem cells (Fig. 1 upper and lower left panels).

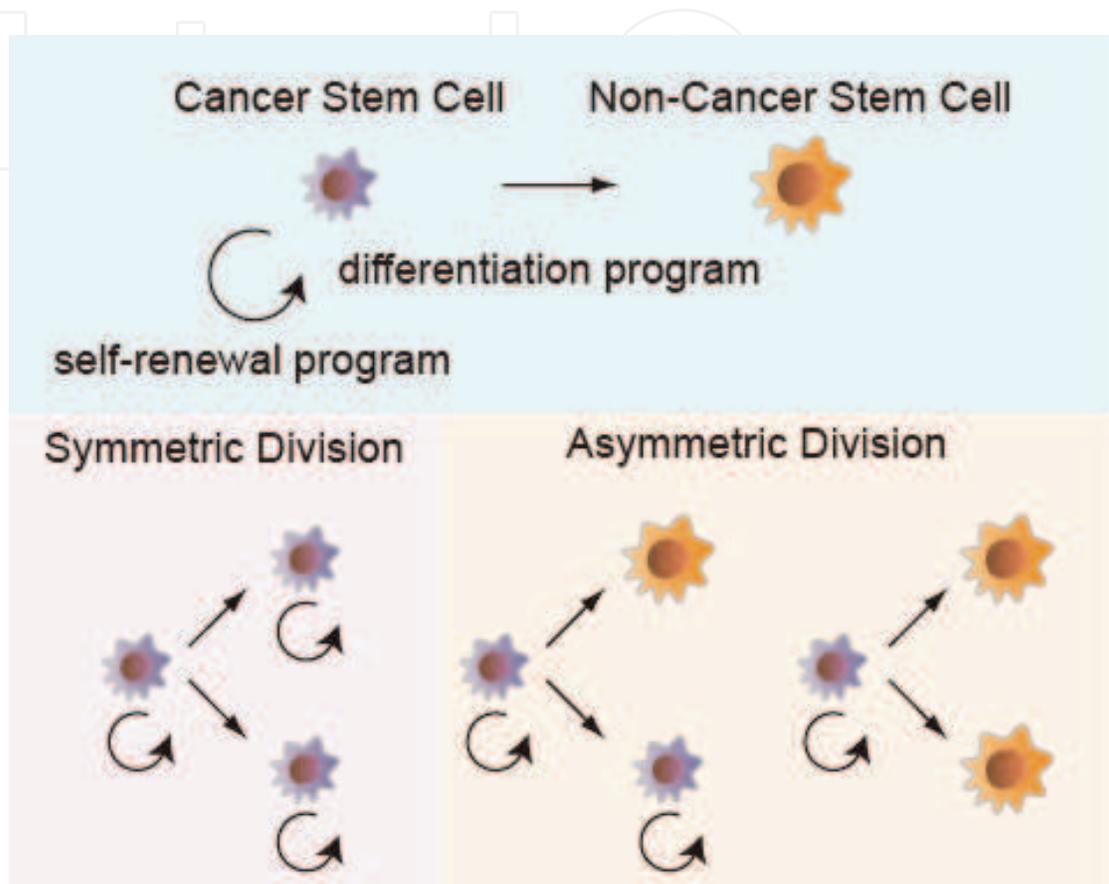


Fig. 1. Symmetric/asymmetric division of a cancer stem cell

Asymmetric cell division could be defined by the generation of one cancer stem cell and one progenitor cell with the loss of self-renewal capacity (Fig. 1 lower right panel). If both progenitors derived from a cancer stem cell lose the capacity of self-renewal by the induction of differentiation, the cancer stem cell population would be depleted and the tumor would subsequently shrink, according to the conventional cancer stem cell model.

2.1 Signaling pathways responsible for the self-renewal of cancer stem cells

A growing body of evidence suggests the similarities of normal stem cells and cancer stem cells in terms of their self-renewal and differentiation programs. Indeed, the self-renewal and differentiation programs in cancer stem cells are considered to be regulated by several signaling pathways that are activated in normal stem cells (Lobo et al., 2007). These signaling pathways seem to be activated during the process of normal organogenesis as well as carcinogenesis in a tissue-dependent manner (Pardal et al., 2003). Therefore, underscoring the significance of these signaling pathways on self-renewal and differentiation is critical for the development of treatment strategies specifically targeting cancer stem cells.

