

Chapter 2

Stem Cells and Cancer Stem Cells

2.1 Stem Cells

Stem cells are undifferentiated cells that can differentiate into specific cell types with clear functions in the tissue or the body. For example, although hematopoietic stem cells cannot transport oxygen, they can be differentiated into erythrocytes, which do transport oxygen. Stem cells, as defined, must be able to self-renew and to differentiate into multiple cell types (multiple-lineage differentiation potential). Self-renewal is the process by which stem cells divide to make more stem cells, perpetuating the stem cell pool throughout life (He, Nakada, & Morrison, 2009). Self-renewal is also a mitotic process that maintains the undifferentiated state of stem cells.

Multiple-lineage differentiation potential is capacity of stem cells to differentiate into specific cell types—the types and number of which depend on the stem cell's own type. Some stem cells, which appear in early embryonic development, are totipotent—i.e., they can differentiate into all cells in the body, included cells of the umbilical cord and placenta. Pluripotent stem cells can differentiate into all cells from one of the three embryonic dermal layers. Multipotent stem cells can differentiate into some kinds of cells, usually of a related tissue type. Finally, stem cells that can differentiate into two kinds of specific cells are usually called progenitor cells or precursor cells rather than stem cells.

As defined, totipotent stem cells only can be derived from zygotes or 2–8-cell embryos. Pluripotent stem cells usually are isolated from inner cell masses of blastocysts. Although pluripotent stem cells have been suggested to be obtainable from adults, almost all stem cells from adults are multi-potent stem cells with differentiation limitations compared with pluripotent stem cells (Fig. 2.1).

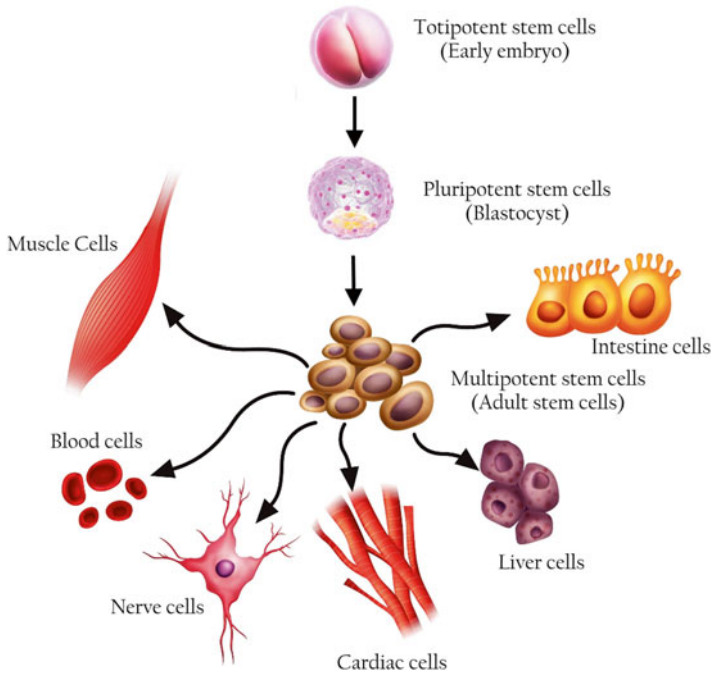


Fig. 2.1 Stem cell pathways. The zygote is totipotent. Blastomeres continuously divide to form the blastocyst, three primary germ layers, and specific tissues with decreased potentials

2.2 Cancer Stem Cells

2.2.1 History of Cancer Stem Cells

The existence of cancer stem cells was suggested more than 50 years ago. The first study of CSCs was performed by Tim and McCulloch in 1963. In their study, they showed that self-renewing cells could form colonies in the spleen (Becker, Mc, & Till, 1963). After 2 years, Brunschwig, Southam, and Levin (1965) successfully proved that only a few cells from malignant tumors could form new tumors when injected back into the same patients. In particular, they suggested a new hypothesis of the heterogeneity of tumor cells, and that tumor cells could exist as a hierarchical system (Brunschwig et al., 1965), in which all cells in a tumor could come from a single cell via continuous mitosis. Later, Hamburger and Salmon (1977) showed that a few cells from a tumor could form colonies in soft agar. This result varied from tumor to tumor, however, they also suggested that one in 1000–5000 tumor cells could form colonies, whereas the remaining cells did not have this capacity (Hamburger & Salmon, 1977). After 20 years, this in vitro result was confirmed in vivo by Bonnet and Dick (1997), who demonstrated that only 1 per 10^6 acute myeloid leukemia cells could cause tumors when injected into NOD/SCID mice.

