Chapter 2
Stem Cells and Cancer Stem Cells: New Insights

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Prologue to Cancer Stem Cell Research

Although the concept of the cancer stem cell (CSC) was advocated more than several decades ahead, it was not accepted widely due to the lack of a direct proof method. However, recent progresses in the stem cell biology and developmental biology revealed that cancers contain the hierarchy similar to normal tissues and that only CSCs in tumors have a strong self-renewal capability and are malignant (Fig. 2.1) (Reya et al. 2001). It is thought that the existence ratio of CSCs is several percent or less in tumors and cancer cell lines and the other cells (non-CSCs) are either cancer precursor cells, which have limited proliferation ability, or nondividing cancer cells. Together these findings suggest that characterization of CSCs is essential for the curable cancer therapy.

Definition of CSCs

CSCs were initially defined by their extensive self-renewal capacity, tumorigenicity, and multipotentiality. As a number of oncogenes, including *inhibitor of differentiation* (*Id*), *hairy and enhancer of splits* (*Hes*) and *Notch*, are expressed in CSCs as well as tissue-specific stem cells (TSCs) and block cell differentiation, it remains uncertain as to whether CSCs actually give rise to multilineage cells. Further evidence also exists suggesting that cancer cells co-express a number of lineage-specific

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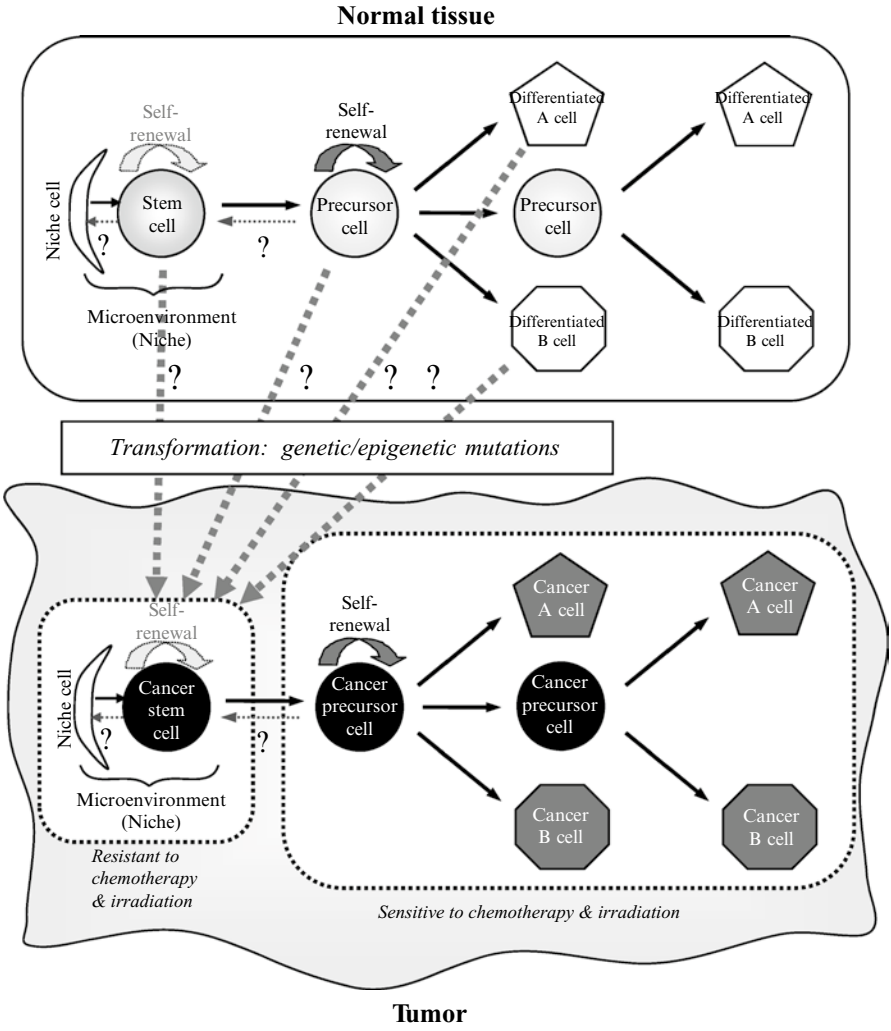

Fig. 2.1 Similarity between normal tissue and tumor. Tumors as well as normal tissues are likely to consist of small number of stem cells that have self-renewal capability and multipotentiality, precursor cells that have limited proliferative potency, and differentiated cells. CSCs are thought to be transformed from TSCs, precursor cells and/or differentiated cells by genetic/epigenetic mutations. Moreover, CSCs exist in special microenvironment "niche" and seem to keep their resistance to a variety of anti-cancer treatment methods

markers, each of which is exclusively expressed in normal differentiated cells, such as neurofilaments in neurons, glial fibrillary acidic protein in astrocytes and galactocerebrocide in oligodendrocytes, raising the question of whether such lineage-marker positive cells are in fact differentiated cells. Seen against this light then the obvious definition that can be applied to CSCs might be their unlimited self-renewal, expression of TSC markers, and tumorigenicity.