2.1.1 Wnt/ β -catenin signaling

Wnt/ β -catenin signaling has been studied primarily in developing embryos and was demonstrated to modulate cell proliferation, migration, and differentiation in a cellular context-dependent manner (Decaens et al., 2008; Giles et al., 2003; Moon et al., 2004; Ober et al., 2006). Wnt signaling is involved in the decision of stem cells to self-renew or differentiate during organogenesis, involving, for example, skin, intestine, bone marrow, kidney, and liver development (Moon et al., 2004; Thompson and Monga, 2007). Moreover, mutations of genes involved in Wnt/ β -catenin signaling have been reported in a wide variety of human cancers including colorectal cancer, gastric cancer, skin cancer, ovarian cancer, liver cancer, and leukemia (Giles et al., 2003; Merle et al., 2005; Takebe et al., 2010; Tan et al., 2008; Vermeulen et al., 2010; Woodward et al., 2007; Zhao et al., 2007).

Wnt signaling is mediated through a core set of proteins to activate the transcriptional programs responsible for cell proliferation and development (Fig. 2). In the absence of Wnt proteins, β -catenin is phosphorylated and degraded by the Axin-APC-GSK3 β complex. Once Wnt proteins bind to their receptor, Frizzled, the degradation complex is inactivated to stabilize β -catenin, which leads to its accumulation in the nucleus and interaction with T-cell factor (TCF) to activate the transcription of target genes (Moon et al., 2004).

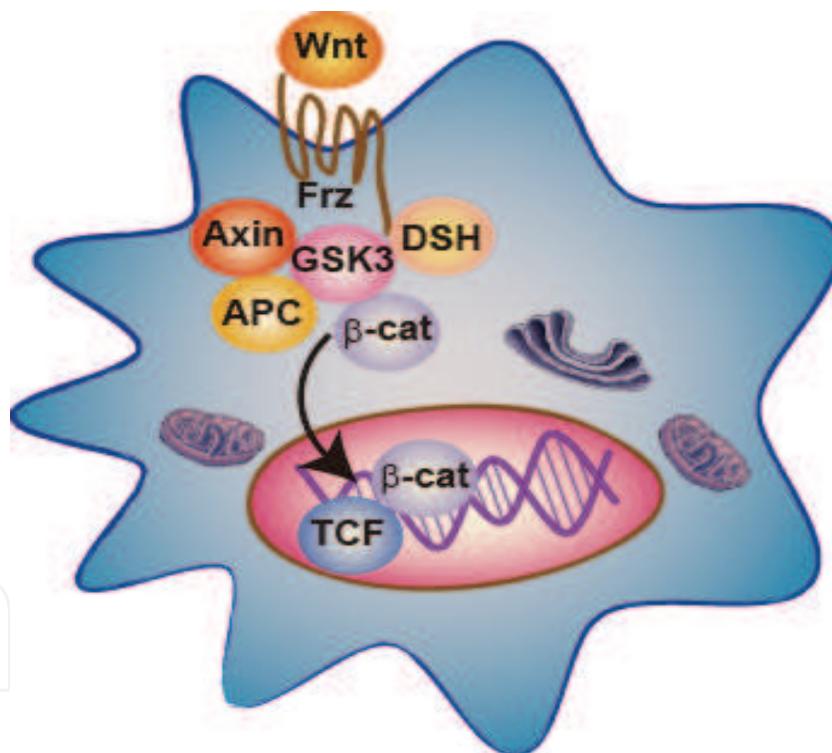


Fig. 2. Wnt/ β -catenin signaling. APC, adenomatous polyposis coli; β -cat, β -catenin; DSH, Dishevelled; Frz, Frizzled; GSK3, glycogen synthase kinase 3; TCF, T-cell factor

Recent studies have demonstrated that Wnt/ β -catenin signaling also plays a role in the maintenance of cancer stem cells, including colorectal cancer (Vermeulen et al., 2010), breast cancer (Li et al., 2003; Woodward et al., 2007), and liver cancer (Yang et al., 2008). We have recently demonstrated that Wnt/ β -catenin signaling augments self-renewal and inhibits the differentiation of liver cancer stem cells by the expression of the stem cell marker EpCAM, which results in the enrichment of the tumor-initiating cell population (Yamashita et al.,

2008a; Yamashita et al., 2009). We have further demonstrated that small molecules, which specifically inhibit the transcriptional activity of the TCF/ β -catenin complex, can suppress the cell proliferation of EpCAM-positive liver cancer cell lines, suggesting the utility of these compounds for the eradication of cancers via the inactivation of Wnt/ β -catenin signaling (Yamashita et al., 2007).