Cell subpopulations with similar properties also determined in the various solid tumors including breast cancer (Al-Hajj, Wicha, Benito-Hernandez, Morrison, & Clarke, 2003), brain cancer (Lenkiewicz, Li, & Singh, 2009), prostate cancer (Vidal et al., 2014), lung cancer (Mather et al., 2013), nasopharyngeal carcinoma (Wei et al., 2014), glioblastoma (Iacopino et al., 2014), head and neck squamous cell carcinoma (Fukusumi et al., 2014), cervical cancer (Wang, Guo, Lin, Yang, & Wang, 2014), melanoma (Luo, Nguyen, & Fujita, 2013), ovarian cancer (He et al., 2014), colon cancer (Prasetyanti, Zimmerlin, De Sousa, & Medema, 2013) and liver cancer (Tomuleasa et al., 2010). As these cells had stem cell properties but existence in tumors, they were called cancer stem cells.

The term “cancer stem cell” was first introduced by Weissman et al. in 2001 (Reya, Morrison, Clarke, & Weissman, 2001). This group reviewed previous observations about stem cells in both normal tissues and tumors. They considered stem cells to be a rare population in normal tissue that maintains tissue growth, whereas cancer stem cells are a rare population in tumors that drive tumor growth (Fig. 2.2).

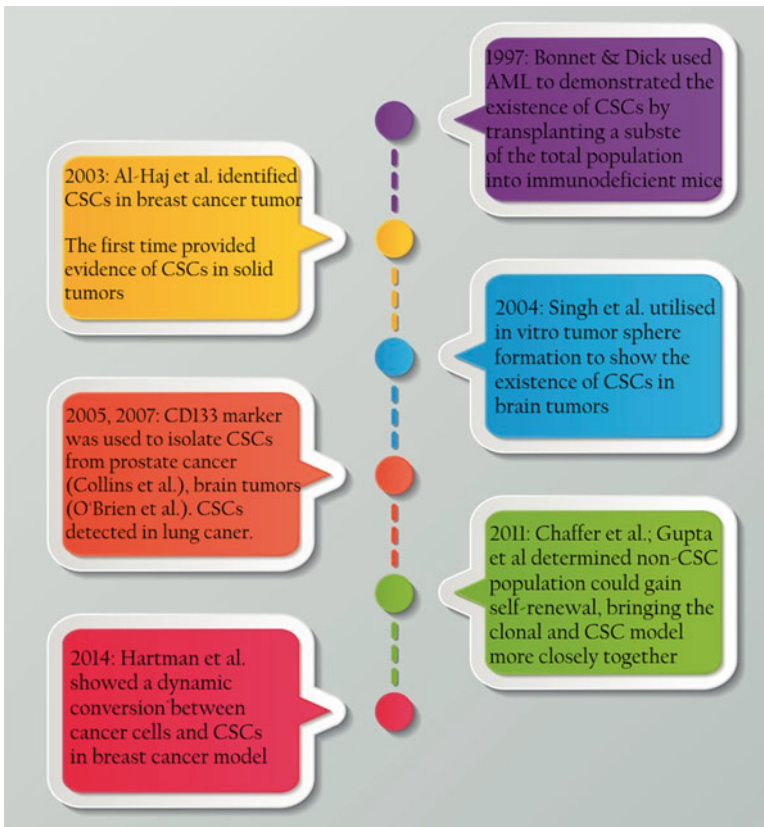


Fig. 2.2 Timeline of cancer stem cell research

2.2.2 Origins of CSCs

CSCs Derived from Stem Cells

The link between cancer and stem cells was first observed by Leroy Stevens and Barry Pierce in 1964 who were studying testicular tumors (called teratomas). They traced the origin of testicular tumors and observed that deviant germ cells migrated to the genital ridge. Transplantation of the genital ridge lacking germ cells into the testes of adult mice did not induce tumor formation (Stevens, 1964). The link between cancer and stem cells was confirmed by Kleinsmith and Pierce (1964). They were the first to prove that a single pluripotent stem cell could form a malignant tumor and showed that isolation of a single cell from a teratoma and its transplantation into mice induced the formation of new tumors. Interestingly, the new tumors had all types of differentiated cells of the original teratoma (Kleinsmith & Pierce, 1964). The results of these studies suggested a link between cancer and stem cells (Fig. 2.3; Table 2.1).