Cell-of-Origin of CSCs

Cancers have traditionally been thought to arise from either differentiated cells or their proliferating precursor cells, which have acquired oncogenic mutations. Since stem cells have been discovered in adult tissues, however, it has been suggested that TSCs might be a principal target of such mutations (Fig. 2.1). This speculation is supported by a number of different findings: First, it is likely that cancers arise from epithelia, which are in contact with the external environment and contain a wide variety of TSCs. Second, many cancers have been immunolabeled for TSC markers and for differentiation markers. Third, while TSCs survive and continue to proliferate throughout life, differentiated cells do not, suggesting that TSCs are more susceptible to accumulating oncogenic mutations. Finally, stem cells and precursor cells, which are transformed with oncogenic genes, have been shown to as developing cancer in vivo. Together, these findings suggest that either TSCs or amplifying precursor cells can be seen as the origin of malignant tumors.

Characteristics of CSCs

Resistance to Chemotherapy

A number of anti-cancer drugs have been successful in eliminating cancers; however, some cancer cells survive and the cancer recurs, indicating that the surviving cells are not only resistant to such anti-cancer drugs but are also malignant (Gottesman et al. 2002; Szakacs et al. 2006). It has been shown that glutathione and its related enzyme apparatus, topoisomerase II, O6-methylguanine-DNA-methyltransferase, dihydrofolate reductase, metallothioneins, and various ATP-binding cassette (ABC) transporters, such as the protein encoded by the multidrug resistant gene (MDR), the multidrug resistant protein (MRP), and the breast cancer resistant protein (BCRP1), contribute to such drug resistance in cancers. It is crucial to investigate relationship between CSCs and these factors.

Resistance to Irradiation

Irradiation is one of the most effective therapies for malignant tumors; however, a small population of cancerous cells tends to survive and cause tumor recurrence, suggesting that CSCs are radioresistant. Recently, Bao et al. (2006) have revealed that CD133-positive glioblastoma CSCs are much more resistant to irradiation than CD133-negative cells.

Invasion/Metastatic Activity

One characteristic of malignant tumor cells is their ability to invade and disseminate into normal tissue and to metastasize into other tissues. Some of the infiltrating cancer cells cannot be removed by surgical operation and causes recurrence, suggesting that CSCs retain high invasion activity. In fact, it has demonstrated that CD133-positive cancer cells highly express CD44 and chemokine receptor CXCR4, both of which mediate cell migration (Hermann et al. 2007; Liu et al. 2006).

Niche for CSCs

The number of TSCs is precisely regulated by both intrinsic mechanism and extracellular signals derived from specialized microenvironment "niche." For example, it was demonstrated that niche provides a limited number of physical anchoring sites, including beta1-integrin and N-cadherin, for TSCs and secretes both growth factors and anti-growth factors, including Wnt, FGF, hedgehog (Hh), bone morphogenic proteins, and Notch (Li and Neaves 2006; Moore and Lemischka 2006). Hypoxia is also shown to be essential for the maintenance of stemness, tumorigenesis, and resistance to anti-cancer treatments, chemotherapy and irradiation (Das et al. 2008; Matsumoto et al. 2009). Moreover, it was shown that the ablation of such niche results in loss of TSCs. It seems likely that CSCs also need niche for tumorigenesis. Kaplan and his colleagues have elegantly demonstrated that bone marrow-derived progenitors form the pre-metastatic niche in the tumor-specific pre-metastatic sites before cancer cells arrive and that the ablation of the niche prevents tumor metastasis (Kaplan et al. 2005). However, since transplanted cancer cells form tumors in any area in vivo, CSCs might be independent of the niche regulation or have a capability to make a new niche by recruiting bone marrow stem cells and other component cells.

Preparation of CSCs

The following methods are commonly used to prepare CSCs from cancers and cancer cell lines using the common characteristics of TSCs, such as cell surface markers, side population (SP), aldehyde dehydrogenase activity (ALDH), and a floating sphere formation.

Cell Surface Markers

Dick and colleagues have been able to show that the acute myeloid leukemia (AML)-initiating cells are found in primitive $CD34^+$ and $CD38^-$ populations, in which hematopoietic stem cells are enriched (Bonnet and Dick 1997; Lapidot et al. 1994).

Al-Hajj et al. have successfully separated tumorigenic breast CSCs from mammary tumors and breast cancer cell lines as $CD44^+$ $CD24^{-/low}$ $Lineage^-$ cells. As few as 100 $CD44^+$ $CD24^{-/low}$ $Lineage^-$ cells formed tumors in NOD/SCID mice, while tens of thousands of other cancer cell populations did not (Al-Hajj et al. 2003; Ponti et al. 2005). Another study by Singh et al. reported their success in separating brain CSCs from human medulloblastoma and glioblastoma multiforme (GBM) using an anti-CD133 antibody that recognizes a variety of different stem cells. Here, as few as 100 $CD133^+$ GBM cells, although not $CD133^-$ cells, formed tumors in NOD/SCID brain (Singh et al. 2004). It has also revealed that colon CSCs are enriched in a $CD133^+$ population (O'brien et al. 2007; Ricci-Vitiani et al. 2007). This is in addition to prostate CSCs being found to be enriched in CD44+ Integrin alpha2 beta1hi CD133+ (Collins et al. 2005). Very recent studies have shown that CD15, also known as stage-specific embryonic antigen 1 (SSEA1) or Lewis X (LeX), is a general CSC marker on GBM and medulloblastoma (Read et al. 2009; Son et al. 2009; Ward et al. 2009). It therefore seems likely that cell surface markers, such as CD133, are useful in separating CSCs from many types of tumors.

