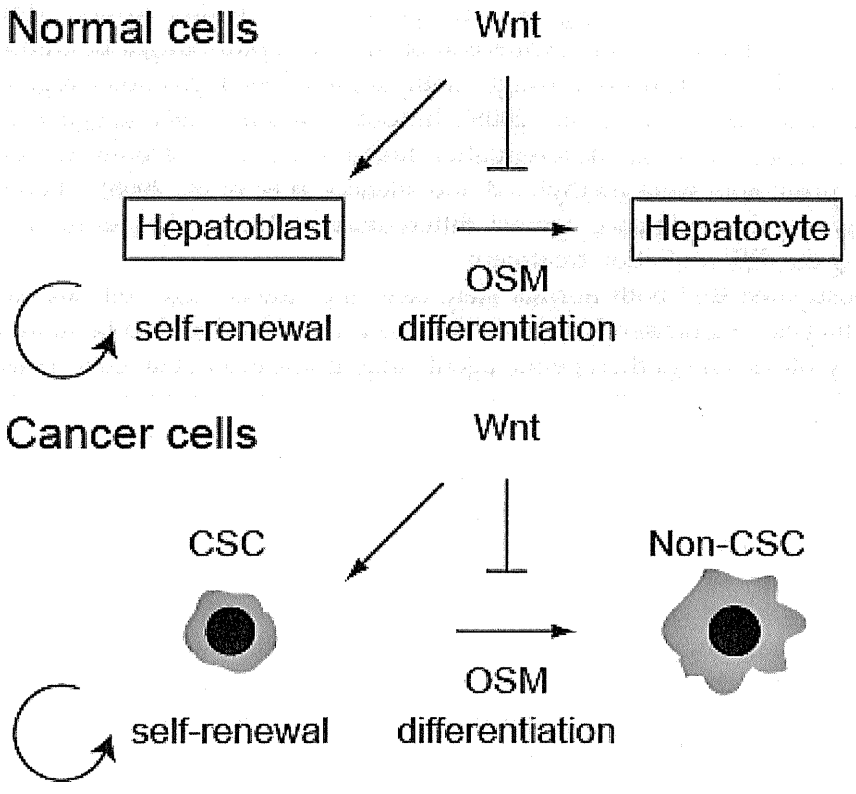

Fig. 5. Signaling pathways responsible for the self-renewal and differentiation of liver cancer stem cells. CSC, cancer stem cell; OSM, oncostatin M

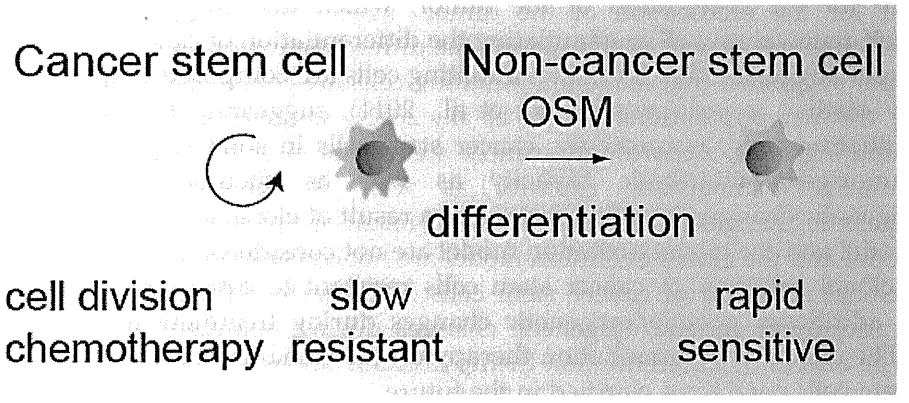

Fig. 6. Effect of oncostatin M (OSM) on exhausting dormant liver cancer stem cells

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.

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