Recent studies have shown that some signaling pathways are common between breast CSCs and normal breast stem cells (Malhotra, Zhao, Band, & Band, 2011). Three signaling pathways, namely, Notch, Wnt, and hedgehog (Hh), that are highly active in normal breast stem cells are also active in breast CSCs (Farnie & Clarke, 2007; Monteiro et al., 2014). However, these pathways are dysregulated in breast CSCs compared with those in normal breast stem cells (Zardawi, O'Toole, Sutherland, & Musgrove, 2009).

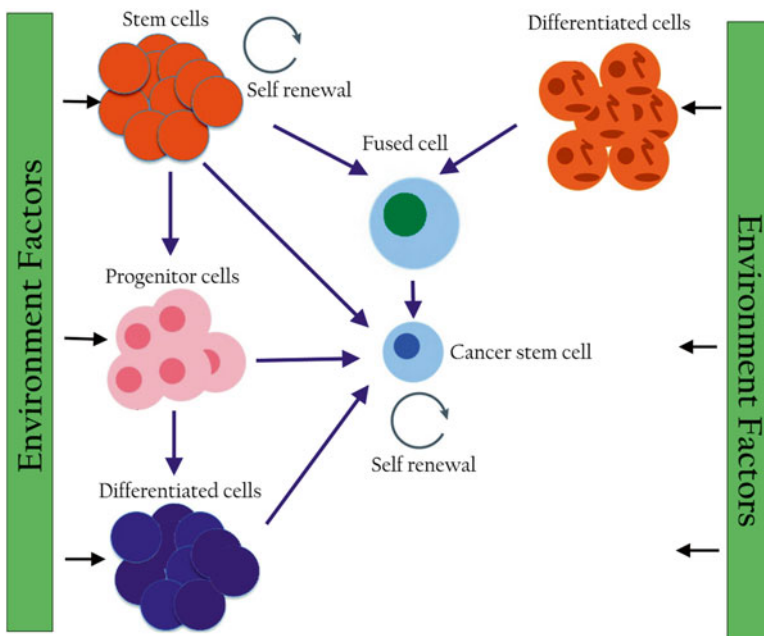


Fig. 2.3 Cancer stem cell hypothesis. Cancer stem cells can be produced from three different ways, included dis-regulation of stem cells, differentiated cells or fusion between different cells

Table 2.1 Tenets of CSCs and clonal evolution models

	CSC model	Clonal evolution model
Tumorigenic cells	CSCs	Any cell
Tumor cell organization	Hierarchical	Stochastic
Capacity of self-renewal with asymmetric divisions	CSCs can self-renew indefinitely whereas terminally differentiated cells have limited proliferative potential	Not applicable
Progression	Driven by CSCs, which account for a small subpopulation of tumor bulk	Driven by the fittest clone under various selective pressures
Source of heterogeneity	Aberrant differentiation and mutations	Epigenetic and genetic aberrations, followed by selection
Type of heterogeneity	Initially, it was perceived to be largely phenotypic; however, recent studies suggest that CSCs may be genetically heterogeneous within a tumor	Genetic and phenotypic heterogeneity
Source of resistance to therapy	CSCs	Resistant subclones harboring specific genetic or epigenetic aberrations

A study by Tomasetti and Vogelstein (2015) showed a strong correlation between the total numbers of divisions of normal stem cells and cancer. They showed that random mutations arising during DNA replication in normal stem cells converted these non-cancerous stem cells to CSCs. These findings may provide insights on why some tissue types give rise to cancers more often than other tissue types (Tomasetti & Vogelstein, 2015). Another study also confirmed that adult stem cells often give rise to epithelial cancers. However, cells that give rise to cancers can be altered intrinsically altering their mutational landscape and cell cycle state as well as extrinsically through inflammation and abnormal stromal signaling (White & Lowry, 2015).

CSCs Derived from Differentiated Cells (Mature Cells)

CSCs can be produced from differentiated cells through three methods, namely, (1) horizontal gene transfer, (2) induction of genomic instability, and (3) microenvironment or de-differentiation (Fig. 2.3).