2.1.2 Hedgehog signaling

The Hedgehog signaling pathway was initially identified as a regulator of segmental patterning in *Drosophila* (Nusslein-Volhard and Wieschaus, 1980). Hedgehog signaling is activated in developing embryos, especially in the skeleton and neural tube, and regulates the cell proliferation, migration, and differentiation of stem cells (Varjosalo and Taipale, 2008). Several types of cancers are reported to have an activated hedgehog signaling pathway, including glioma (Clement et al., 2007), prostate cancer (Sanchez et al., 2005), breast cancer (Liu et al., 2006), pancreatic cancer (Li et al., 2007), and hematological malignancies (Zhao et al., 2009).

Hedgehog signaling is regulated by several proteins, including ligands (Sonic Hedgehog, Desert Hedgehog, and Indian Hedgehog), the Patched (Ptch) receptor, the Smoothed (Smo) transmembrane protein, and the zinc finger transcription factor Gli (Merchant and Matsui, 2010) (Fig. 3). In the absence of ligands, Ptch represses the activity of Smo and the Gli-mediated transcriptional program is constitutively suppressed (Gli- suppressed). Once ligands bind to Ptch, the repression of Smo is released and the Gli-mediated transcriptional program is activated (Gli-activated).

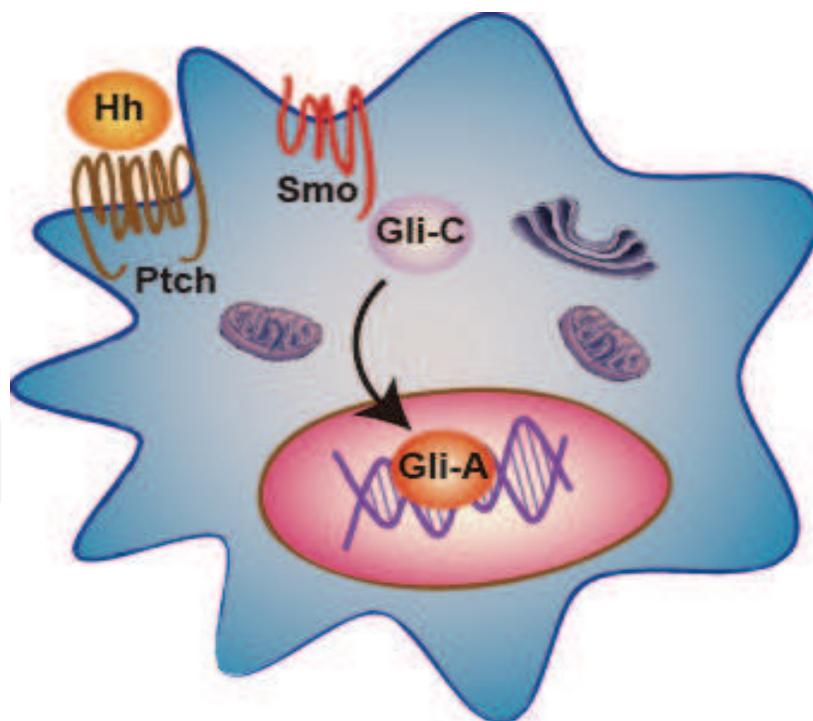


Fig. 3. Hedgehog signaling. Gli-C, Gli complex; Gli-A, Gli-activated; Hh, Hedgehog; Ptch, Patched; Smo, Smoothed

Accumulating evidence suggests that Hedgehog signaling regulates the self-renewal of cancer stem cells in several types of cancer, including glioblastoma and leukemia (Clement

et al., 2007; Zhao et al., 2009). Accordingly, Hedgehog signaling inhibitors have been clinically tested and might be beneficial for patients with advanced medulloblastoma or basal cell carcinoma, although Smo mutations in cancer cells confer resistance against such inhibitors (Rudin et al., 2009; Von Hoff et al., 2009; Yauch et al., 2009).