Side Population

It was revealed that cancer cells, as well as many kinds of normal stem cells, express a number of ABC transporters. BCRP1, for example, excludes the fluorescent dye Hoechst 33342, identifying a SP (Goodell et al. 1996), which is enriched for the various types of TSCs, although some research has shown that TSCs exist in both SP and non-SP and that SP cells do not express stem cell markers (Mitsutake et al. 2007; Morita et al. 2006). A number of research groups have found that some established cancer cell lines, which have been maintained in culture for decades, and tumors, such as AML, neuroblastoma, nasopharyngeal carcinoma, and ovarian cancer, contain a small SP. These studies have demonstrated that SP cells – but not non-SP cells – self-renew in culture, are resistant to anti-cancer drugs including Mitoxantrone, and form tumors when transplanted in vivo (Haraguchi et al. 2006; Hirschmann-Jax et al. 2004; Kondo et al. 2004; Patrawala et al. 2005; Ponti et al. 2005; Szotek et al. 2006). However, since many cancer cell lines do not contain any SP fraction and non-SP cells in some cancer cell lines likely generate SP fraction during culture, it is needed to evaluate whether SP is a general method to prepare CSCs.

Aldehyde Dehydrogenase Activity

ALDH is another detoxifying enzyme oxidizing intracellular aldehydes to carboxylic acids and blocking alkylating agents. Since it has been shown that ALDH increases in TSCs (Jones et al. 1995; Cai et al. 2004), it is now possible to identify and purify

many types of TSCs, including hematopoietic stem cells and neural stem cells (NSCs), using fluorescent substrates of this enzyme and flow cytometry. There is increasing evidence that many types of CSCs strongly express ALDH and can be purified from tumors and cancer cell lines (Ginestier et al. 2007; Korkaya et al. 2008; Pearce et al. 2005).

Sphere Formation Assay

An increasing evidence points to the fact that CSCs as well as TSCs, such as NSCs and mammary gland stem cells, can form floating aggregates (tumor spheres) and be enriched in the spheres when cultured in serum-free medium with proper mitogens, such as bFGF and EGF (Fig. 2.2c) (Haraguchi et al. 2006; Hirschmann-Jax et al. 2004; Kondo et al. 2004; Ponti et al. 2005). Although many CSC researchers use sphere formation methods to concentrate their CSCs in culture, monolayer culture method might be better used to characterize CSCs as monolayer-cultured CSCs can be expanded as a homogenous population (Pollard et al. 2009).

Signaling Pathways Involved in CSC Maintenance

Since genetic alterations cause TSCs, amplifying precursors, or differentiated cells to transform to CSCs, it is important to classify the relationship between genetic alterations and tumor phenotype and malignancy.

p53 Pathway

It is well known that the loss of p53 function promotes the accelerated cell proliferation and malignant transformation (Toledo and Wahl 2006). Indeed, it was shown that over 65% of human glioma contains TP53 gene deletion and mutation (Kleihues and Ohgaki 1999). Moreover, additional evidences also indicated that other p53 signaling factors, including Murin-double-minute 2 (MDM2), which binds to, destabilizes, and inactivates p53, and chromodomain helicase DNA-binding domain 5 (Chd5), which regulates cell proliferation, cellular senescence, apoptosis, and tumorigenesis, are mutated in malignant glioma (Bagchi et al. 2007; Kleihues and Ohgaki 1999; Reifenberger et al. 1993; Toledo and Wahl 2006) In total, it was revealed that about 90% of human GBM have mutations in p53 signaling pathway (Cancer Genome Atlas Research Network 2008; Parsons et al. 2008). Although the effector molecule of p53 pathway is the p21 cyclin-dependent kinase (cdk) inhibitor that regulates progression of cells through the G1 cell-cycle phase, it has not been demonstrated that p21 gene itself is an oncogenic target in human cancers.

Rb Pathway

Retinoblastoma (Rb) is another essential tumor suppressor protein that regulates the G1 checkpoint (Classon and Harlow 2002). Hypophosphorylated form of Rb sequesters E2F transcription factor and arrest cells at the G1 checkpoint. Once Rb is hyperphosphorylated by cyclin D and cdk4/6 complex, phosphorylated Rb releases E2F, E2F induces the expression of cell cycle regulators, and then the cells enter S phase. In contrast, p16/Ink4a cdk inhibitor binds to cdk4/6, prevents the complex formation of cdk4/6 and cyclin D, and maintains Rb hypophosphorylation. Mutations in Rb pathway have been frequently identified in many types of malignant tumors. For example, mutations in Rb signaling pathway, including cdk4 amplification and p16/Ink4a deletion, was found in about 80% of GBM (Cancer Genome Atlas Research Network 2008; Parsons et al. 2008; Schmidt et al. 1994).