CSCs can be derived from differentiated cells through horizontal gene transfer (Bergsmedh et al., 2001; Bergsmedh, Szeles, Spetz, & Holmgren, 2002). Horizontal gene transfer includes three steps (1) delivery of donor DNA into recipient cells, (2) insertion of the donor DNA sequence into the recipient cell genome, and (3) expression of the incorporated DNA sequence in the recipient cells. During phagocytosis and endocytosis, DNA is transferred from apoptotic cells to recipient cells through horizontal gene transfer. Horizontal gene transfer results in the nuclear reprogramming of recipient cells (Holmgren et al., 1999). More importantly, fragmented DNA can also be taken up by tumor cells (Bjerkvig, Tysnes, Aboody, Najbauer, & Terzis, 2005). At present, whole chromosomes or fragments can be transferred to recipient tumor cells through phagocytosis (Bergsmedh et al., 2001, 2002).

Genetic instability is the basis of cell transformation. Genetic instability may occur at the chromosome level through the gain, loss, or derangement of chromosomes or at the molecular level through point mutations in tumor suppressor genes or proto-oncogenes. Chromosomal instability leads to an imbalance in chromosome number and loss of heterozygosity (LOH). LOH of important tumor suppressor genes can enhance the susceptibility of cells to carcinogens or mutagens, thus accelerating tumorigenesis (Bachoo et al., 2002; Ilyas, Straub, Tomlinson, & Bodmer, 1999). Some studies indicate that aneuploidy leads to cancer initiation (Bartkova et al., 2005; Gorgoulis et al., 2005). In addition, gene mutations and chromosome derangement in stem cells, progenitor cells, and even differentiated cells may give rise to CSCs and tumors.

The microenvironment of cells also plays an important role in their selective clonal expansion. Several factors regulate stem cell differentiation and transformation and trigger the initial steps of tumorigenesis. Inflammatory cytokines such as interleukin-6 (IL-6) may participate in CSC formation and may regulate their dynamic equilibrium with non-CSCs (Iliopoulos, Hirsch, Wang, & Struhl, 2011). IL-6 produced by CSCs facilitates the de-differentiation of non-CSCs into CSCs. Some studies indicate that inflammatory cytokines and factors such as IL-6 and NF- κ B also maintain the proportion of CSCs and non-CSCs (Iliopoulos, Hirsch, & Struhl, 2009).

A recent study showed that differentiated cells could de-differentiate into CSCs under certain conditions. Hashimoto et al. (2014) successfully de-differentiated human hepatocellular carcinoma cell lines SK-HEP-1, HLE, Hep3B, and Huh-7 into CSCs by culturing these cell lines in an induction medium supplemented with neural survival factor-1.

CSCs Obtained by Fusion

Cell fusion is an important biological process associated with various physiological activities such as fertilization; formation placenta, bone, and muscle tissue; immune response; and tissue repair and regeneration. Recent studies indicate that cell fusion is also involved in cancer initiation, e.g., tumor cells fuse with lymphocytes to form metastatic cancer cells (Duelli & Lazebnik, 2003; Mekler, 1971; Pawelek, 2014). Cell fusion promotes phenotypic and genotypic diversity in tumors (Rachkovsky et al., 1998; Warner, 1975).

Stem cells can fuse with differentiated cells to form CSCs. These fused cells are called heterokaryons. Sendai virus promotes the fusion of Ehrlich ascites with human HeLa cells in vitro to produce heterokaryons (Harris & Watkins, 1965). These heterokaryons exhibit the properties of both the parent stem cells and cancer cells. If cancer cells were gained the stemness, they so-called as CSCs. Another type of fusion cell in the human body is called synkaryon. Synkaryons are different from heterokaryons and are generally formed by chromosome loss. This process is similar to hybridoma formation by the fusion of murine myeloma cells with B cells (Pomerantz & Blau, 2004).

In fact, tumors contain some fusogenic cells. These fusion cells are suggested to have formed by the fusion of normal somatic cells with cancer cells and are more malignant than parental tumor cells (Aractingi et al., 2005; Pawelek, 2000). Aractingi et al. (2005) showed that stem cells originating from a grafted kidney may migrate to the skin, fuse with keratinocytes, and undergo malignant transformation.