2.1.3 Notch signaling

Notch signaling has a pivotal role in regulating cell-to-cell communication during embryogenesis (Artavanis-Tsakonas et al., 1999), and is known to regulate stem cell fate in various organs (Androutsellis-Theotokis et al., 2006; Fre et al., 2005). Mammalian Notch ligands consist of the two structurally distinct families Delta-like ligands (DLLs) and Jagged ligands (JAGs), and these ligands are bound to the cell membrane (Fig. 4). The activation of Notch signaling is initiated by the binding of these membrane-bound ligands to Notch receptors, which results in the release of the Notch intracellular domain into the cytoplasm and nucleus by the γ -secretase complex to activate the Notch-specific transcriptional program.

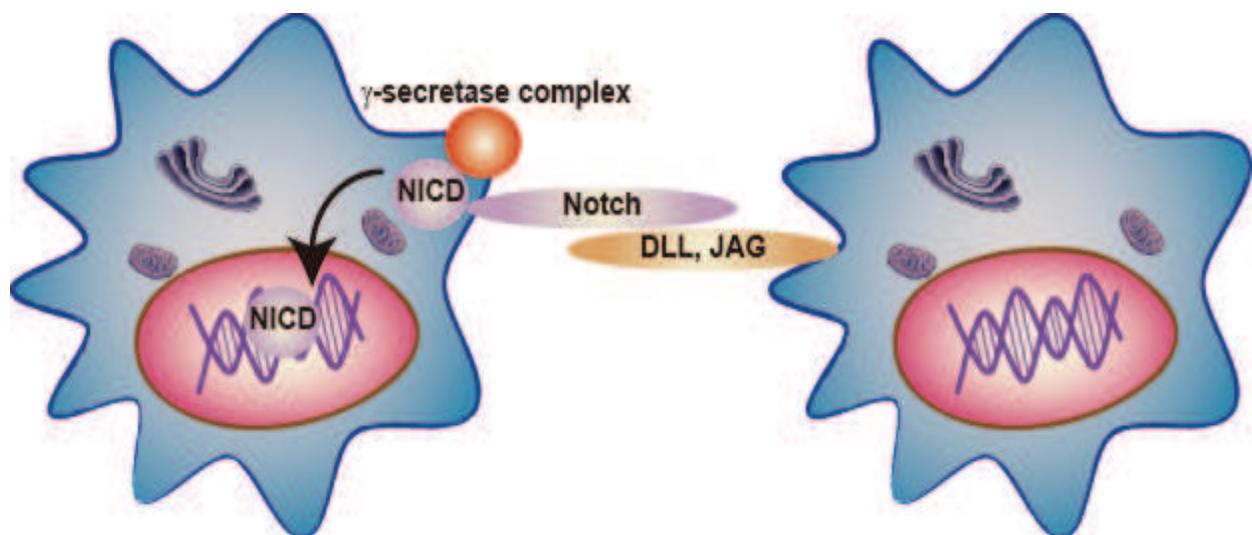


Fig. 4. Notch signaling. DLL, Delta-like ligand; JAG, Jagged; NICD, Notch intracellular domain

Notch signaling has been implicated in various types of cancers, including solid tumors and leukemia (Pannuti et al., 2010). A growing number of recent studies has demonstrated that the activation of the Notch signaling pathway can drive tumor growth via the expansion of the cancer stem cell population (Korkaya and Wicha, 2009; Peacock and Watkins, 2008; Wilson and Radtke, 2006). Indeed, the Notch signaling pathway has been demonstrated to be active in cancer stem cells and to play a critical role in the self-renewal of cancer stem cells (Fan and Eberhart, 2008; Fan et al., 2010; Wang et al., 2009). Thus, Notch signaling is considered to be a good target for pharmacological inhibition to eradicate cancer stem cells, and the effect of Notch inhibitors against Notch, including γ -secretase inhibitors or monoclonal antibodies, have been extensively evaluated (Pannuti et al., 2010).

2.2 Signaling pathways responsible for cancer stem cell differentiation

Although self-renewal pathways are considered to be critical targets for the eradication of cancer stem cells, it is still debatable if differentiation pathways are equally effective for their

eradication. Several recent studies have provided evidence of the utility and limitation of the cancer stem cell differentiation strategy by modulating the signaling pathways responsible for the differentiation of normal stem/progenitor cells.

