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Miyayama S, （宮山）	Portal blood supply to locally progressed hepatocellular carcinoma after transcatheter arterial chemoembolization: observation on CT during arterial portography.	Hepatol Res	41	853-866	2011
Miyayama S, （宮山）	Efficacy of cone-beam computed tomography during transcatheter arterial chemoembolization for hepatocellular carcinoma.	Jpn J Radiol	29	371-377	2011

Miyayama S, （宮山）	Origins of feeding arteries of hepatocellular carcinoma located near the umbilical fissure of the left hepatic lobe: angiographic evaluation.	Cardiovasc Intervent Radiol	-	-	(in press)
Miyayama S, （宮山）	Comparison of local control effects of superselective transcatheter arterial chemoembolization using epirubicin plus mitomycin C and miriplatin for hepatocellular carcinoma.	Jpn J Radiol	-	-	(in press)
Miyayama S, （宮山）	Main bile duct stricture occurring after transcatheter arterial chemoembolization for hepatocellular carcinoma.	Cardiovasc Intervent Radiol	33	1168-1179	2010
Miyayama S, （宮山）	Inferior phrenic arteries: angiographic anatomy, variations, and catheterization technique for transcatheter arterial chemoembolization.	Jpn J Radiol	28	502-511	2010
Miyayama S, （宮山）	Hepatocellular carcinoma in the caudate lobe of the liver: variations of its feeding branches on arteriography.	Jpn J Radiol	28	555-562	2010
Miyayama S, （宮山）	Chemoembolization for the treatment of large hepatocellular carcinoma.	J Vasc Interv Radiol	21	1226-1234	2010
Miyayama S, （宮山）	The march of extrahepatic collaterals: analysis of blood supply to hepatocellular carcinoma located in the bare area of the liver after chemoembolization.	Cardiovasc Intervent Radiol	33	513-522	2010
Miyayama S, （宮山）	Hepatocellular carcinoma supplied by the right lumbar artery.	Cardiovasc Intervent Radiol	33	53-60	2010
Miyayama S, （宮山）	Histopathological findings after ultraselective transcatheter arterial chemoembolization for hepatocellular carcinoma.	Hepatol Res	39	374-381	2009
Miyayama S, （宮山）	Detection of hepatocellular carcinoma by CT during arterial portography using a cone-beam CT technology: comparison with conventional CTAP.	Abdom Imaging	34	502-506	2009
Miyayama S, （宮山）	Usefulness of cone-beam computed tomography during ultraselective transcatheter arterial chemoembolization for small hepatocellular carcinoma that cannot be demonstrated on angiography.	Cardiovasc Intervent Radiol	32	255-264	2009
Imai Y, （今井）	Usefulness of miriplatin as an anticancer agent for transcatheter arterial chemoembolization in patients with unresectable hepatocellular carcinoma.	J Gastroenterol	-	-	(in press)

Ⅴ. 研究成果の刊行物・別刷

17

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).