Li et al. (2014) fused human HepG2 cells with bone marrow mesenchymal stem cells (MSCs) having low metastatic potential. These fused cells showed increased invasion and migration in vitro (Li et al., 2014). These cells also showed increased pneumo-sphere-forming capacity and tumor-forming ability in NOD/SCID mice (Xu et al., 2014).

Some fusogenic proteins such as CD44, CD47, and macrophage receptor factor PTPNS1 trigger cell fusion in vivo (Vignery, 2000). These proteins are highly expressed in cancer cells as well as CSCs. CD44 is a known marker of some CSCs, including breast (Al-Hajj et al., 2003) and gastric CSCs (Lau et al., 2014), while CD47 is a marker of cancer cells that escape immune surveillance (Chao, Weissman, & Majeti, 2012; Sarfati, Fortin, Raymond, & Susin, 2008). In addition to fusogenic proteins, some cytokines and chemokines such as IL-4 promote cell fusion (Horsley, Jansen, Mills, & Pavlath, 2003; Horsley & Pavlath, 2004).

However, Fan and Lu (2014) showed that fusion of HSCs or umbilical cord blood-derived MSCs with esophageal cancer cells did not produce esophageal CSCs (Wang et al., 2012).

2.2.3 Markers of CSCs

There are no universal markers of CSCs because these cells change their phenotypes depending on their microenvironment. Some molecules have been identified as markers of CSCs. These include surface proteins present on CSCs that can be used to identify as well as enrich CSC population. CSCs can be identified by two groups of markers, i.e., membrane antigens and transcription factors (Table 2.2).

As mentioned above, acute myeloid leukemia was first cancer to be identified as having CSCs. These leukemic stem cells exhibited CD34⁺CD38⁻ phenotype (Lapidot et al., 1994). Breast cancer was the first solid tumor to be identified as having CSCs. The first study showed that CD44⁺/CD24⁻ cells initiated the formation of secondary tumors after transplantation into NOD/SCID mice compared with cells having other phenotypes (Al-Hajj et al., 2003). Most CD44⁺/CD24⁻ cells identified to date are breast CSCs.

After the first study on CSCs from breast cancer, some studies have identified CSCs in other cancers such as prostate cancer, pancreatic cancer, head and neck squamous cell carcinoma, brain cancer, lung cancer, and hepatocellular carcinoma. Because of the essential role of CD44 in CSCs from breast cancer and some other cancers, it is used as a marker of CSCs from prostate cancer (Collins, Berry, Hyde, Stower, & Maitland, 2005), pancreatic cancer (Li et al., 2007), and head and neck squamous cell carcinoma (Prince et al., 2007).

Table 2.2 CSCs present in some cancer types

Types of cancers	CSC phenotypes	References
Leukemia	CD34 ⁺ CD38 ⁻ HLA-DR ⁻ CD71 ⁻ CD90 ⁻ CD117 ⁻ CD123 ⁺	Guzman and Jordan (2004)
Breast cancer	ESA ⁺ CD44 ⁺ CD24 ^{-low} Lineage ⁻ , ALDH1 ^{high}	Al-Hajj et al. (2003), Ginestier et al. (2007)
Liver cancer	CD133 ⁺ , CD49f ⁺ , CD90 ⁺	Rountree, Senadheera, Mato, Crooks, and Lu (2008), Yang et al. (2008)
Brain cancer	CD133 ⁺ , BCRP1 ⁺ , A2B5 ⁺ , SSEA-1 ⁺	Gilbert and Ross (2009), Singh et al. (2004)
Lung cancer	CD133 ⁺ , ABCG2 ^{high}	Eramo et al. (2008), Ho, Ng, Lam, and Hung (2007)
Colon cancer	CD133 ⁺ , CD44 ⁺ , CD166 ⁺ , EpCAM ⁺ , CD24 ⁺	Dalerba et al. (2007), O'Brien, Pollett, Gallinger, and Dick (2007), Yeung, Gandhi, Wilding, Muschel, and Bodmer (2010)
Multiple myeloma	CD138 ⁻	Matsui et al. (2004)
Prostate cancer	CD44 ⁺ , $\alpha 2\beta 1^{high}$, CD133 ⁺	Collins et al. (2005)
Pancreatic	CD133 ⁺ , CD44 ⁺ , EpCAM ⁺ , CD24 ⁺	Li et al. (2007), Simeone (2008)
Melanoma	CD20 ⁺	Fang et al. (2005)
Head and neck cancer	CD44 ⁺	Prince et al. (2007)