Activation of Receptor Tyrosine Kinase Pathway

Signaling pathways (Ras/Raf/MAPK and PTEN/AKT pathways) of Receptor Tyrosine Kinases (RTKs) including PDGFR, EGFR, FGFR, and IGFR, many of which play a role for the maintenance of TSCs and amplifying precursors, are frequently mutated in tumors (Schubbert et al. 2007). For instance, activation of RTK pathway was found in about 90% of GBM (Cancer Genome Atlas Research Network 2008; Parsons et al. 2008). In particular, it has been shown that small GTP protein Ras, one of essential oncogenes, and its negative regulator, type1 Neurofibromas gene (NF1), are mutated in many kinds of human cancers and that phosphatase tensin homolog (PTEN), which inhibits function of phosphoinositol tri-phosphate kinase (PI3K) that activates Akt, is frequently inactivated in malignant tumors (Duerr et al. 1998).

Notch Signaling Pathway

Notch receptors are involved in a number of biological functions, including cell proliferation, differentiation, survival, and tumorigenesis (Radtke and Raj 2003). There are four known mammalian Notch receptors, Notch 1–4, and five ligands, Delta-like-ligand (Dll) 1, 3, and 4, and Jagged 1 and 2 in mammals. Following the activation, Notch is cleaved in its extracellular region by metalloproteases and in its intracellular region by presenilins (PS), releasing the Notch intracellular domain (NICD) from the plasma membrane. The NICD then translocates into the nucleus, associates with the CSL transcription factor CBF1/RBP-Jk, and activates a number of target genes, including the hairy and enhancer-of-split (Hes) genes

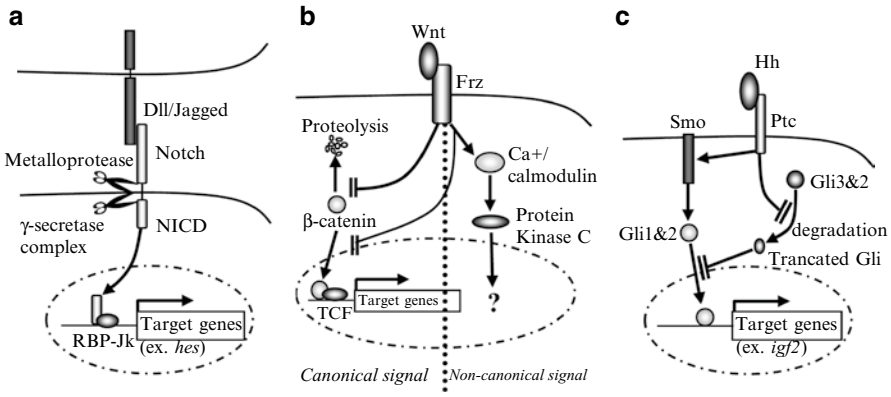

Fig. 2.2 Notch, Wnt, Hh signaling pathways are involved in CSC maintenance. Notch (**a**), Wnt/Frz (**b**), or Hh/Ptc/Smo (**c**) signaling pathway activates a number of genes, which regulate cell proliferation and cell fates. The constitutive activation of any of these pathways leads to abnormal development and tumorigenesis

(Fig. 2.2a). It has been shown that the inactivation of Notch signaling leads to serious developmental defects: Jagged1, Notch1, Notch2, and PS1and 2 knockout mice are all embryonically or perinatally lethal (Krebs et al. 2000; Swiatek et al. 1994; Xue et al. 1999). There is accumulating evidence that Notch activation not only maintains the multipotentiality of NSCs but is also involved in tumorigenesis. Depletion of Notch1, Dll1, or Jagged1 by RNAi was shown to block proliferation of glioma cells in vivo and in vitro (Purow et al. 2005). Together, these findings suggest that Notch signaling is involved in tumorigenesis, as well as in normal development.

Wnt Signaling Pathway

The Wnt family of secreted proteins coordinates diverse developmental processes, including cell proliferation and fate decisions (Logan and Nusse 2004; Moon et al. 2004; Reya and Clevers 2005). In mammals, there are 20 Wnt members, 10 Wnt receptors (called Frizzled, Frz), and 5 soluble forms of Frz, which are natural inhibitors of Wnt signaling. Once Frz is activated, β-catenin, which is a central player in canonical Wnt signaling, accumulates in the nucleus and induces the expression of Wnt target genes, including *c-myc* and *cyclin D1*, by associating with LEF/TCF transcription factors (Fig. 2.2b). The noncanonical Wnt signaling pathway activates calcium/calmodulin-dependent protein kinase and protein kinase C, although the molecular details are still uncertain (Logan and Nusse 2004; Moon et al. 2004; Reya and Clevers 2005).

Wnt signaling is also crucial for CNS development. Wnt1 and 3a, Frz5 and β-catenin, for example, are expressed in the ventricular and subventricular zones (VZ/SVZ) in the developing brain (Chenn and Walsh 2002; Ikeya et al. 1999; Lee et al. 2000). Inactivation of Wnt1, Wnt3a, or β-catenin causes developmental brain defects (McMahon and Bradley 1990; Reya and Clevers 2005). Moreover, overexpression of a stabilized form of β-catenin in neural precursor cells caused a hyperplasia of lateral ventricles (Chenn and Walsh 2002). Some factors in the Wnt signaling pathway, including β-catenin and axin1 (an inhibitor in the pathway), are mutated in medulloblastomas (Dahmen et al. 2001; Zurawel et al. 1998). Thus these findings suggest that hyper-activation of Wnt signaling may promote brain tumorigenesis.