2.2.1 Bone morphogenic protein signaling

Bone morphogenic protein (BMP) signaling is known to be activated during embryogenesis and to play a pivotal role in the differentiation of neural and intestinal stem cells (Varga and Wrana, 2005). BMPs belong to a subgroup of the transforming growth factor- β superfamily and activate signaling through the BMP-receptor (BMPR)-mediated phosphorylation of Smad proteins. Interestingly, recent studies have suggested the utility of BMPs to induce the differentiation of brain cancer stem cells and facilitate brain tumor eradication (Lee et al., 2008; Piccirillo et al., 2006). More recently, colorectal cancer stem cells have been shown to lack the expression of BMP4, and the administration of BMP4 enhanced the terminal differentiation, apoptosis, and chemosensitization of colorectal cancer stem cells (Lombardo et al., 2011). Interestingly, the effects of BMP4 on the differentiation of colorectal cancer stem cells appeared to be independent of the phosphorylation status of Smad, suggesting the importance of non-canonical signaling pathways activated by BMP4 for the differentiation of these cells.

2.2.2 Oncostatin M signaling

Oncostatin M (OSM) is a pleiotropic cytokine that belongs to the IL-6 family, which includes IL-6, IL-11, and leukemia inhibitory factor (LIF). These cytokines share the gp130 receptor subunit as a common signal transducer, and activate Janus tyrosine kinases and the signal transducer and activator of transcription 3 (STAT3) pathways. However, gp130 forms a heterodimer with a unique partner, for example, the IL6 receptor, LIF receptor, or OSM receptor (OSMR); thus, each cytokine uniquely induces a certain signaling pathway (Heinrich et al., 2003), and OSM is known to exploit distinct signaling in an OSMR-specific manner (Kinoshita and Miyajima, 2002). Of note, OSM is known to activate the hepatocytic differentiation program in hepatoblasts in an OSMR-specific manner (Kamiya et al., 1999; Kinoshita and Miyajima, 2002).

We recently identified that OSMR is expressed in a subset of liver cancer stem cells (Yamashita et al., 2010). Interestingly, OSMR-positive hepatocellular carcinoma (HCC) was characterized by the abundant expression of stem cell markers and poorly differentiated morphology, suggesting that OSMR is more likely to be expressed in HCC with stem/progenitor cell features (Yamashita et al., 2008a). Of note, the OSM-OSMR signaling pathway was maintained in these HCCs, and OSM induced hepatocytic differentiation in liver cancer stem cells (Fig. 5).

Unexpectedly, we identified that the hepatocytic differentiation of liver cancer stem cells by OSM resulted in enhanced cell proliferation *in vitro* and modest anti-tumor activity *in vivo* when administered alone. However, we have further demonstrated that OSM-mediated hepatocytic differentiation of liver cancer stem cells effectively suppresses HCC growth when combined with conventional chemotherapy. It is possible that OSM may boost the anti-tumor activity of 5-FU by “exhausting dormant cancer stem cells” through hepatocytic differentiation and active cell division (Fig. 6). A similar chemosensitization effect was observed in colorectal cancer stem cells differentiated by BMP4 administration (Lombardo et al., 2011).