CD133 is a specific marker of some CSCs. CD133 was first identified in brain CSCs (Singh et al., 2004). In fact, only CD133⁺ brain tumor cells formed brain tumors in NOD/SCID mice, with only 100 cells successfully forming tumors in these mice (Singh et al., 2004). CD133 is a marker of CSCs from colorectal cancer (Ricci-Vitiani et al., 2007), melanoma (Sabet, Rakhshan, Erfani, & Madjd, 2014), and lung cancer (Eramo et al., 2008). However, in contrast to the above cancers, which showed high expression of CD44 or CD133, CSCs from hepatocellular carcinoma had CD90⁺CD45⁻ phenotype (Vu et al., 2013; Yang et al., 2008).

Besides surface markers, some CSCs express transcription factors responsible for their pluripotent capacity. Prostate CSCs highly express OCT3/4, NANOG, and SOX2, which are also highly expressed by induced pluripotent stem cells (Gu, Yuan, Wills, & Kasper, 2007), while breast CSCs, glioblastoma CSCs, and urinary bladder CSCs highly express OCT4 (Ma et al., 2011; Wang et al., 2003; Zhao et al., 2015).

Aldehyde dehydrogenases (ALDHs), which include 18 isoenzymes expressed in humans, are more robust markers of CSCs. ALDH1 is a retinaldehyde dehydrogenase that oxidizes retinal to retinoic acid. Expression of ALDH1 is increased in CD34⁺ hematopoietic progenitor cells. The activity of ALDH1 was first detected in breast CSCs (Ginestier et al., 2007). This enzyme has also been detected in some

other CSCs, including those from acute myeloid leukemia (Pearce et al., 2005), prostate cancer (Li et al., 2010), hepatocellular carcinoma (Ma et al., 2008), head and neck squamous cell carcinoma (Chen et al., 2011), colorectal cancer (Zhou et al., 2014), and lung cancer (Jiang et al., 2009).

By using CD44⁺CD24⁻ and ALDH1⁺, Ginestier et al. successfully selected breast CSCs that could induce tumor formation in NOD/SCID mice from as few as 20 cells (Ginestier et al., 2007). High expression of ALDH1 is associated with poor clinical prognosis in patients with breast (Bane et al., 2013; Kang et al., 2014) and ovarian cancers (Chang et al., 2009).

2.2.4 CSCs and Tumor-Initiating Cells

Both CSCs and normal stem cells possess self-renewal capacity. However, self-renewal of CSCs is a deregulation process. It is difficult to identify cells that can self-renew or proliferate. Cell propagation occurs through two mechanisms, namely, long-term repopulation and self-renewal. To date, self-renewal is considered as the property of CSCs while long-term repopulation is considered as the property of cancer cells.

Tumors contain some transitory cells with high repopulation capacity. These are recognized as CSCs but do not satisfy the criteria of CSCs; hence, these cells are called tumor-initiating cells (TICs). Characteristics of TICs include (1) successful generation of parent tumors after xenografting, (2) self-renewal during serial passaging, and (3) differentiation into non-cancerous daughter cells.

2.2.5 Properties of CSCs

Properties of CSCs include indefinite self-renewal for growth and survival to resist therapy and differentiation into diverse cell populations present in tumors (Box 2.1).

Box 2.1. Five Key Characteristics of CSCs

1. A small portion of the tumor cells in a tumor have high tumorigenic potential.
2. The CSC subpopulation can be separated from other tumor cells by sorting with distinctive cell surface markers.
3. Tumors resulting from CSCs contain the mixed tumorigenic and non-tumorigenic cells of the original tumor (differentiation potential).
4. The CSC subpopulation can be serially transplanted through multiple generations (self-renewal).
5. CSCs tend to be resistant to conventional therapies such as radiation, hormones, cytokines, and chemotherapy.

Self-Renewal

Self-renewal is the ability of stem cells to form new stem cells through symmetric division (producing two similar stem cells) or asymmetric division (producing a stem cell and a differentiated cell). Self-renewal allows the maintenance of a pool of stem cells for long-term. Self-renewal of stem cells involves proto-oncogenic pathways such as Wnt/ β -catenin and Notch pathways. Another regulator of self-renewal during embryogenesis is sonic Hh signaling pathway, which is also present in multiple myeloma cells. However, limited information is available on the role of these pathways in CSCs.