Hedgehog Signaling Pathway

Hh signaling is also involved in proliferation, development, and tumorigenesis (Pasca di Magliano and Hebrok 2003; Ruiz i Altaba et al. 2002a, b). In mammals, there are three Hh members, Sonic, Desert, and Indian, all of which are secreted proteins. When Sonic Hh (Shh), for example, binds to the Patched1 (Ptc1) transmembrane receptor, another transmembrane protein, Smoothened (Smo), which is normally restrained by Ptc, is relieved and activates the zinc-finger transcription factor Gli. Activated Gli accumulates in the nucleus and induces the expression of target genes, including *wnt*, *insulin-growth factor 2 (igf2)*, and *pdgf receptor* α (Fig. 2.2c). There are three Gli transcription factors in mammals. Gli1 and 2 function as activators of Shh signaling, whereas the cleaved form of either Gli2 or Gli3 antagonizes the Shh-Gli1/2 signaling pathway. The Shh signaling pathway is essential for CNS development: Shh, Ptc, Gli2, or Gli3 knockout mice die before birth with severe defects in the brain, although Gli1 knockout mice develop normally (Ding et al. 1998; Matise et al. 1998; Palma and Ruiz i Altaba 2004; Park et al. 2000). Conditional inactivation of Smo blocks NSC proliferation in vivo and in vitro (Machold et al. 2003). Together with the finding that Glis, Ptc1, and Smo are all expressed in the VZ/SVZ, these observations suggest that Shh signaling may be essential for the maintenance of NSCs.

Ectopic activation of Hh signaling in CNS is likely to lead to brain tumor formation (Pasca di Magliano and Hebrok 2003; Ruiz i Altaba et al. 2002a, b). For example, Gli1 is highly activated in many brain cancers, including medulloblastoma, glioblastoma, and primitive neuroectodermal tumors, some of which also have mutations in Ptc1 (Goodrich et al. 1997). It was shown that overexpression of Gli1 in the developing tadpole CNS gives rise to brain tumors (Dahmane et al. 2001). Moreover, cyclopamine, which is a specific inhibitor of Smo, blocks the growth of several primary gliomas, medulloblastomas, and glioma cell lines (Berman et al. 2002; Dahmane et al. 2001). Taken together, these findings suggest that Hh signaling plays an important role in brain tumorigenesis.

CSC Models

In Vivo Models

Using a combination of transgenic mice and a retrovirus system, some groups have demonstrated that TSCs and differentiating cells form tumors in vivo. For instance, Holland and his colleagues infected transgenic mice that expressed the avian leukosis virus (ALV) receptor under the regulation of either a *nestin* enhancer or a *gfap* promoter, with recombinant ALVs encoding oncogenic genes, such as platelet-derived growth factor (PDGF) receptor beta, or activated Akt, or activated Ras, and found GBM had developed in the brain (Dai et al. 2001; Uhrbom et al. 2002). De Pinho and colleagues overexpressed a constitutively active form of epidermal growth factor (EGF) receptor in either NSCs or astrocytes from Ink4a/Arf$^{-/-}$ mice, transplanted them into the brain, and found that the cells formed high-grade gliomas (Bachoo et al. 2002). Thus, these findings suggest that NSCs and astrocytes are cells of origin for brain tumors. However, since tumors would be, in theory, generated from one transformed cell, these tumor models, in which many transformed cells are generated or injected at the same time, may not provide an answer to whether NSCs and astrocytes are *bona fide* cells of origin for malignant glioma.

In Vitro Models

It still remains controversial whether CSCs arise from TSCs, committed precursor cells, or differentiated cells. In addition, the relationship between cell of origin for CSCs and genetic alterations have not yet been elucidated, although a number of oncogenes and tumor suppressor genes have been well characterized in tumorigenesis. Using cell lineage markers and new methods including Fluorescence-activated cell sorting, it is possible to purify the cells. We can then overexpress oncogenes or knock down tumor-suppressor genes in the cells, examine the relationship between cell of origin for tumors and genetic alterations and find therapeutic targets (Fig. 2.3). Indeed, it has been demonstrated that overexpression of exogenous oncogenes can induce hematopoietic stem/progenitor cells to transform into leukemic stem cells (Cozzio et al. 2003; Huntly et al. 2004; Krivtsov et al. 2006). We and others also succeeded in generating glioma stem cells by overexpressing glioma-related oncogenes in neural lineage cells and in finding therapeutic targets by comparing gene expression profile of induced CSC models with that of human tumor spheres (Hide et al. 2009; Hide et al. 2011; Ligon et al. 2007). Thus these data suggest that, using similar methods, we might generate any CSCs from TSCs, amplifying precursor cells and/or differentiated cells, characterize them, and identify targets for curable therapy.