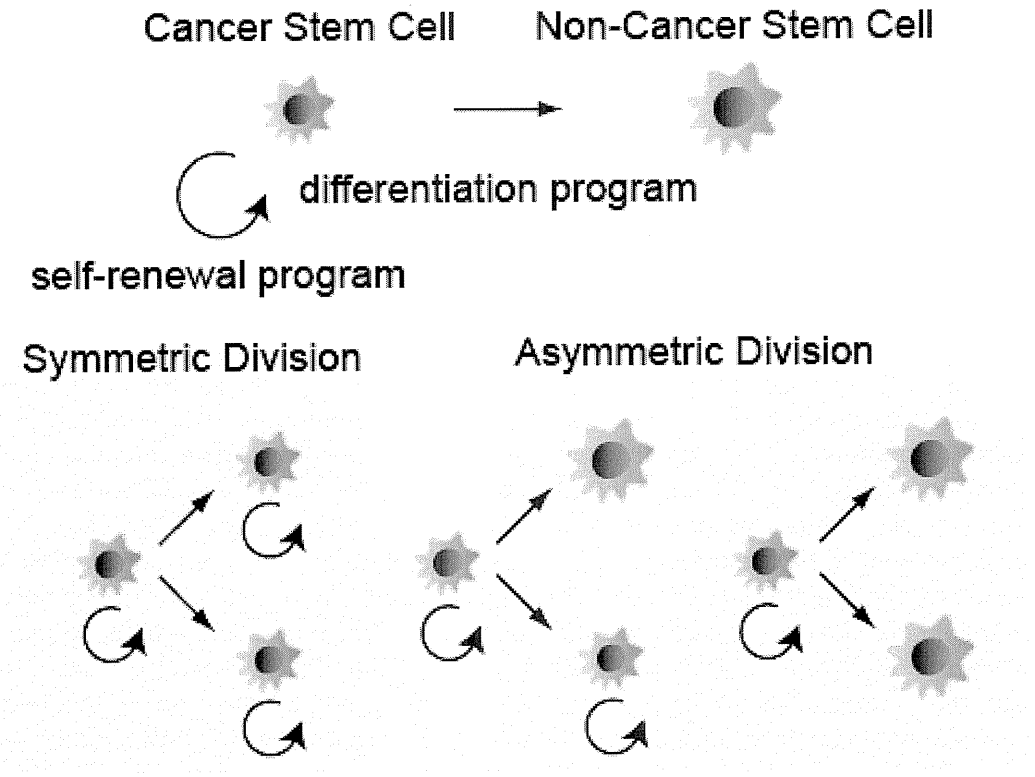

Fig. 1. Symmetric/asymmetric division of a cancer stem cell

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-GSK3β 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).

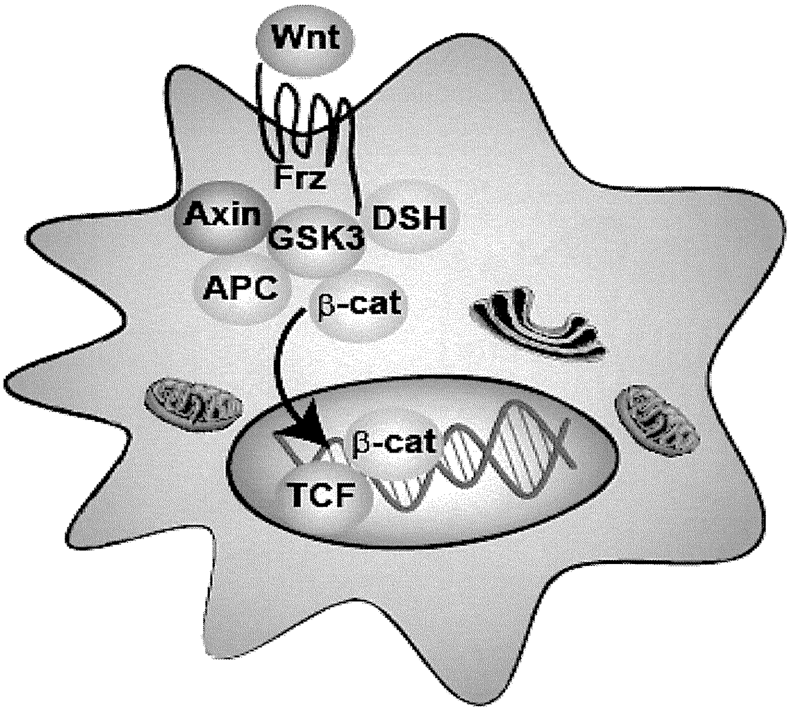

Fig. 2. Wnt/β-catenin signaling. APC, adenomatous polyposis coli; β-cat, β-catenin; DSH, Dishevelled; Frz, Frizzled; GSK3, glycogen synthase kinase 3; TCF, T-cell factor

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 Smoothened (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).