High expression of Hh in CSCs was first reported in a pancreatic cancer xenograft model (Li et al., 2007). After that, the aberrant activity of the Hh pathway has been detected in several solid cancers, including the colon (Varnat et al., 2009) and gastric cancers (Song et al., 2011). The Wnt pathway promotes the self-renewal of colon CSCs (Ong, Vega, & Houchen, 2014). The Wnt/ β -catenin pathway is essential for the self-renewal of CSCs from human gastric cancer (Cai & Zhu, 2012) and for the regulation of stemness and tumorigenicity of CSCs from glioma (Gong & Huang, 2012).

Self-renewal of CSCs is also associated with their niche, which is an anatomically distinct microenvironment. Cells in the CSC niche produce factors that stimulate CSC self-renewal, induce angiogenesis, and recruit immune and other stromal cells that secrete additional factors to promote tumor invasion and metastasis (Dong et al., 2013; Kano et al., 2013; Matsuda et al., 2014; Takakura, 2012).

Differentiation

Differentiation is the ability of stem cells to develop a heterogeneous progeny of cells and is observed in both normal stem cells and CSCs. A recent study showed that single-cell-cloned CSCs from hepatocellular carcinoma cultured in different tumor cell-derived conditioned media differentiated into corresponding tumor cells and expressed specific markers of these cells (Liu et al., 2013). Breast CSCs differentiated into breast cancer cells when CD44 expression was silenced (Pham et al., 2011).

CSCs treated with chemicals show loss of stemness and cannot differentiate into cancer cells. For example, FC85 and ISA27 block the proliferation and promote the differentiation of glioma CSCs (Daniele et al., 2015). MC1742 and MC2625, which inhibit HDACs, increase the levels of acetyl-H3 and acetyl-tubulin and inhibit the growth of sarcoma CSCs by inducing their apoptosis. Moreover, MC1742 promotes osteogenic differentiation at nontoxic doses (Di Pompo et al., 2015).

2.3 Breast CSCS

2.3.1 *From the Beginning*

CSCs in breast tumors were first discovered by Al-Hajj et al. from the University of Michigan in 2003 (Al-Hajj et al., 2003). Al-Hajj et al. cultured primary breast tumors and analyzed the tumor cells for the expression of CD44, CD24, and ESA

by performing FACS. They observed that cancer cells with $CD44^+CD24^{-/low}ESA^+$ phenotype were highly tumorigenic, with only 200 of these cells inducing tumor formation when injected in NOD/SCID mice. In contrast, cells with $CD44^-CD24^+$ phenotype did not induce tumor formation, with 20,000 of these cells not inducing tumor formation when injected in NOD/SCID mice. They also observed that cells with $CD44^+CD24^{-/low}ESA^+$ phenotype could maintain their tumorigenic potential when serially passaged for long-term. Interestingly, tumors that developed from $CD44^+CD24^{-/low}$ cells included heterogenic cell populations. Based on these results, Al-Hajj et al. concluded that $CD44^+CD24^{-/low}$ cells satisfied the criteria for CSCs, such as self-renewal, differentiation, and high tumorigenicity. These results were further confirmed by several other studies (Cho et al., 2008; Liang et al., 2013; Pece et al., 2010; Pham et al., 2011; Ponti et al., 2005; Saadin & White, 2013; Vassilopoulos et al., 2008; Walia & Elble, 2010).

2.3.2 *Origin of Breast CSCs*

CSCs can be formed through different mechanisms. Breast CSCs are formed through these mechanisms. Some in vitro studies and clinical investigations suggest that breast CSCs are produced in vivo through the following two mechanisms (1) accumulation of mutations in mammary stem cells during development that causes these cells to lose their self-renewal capacity and (2) development of breast CSCs from non-stem cells through different evolutionary mechanisms.

Breast CSCs Derived from Mammary Stem Cells

Increased risk of breast cancer in children exposed to radiation indicates that breast cancer may develop directly from long-lived stem or progenitor cells present in the mammary glands (Miller et al., 1989; Modan, Chetrit, Alfandary, & Katz, 1989). Importantly, luminal progenitor cells are known to induce the formation of *BRCA1*-driven tumors (Lim et al., 2009; Molyneux et al., 2010; Proia et al., 2011). Pece et al. (2010) showed that poorly differentiated cancers had higher number of CSCs than well-differentiated cancers (Fig. 2.4).