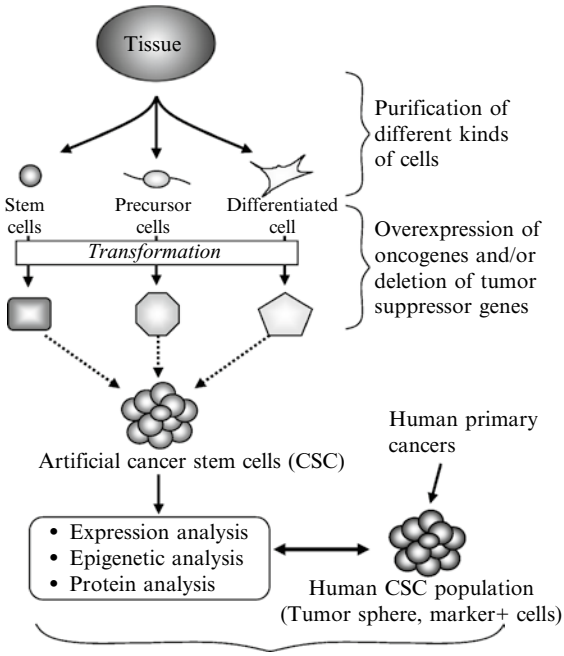

Fig. 2.3 Strategy for identifying factors specific to CSCs. Purified TSCs, committed precursor cells, and differentiated cells that are transfected with various types of oncogenes and/or siRNA/shRNA for tumor suppressor genes, transform into CSCs that are capable of self-renewal, positive for TSC markers and show malignancy. By comparing gene expression profiles of such induced CSCs with that of human CSC-enriched population (tumor spheres and TSC marker-positive cells), novel CSC markers and therapeutic targets would be identified

Conclusion

A number of new stem cell markers and techniques have been utilized to identify and purify CSCs during last several years. However, it is not yet known whether or not such CSCs consist of homogenous population, as $CD133^-$ and non-SP cells as well as $CD133^+$ and SP cells contain tumorigenic cells. Therefore it is still essential to establish experimental strategies, including the single cell analysis, to identify bona fide CSCs and to characterize them, leading to the discovery of novel therapeutic targets and methods.

Conflict of Interest

None declared.

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References

Al-Hajj M, Wicha MS, Benito-Hernandez A et al (2003) Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100:3983–3988

Bachoo RM, Maher EA, Ligon KL et al (2002) Epidermal growth factor receptor and Ink4a/Arf: convergent mechanisms governing terminal differentiation and transformation along the neural stem cell to astrocyte axis. Cancer Cell 1:267–277

Bagchi A, Papazoglu C, Wu Y et al (2007) CHD5 is a tumor suppressor at human 1p36. Cell 128:459–475

Bao S, Wu Q, McLendon RE et al (2006) Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature 444:756–760

Berman DM, Karhadkar SS, Hallahan AR et al (2002) Medulloblastoma growth inhibition by hedgehog pathway blockade. Science 297:1559–1561

Bonnet D, Dick JE (1997) Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 3:730–737

Cai J, Cheng A, Luo Y et al (2004) Membrane properties of rat embryonic multipotent neural stem cells. J Neurochem 88:212–226

Cancer Genome Atlas Research Network (2008) Comprehensive genomic characterization defines human glioblastoma genes and core pathways. Nature 455:1061–1068

Chenn A, Walsh CA (2002) Regulation of cerebral cortical size by control of cell cycle exit in neural precursors. Science 297:365–369

Classon M, Harlow E (2002) The retinoblastoma tumour suppressor in development and cancer. Nat Rev Cancer 2:910–917

Collins AT, Berry PA, Hyde C et al (2005) Prospective identification of tumorigenic prostate cancer stem cells. Cancer Res 65:10946–10951

Cozzio A, Passegué E, Ayton PM et al (2003) Similar MLL-associated leukemias arising from self-renewing stem cells and short-lived myeloid progenitors. Genes Dev 17:3029–3035

Dahmen RP, Koch A, Denkhaus D et al (2001) Deletions of AXIN1, a component of the WNT/wingless pathway, in sporadic medulloblastomas. Cancer Res 61:7039–7043

Dahmane N, Sanchez P, Gitton Y et al (2001) The Sonic Hedgehog-Gli pathway regulates dorsal brain growth and tumorigenesis. Development 128:5201–5212

Dai C, Celestino JC, Okada Y et al (2001) PDGF autocrine stimulation dedifferentiates cultured astrocytes and induces oligodendrogliomas and oligoastrocytomas from neural progenitors and astrocytes in vivo. Genes Dev 15:1913–1925

Das B, Tsuchida R, Malkin D et al (2008) Hypoxia enhances tumor stemness by increasing the invasive and tumorigenic side population fraction. Stem Cells 26:1818–1830

Ding Q, Motoyama J, Gasca S et al (1998) Diminished Sonic hedgehog signaling and lack of floor plate differentiation in Gli2 mutant mice. Development 125:2533–2543

Duerr EM, Rollbrocker B, Hayashi Y et al (1998) PTEN mutations in gliomas and glioneuronal tumors. Oncogene 16:2259–2264

Ginestier C, Hur MH, Charafe-Jauffret E et al (2007) ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. Cell Stem Cell 1:555–567