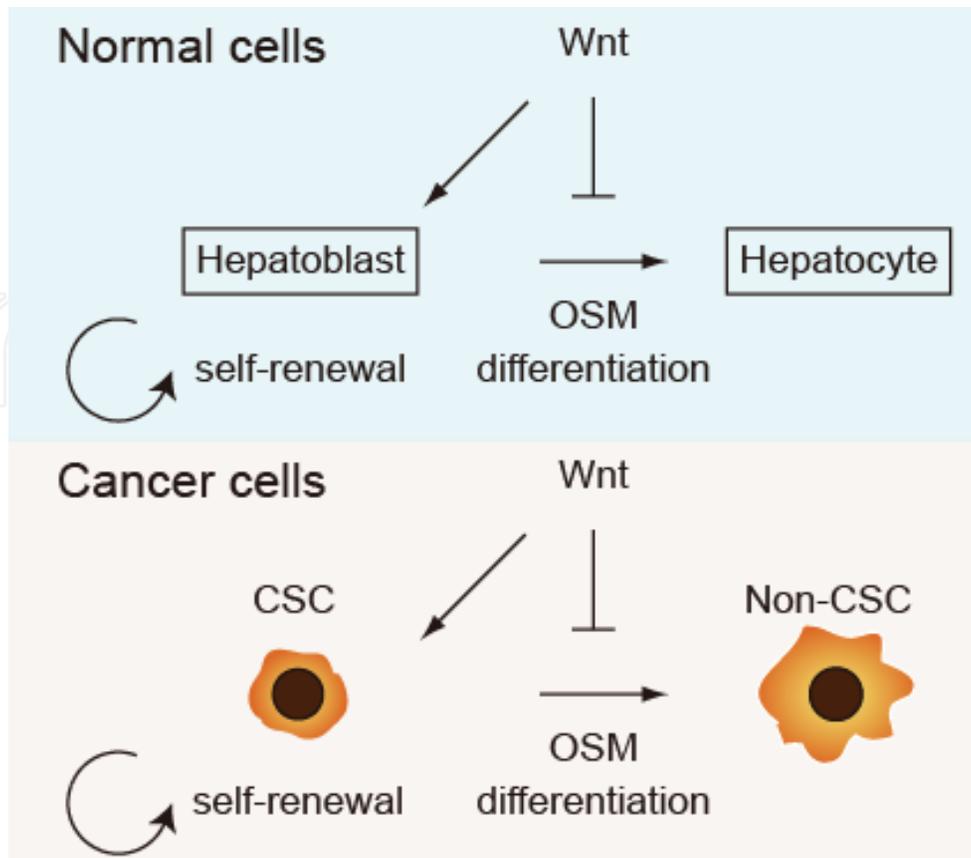


Fig. 5. Signaling pathways responsible for the self-renewal and differentiation of liver cancer stem cells. CSC, cancer stem cell; OSM, oncostatin M

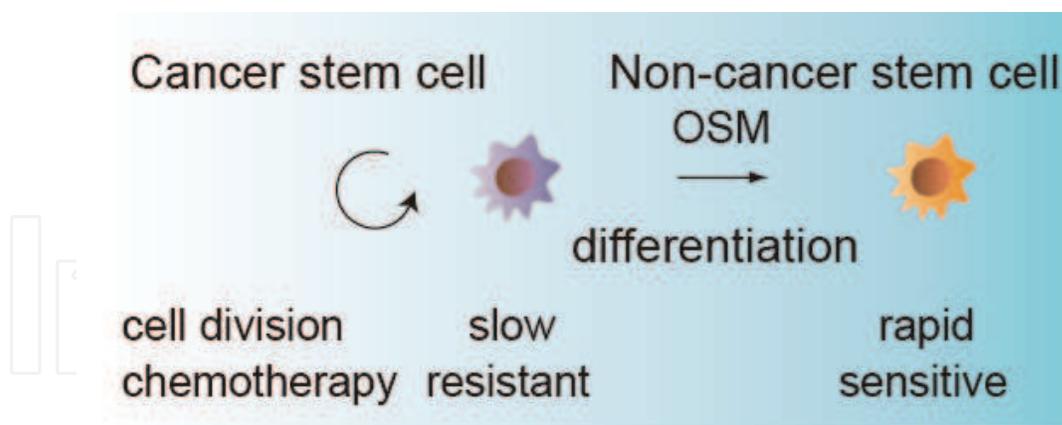


Fig. 6. Effect of oncostatin M (OSM) on exhausting dormant liver cancer stem cells

3. Limitation of cancer stem cell differentiation

As described above, some of the signaling pathways for the differentiation of normal stem cells may be maintained in cancer stem cells. To induce the differentiation of cancer stem cells by specific ligands, the expression of the corresponding receptors bound to ligands is clearly required, suggesting the importance of clarifying the mechanisms for receptor expression regulation. Interestingly, BMPRs and OSMR were detected in colorectal and liver

cancer stem cells, respectively, suggesting the possibility of ligand-induced differentiation therapy in the clinic. However, the expression of these receptors might be transcriptionally suppressed in a subset of cancers through methylation of their promoter regions (Deng et al., 2009; Kim et al., 2009; Lee et al., 2008). Indeed, a recent study suggested that BMP-mediated brain cancer stem cell differentiation failed in a subset of brain tumors in which BMP receptor promoters were methylated and silenced (Lee et al., 2008). Therefore, cancer stem cells may acquire resistance against differentiation therapy by additional epigenetic changes during the differentiation treatment.