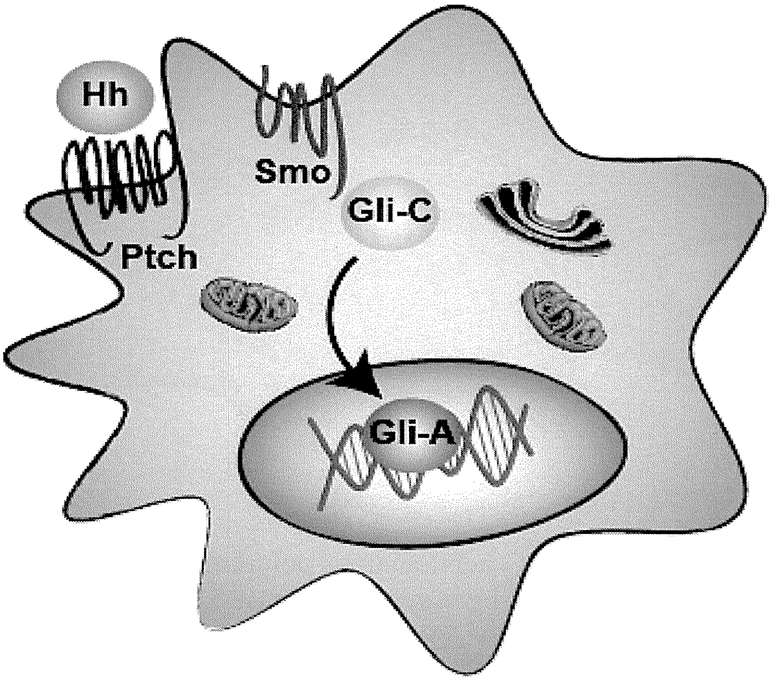

Fig. 3. Hedgehog signaling. Gli-C, Gli complex; Gli-A, Gli-activated; Hh, Hedgehog; Ptch, Patched; Smo, Smoothened

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.

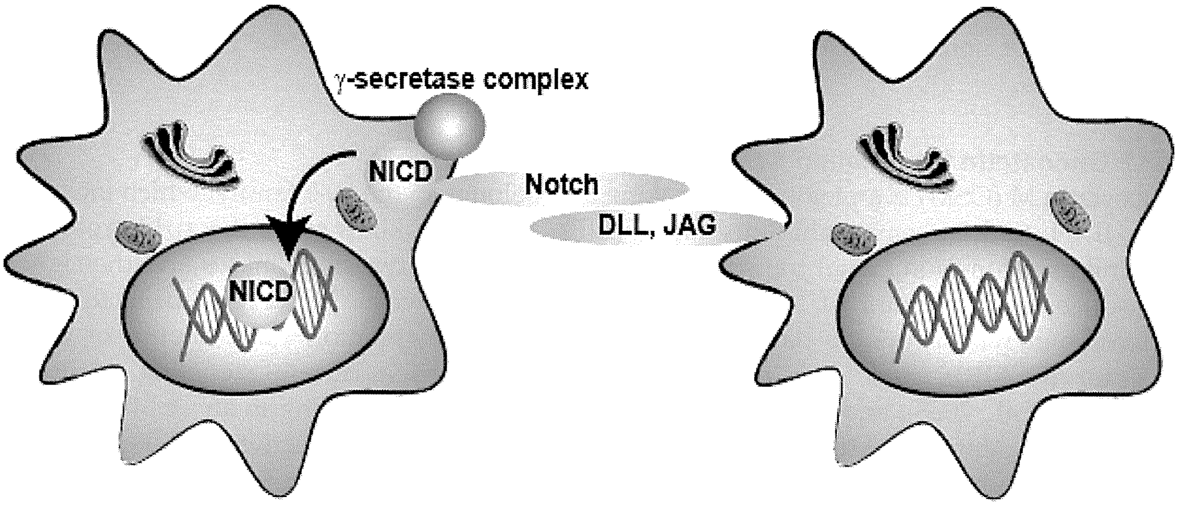

Fig. 4. Notch signaling. DLL, Delta-like ligand; JAG, Jagged; NICD, Notch intracellular domain

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