Goodell MA, Brose K, Paradis G et al (1996) Isolation and functional properties of murine hematopoietic stem cells that are replicating in vivo. J Exp Med 183:1797–1806

Goodrich LV, Milenkovic L, Higgins KM et al (1997) Altered neural cell fates and medulloblastoma in mouse patched mutants. Science 277:1109–1113

Gottesman MM, Fojo T, Bates SE (2002) Multidrug resistance in cancer: role of ATP-dependent transporters. Nat Rev Cancer 2:48–58

Haraguchi N, Utsunomiya T, Inoue H et al (2006) Characterization of a side population of cancer cells from human gastrointestinal system. Stem Cell 24:506–513

Hermann PC, Huber SL, Herrler T et al (2007) Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 1:313–323

Hide T, Takezaki T, Nakatani Y et al (2009) Sox11 prevents tumorigenesis of glioma-initiating cells by inducing neuronal differentiation. Cancer Res. 69:7953–7959

Hide T, Takezaki T, Nakatani Y et al (2011) Combination of a ptgs2 inhibitor and an epidermal growth factor receptor-signaling inhibitor prevents tumorigenesis of oligodendrocyte lineage-derived glioma-initiating cells. Stem Cells 29:590–599

Hirschmann-Jax C, Foster AE, Wulf GG et al (2004) A distinct "side population" of cells with high drug efflux capacity in human tumor cells. Proc Natl Acad Sci USA 101:14228–14233

Huntly BJ, Shigematsu H, Deguchi K et al (2004) MOZ-TIF2, but not BCR-ABL, confers properties of leukemic stem cells to committed murine hematopoietic progenitors. Cancer Cell 6:587–596

Ikeya M, Lee SM, Johnson JE et al (1999) Wnt signalling required for expansion of neural crest and CNS progenitors. Nature 389:966–970

Jones RJ, Barber JP, Vala MS et al (1995) Assessment of aldehyde dehydrogenase in viable cells. Blood 85:2742–2746

Kaplan RN, Riba RD, Zacharoulis S et al (2005) VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. Nature 438:820–827

Kleihues, P, Ohgaki H (1999) Primary and secondary glioblastoma: from concept to clinical diagnosis. Neuro-Oncol 1:44–51

Kondo T, Setoguchi T, Taga T (2004) Persistence of a small subpopulation of cancer stem-like cells in the C6 glioma cell line. Proc Natl Acad Sci USA 101:781–786

Korkaya H, Paulson A, Iovino F et al (2008) HER2 regulates the mammary stem/progenitor cell population driving tumorigenesis and invasion. Oncogene 27:6120–6130

Krebs LT, Xue Y, Norton CR et al (2000) Notch signaling is essential for vascular morphogenesis in mice. Genes Dev 14:1343–1352

Krivtsov AV, Twomey D, Feng Z et al (2006) Transformation from committed progenitor to leukaemia stem cell initiated by MLL-AF9. Nature 442:324–331

Lapidot T, Sirard C, Vormoor J et al (1994) A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature 367:645–648

Lee SMK, Tole S, Grove E et al (2000) A local Wnt-3a signal is required for development of the mammalian hippocampus. Development 197:457–467

Li L, Neaves WB (2006) Normal stem cells and cancer stem cells: The niche matters. Cancer Res 66:4553–4557

Ligon KL, Huillard E, Mehta S et al (2007) Olig2-regulated lineage-restricted pathway controls replication competence in neural stem cells and malignant glioma. Neuron 53:503–517

Liu G, Yuan X, Zeng Z et al (2006) Analysis of gene expression and chemoresistance of CD133+ cancer stem cells in glioblastoma. Mol Cancer 5:67–78

Logan CY, Nusse R (2004) The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol 20:781–810

Machold R, Hayashi S, Rutlin M et al (2003) Sonic hedgehog is required for progenitor cell maintenance in telencephalic stem cell niches. Neuron 39:937–950

Matise MP, Epstein DJ, Park HL et al (1998) Gli2 is required for induction of floor plate and adjacent cells, but not most ventral neurons in the mouse central nervous system. Development 125:2759–2770

Matsumoto K, Arao T, Tanaka K et al (2009) mTOR signal and hypoxia-inducible factor-1 alpha regulate CD133 expression in cancer cells. Cancer Res 69:7160–7164

McMahon AP, Bradley A (1990) The Wnt-1 (int-1) proto-oncogene is required for development of a large region of the mouse brain. Cell 62:1073–1085

Mitsutake N, Iwao A, Nagai K et al (2007) Characterization of side population in thyroid cancer cell lines: cancer stem-like cells are enriched partly but not exclusively. Endocrinology 148:1797–1803

Moon RT, Kohn AD, De Ferrari GV et al (2004) WNT and beta-catenin signalling: diseases and therapies. Nat Rev Genet 5:691–701

Moore KA, Lemischka IR (2006) Stem cells and their niches. Science 311:1880–1885

Morita Y, Ema H, Yamazaki S et al (2006) Non-side-population hematopoietic stem cells in mouse bone marrow. Blood 108:2850–2856

O'brien CA, Pollett A, Gallinger S et al (2007) A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. Nature 445:106–110