It has been postulated that both normal stem cells and cancer stem cells are dormant and show slow cell cycles. Consistently, cancer stem cells are considered to be more resistant to conventional cytotoxic chemotherapeutic agents than non-cancer stem cells, possibly due to slow cell cycles as well as the increased expression of ATP-binding cassette (ABC) transporters, robust DNA damage responses, and activated anti-apoptotic signaling (Bao et al., 2006; Dean et al., 2005; Viale et al., 2009). Therefore, the induction of differentiation programs in cancer stem cells may result in cell proliferation of the tumor. Indeed, we recently demonstrated that differentiation of liver cancer stem cells by OSM increased cell proliferation, at least *in vitro* (Yamashita et al., 2010). Our data clearly suggested the necessity of conventional chemotherapy in addition to differentiation therapy to eradicate non-cancer stem cells originating from cancer stem cells. Furthermore, although the combination of OSM and conventional chemotherapy effectively inhibited tumor growth in our model, we did not observe tumor shrinkage (Yamashita et al., 2010). If both progenitors derived from a cancer stem cell lose their self-renewal capacity by the induction of differentiation, the tumor should subsequently shrink following the depletion of cancer stem cells. However, it is possible that ligand-based differentiation programs cannot completely inhibit the self-renewal programs of target cancer stem cells. Thus, the induction of differentiation in cancer stem cells with the eradication of non-cancer stem cells might not be sufficient for the eradication of the tumor, which may suggest the importance of inhibiting self-renewal as well as stimulating the differentiation of cancer stem cells.

A recent paper suggested that leukemia-initiating cells are composed of genetically diverse, functionally distinct populations (Notta et al., 2011), suggesting the clonal evolution of leukemia-initiating cells. Accordingly, cancer stem cells in solid tumors may also have a distinct tumorigenic/metastatic capacity as well as chemoresistance with certain genetic/epigenetic changes in each subclone as a result of clonal evolution. Thus, the cancer stem cell model and the clonal evolution model are not considered to be mutually exclusive. Therefore, clonal selection of cancer stem cells resistant to differentiation therapy might occur with additional genetic/epigenetic changes during treatment as a result of clonal evolution. The effects of differentiation therapy on the clonal evolution or genetic diversity of cancer stem cells need to be clarified in the future.

4. Conclusion

The recent re-emergence of the cancer stem cell hypothesis has provided novel insights on the effect of differentiation programs on cancer stem cells for the potential eradication of tumors. Although the activation of several signaling pathways by certain cytokines may be effective for the differentiation of cancer stem cells, their utility and limitation for tumor eradication should be clarified in future to provide novel therapeutic opportunities for cancer patients.

5. Acknowledgment

This work was supported in part by a grant from The Japanese Society of Gastroenterology.

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Cancer Stem Cells - The Cutting Edge

Edited by Prof. Stanley Shostak

ISBN 978-953-307-580-8

Hard cover, 606 pages

Publisher InTech

Published online 01, August, 2011

Published in print edition August, 2011

Over the last thirty years, the foremost inspiration for research on metastasis, cancer recurrence, and increased resistance to chemo- and radiotherapy has been the notion of cancer stem cells. The twenty-eight chapters assembled in *Cancer Stem Cells - The Cutting Edge* summarize the work of cancer researchers and oncologists at leading universities and hospitals around the world on every aspect of cancer stem cells, from theory and models to specific applications (glioma), from laboratory research on signal pathways to clinical trials of bio-therapies using a host of devices, from solutions to laboratory problems to speculation on cancers' stem cells' evolution. Cancer stem cells may or may not be a subset of slowly dividing cancer cells that both disseminate cancers and defy oncotoxic drugs and radiation directed at rapidly dividing bulk cancer cells, but research on cancer stem cells has paid dividends for cancer prevention, detection, targeted treatment, and improved prognosis.

How to reference

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Taro Yamashita, Masao Honda and Shuichi Kaneko (2011). Differentiation of Cancer Stem Cells, *Cancer Stem Cells - The Cutting Edge*, Prof. Stanley Shostak (Ed.), ISBN: 978-953-307-580-8, InTech, Available from: <http://www.intechopen.com/books/cancer-stem-cells-the-cutting-edge/differentiation-of-cancer-stem-cells>

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