Palma V, Ruiz i Altaba A (2004) Hedgehog-GLI signaling regulates the behavior of cells with stem cell properties in the developing neocortex. Development 131:337–345
Park HL, Bai C, Platt KA et al (2000) Mouse Gli1 mutants are viable but have defects in SHH signaling in combination with a Gli2 mutation. Development 127:1593–1605
Parsons DW, Jones S, Zhang X et al (2008) An integrated genomic analysis of human glioblastoma multiforme. Science 321:1807–1812
Pasca di Magliano M, Hebrok M (2003) Hedgehog signalling in cancer formation and maintenance. Nat Rev Cancer 3:903–911
Patrawala L, Calhoun T, Schneider-Broussard R et al (2005) Side population is enriched in tumorigenic, stem-like cancer cells, whereas ABCG2+ and ABCG2- cancer cells are similarly tumorigenic. Cancer Res 65:6207–6219
Pearce DJ, Taussig D, Simpson C et al (2005) Characterization of cells with a high aldehyde dehydrogenase activity from cord blood and acute myeloid leukemia samples. Stem Cells 23:752–760
Ponti D, Costa A, Zaffaroni N et al (2005) Isolation and in vitro propagation of tumorigenic breast cancer cells with stem/progenitor cell properties. Cancer Res 65:5506–5511
Pollard SM, Yoshikawa K, Clarke ID et al (2009) Glioma stem cell lines expanded in adherent culture have tumor-specific phenotypes and are suitable for chemical and genetic screens. Cell Stem Cell 4:568–580
Radtke F, Raj K (2003) The role of Notch in tumorigenesis: oncogene or tumour suppressor? Nat Rev Cancer 3:756–767
Purow BW, Haque RM, Noel MW et al (2005) Expression of Notch-1 and its ligands, Delta-like-1 and Jagged-1, is critical for glioma cell survival and proliferation. Cancer Res 65:2353–2363
Read TA, Fogarty MP, Markant SL et al (2009) Identification of CD15 as a marker for tumor-propagating cells in a mouse model of medulloblastoma. Cancer Cell 15:135–147
Reifenberger G, Liu L, Ichimura K et al (1993) Amplification and overexpression of the MDM2 gene in a subset of human malignant gliomas without p53 mutations. Cancer Res 53:2736–2739
Reya T, Clevers H (2005) Wnt signalling in stem cells and cancer. Nature 434:843–850
Reya T, Morrison SJ, Clarke MF et al (2001) Stem cells, cancer, and cancer stem cells. Nature,414: 105–111
Ricci-Vitiani L, Lombardi DG, Pilozzi E et al (2007) Identification and expansion of human colon-cancer-initiating cells. Nature 445:111–115
Ruiz i Altaba A, Palma V, Dahmane N (2002a) Hedgehog-Gli signalling and the growth of the brain. Nat Rev Neurosci 3:24–33
Ruiz i Altaba A, Sanchez P, Dahmane N (2002b) Gli and hedgehog in cancer: tumours, embryos and stem cells. Nat Rev Cancer 2:361–372
Schmidt EE, Ichimura K, Reifenberger G et al (1994) CDKN2 (p16/MTS1) gene deletion or CDK4 amplification occurs in the majority of glioblastomas. Cancer Res 54:6321–6324
Schubbert S, Shannon K, Bollag G (2007) Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer 7:295–308
Singh SK, Hawkins C, Clarke ID et al (2004) Identification of human brain tumour initiating cells. Nature 432:396–401
Son MJ, Woolard K, Nam DH et al (2009) SSEA-1 is an enrichment marker for tumor-initiating cells in human glioblastoma. Cell Stem Cell 4:440–452
Swiatek PJ, Lindsell CE, del Amo FF et al (1994) Notch1 is essential for postimplantation development in mice. Genes Dev 8:707–719
Szakacs G, Paterson JK, Ludwig JA et al (2006) Targeting multidrug resistance in cancer. Nat Rev Drug Discov 5:219–234
Szotek PP, Pieretti-Vanmarcke R, Masiakos PT et al (2006) Ovarian cancer side population defines cells with stem cell-like characteristics and Mullerian Inhibiting Substance responsiveness. Proc Natl Acad Sci USA 103:11154–11159
Toledo F, Wahl GM (2006) Regulating the p53 pathway: in vitro hypotheses, in vivo veritas. Nat Rev Cancer 6:909–923
Uhrbom L, Dai C, Celestino JC et al (2002) Ink4a-Arf loss cooperates with KRas activation in astrocytes and neural progenitors to generate glioblastomas of various morphologies depending on activated Akt. Cancer Res 62:5551–5558

Ward RJ, Lee L, Graham K et al (2009) Multipotent CD15+ cancer stem cells in patched-1-deficient mouse medulloblastoma. Cancer Res 69:4682–4690

Xue Y, Gao X, Lindsell CE et al (1999) Embryonic lethality and vascular defects in mice lacking the Notch ligand Jagged1. Hum Mol Genet 8:723–730

Zurawel RH, Chiappa SA, Allen C et al (1998) Sporadic medulloblastomas contain oncogenic beta-catenin mutations. Cancer Res 58:896–899

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