In a study involving 61 patients with breast cancer, normal breast tissue and breast tumor tissue from the same patients were analyzed to determine the presence of stem cells in both the tissues. In all, nine patients had triple-negative cancer (TNC) and 52 patients had ER^+ and $Her2^+$ cancer. The results showed that 100 % (9/9) patients with TNC had CSCs with $CD44^+CD49f^+CD133/2^+$ phenotype in both the normal and tumor tissues and that only 13.4 % (7/52) patients with ER^+ and/or $Her2^+$ cancer had CSCs in the normal breast tissue. Based on this result, Atkinson et al. (2013) proposed that CSCs in breast cancer originated from mutated mammary stem cells present in the normal breast tissue.

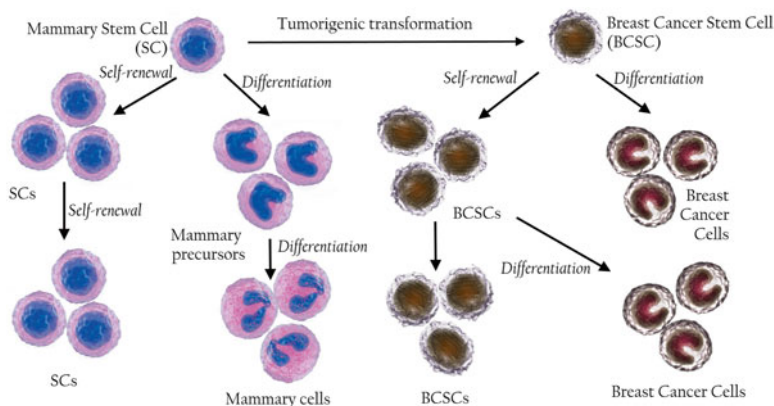


Fig. 2.4 Relations of breast cancer stem cells and normal mammary stem cells

Breast CSCs Derived from Non-stem Cells

The idea that breast CSCs were derived from non-stem cells originated from the heterogeneity of breast cancer cell lines. Almost all breast cancer cell lines contain a subpopulation of cells with breast CSC phenotypes. Interestingly, some studies have shown that different subpopulations of cells in the same breast cancer cell line can interconvert between phenotypes.

Analysis of some commercial breast cancer cell lines such as SUM159, SUM149, Ca1a, MDA-MB-231, BT474, SKBR3, and MCF7 indicated that these cell lines included a small population of stem cells that underwent self-renewal to form mammospheres in serum-free cultures and differentiation to generate other cells that resulted in heterogeneity (Gupta et al., 2011; Meyer et al., 2009; Piggott, Omidvar, Marti Perez, Eberl, & Clarkson, 2011).

Interconversion of CSCs in breast cancer cell lines was clearly recorded by Gupta et al. (2011). They sorted breast CSCs with stem-like basal and luminal phenotypes from two breast cancer cell lines SUM159 and SUM149 and observed that these cells exhibited the properties of their parental cell lines after 11 days in culture (Gupta et al., 2011). In another study, Piggott et al. (2011) depleted CSCs from BT474 breast cancer cell line and observed that this depleted cell line re-established progenitor-like cells after 4 weeks in culture. In some cell lines such as Ca1a, MCF7, SUM159, and MDA-MB-231, breast cells without a CSC phenotype ($CD44^+CD24^+$) produced breast CSCs with $CD44^+CD24^-$ phenotype in vitro (Meyer et al., 2009). In addition, non-CSCs ($CD44^+CD24^+$ phenotype) isolated from Ca1a, ZR75-1, and MCF7 cell lines successfully produced heterogeneous tumors showing local invasion in immuno compromised mice (Meyer et al., 2009). These evidence confirmed that breast non-CSCs could be automatically converted into CSCs both in vitro and in vivo.

Some recent studies have shown that actively trans differentiated breast non-CSCs can be converted into CSCs after treatment with some defined factors. CSC-like cells were produced after the transfection of MCF10A cells with *SRC* oncogene (Iliopoulos et al., 2011). Moreover, the CSC-conditioned medium can convert non-CSCs into CSCs (Iliopoulos et al., 2011). Shaffer et al. also produced CSCs by transfecting non-CSCs with SV40 and H-ras (Chaffer et al., 2011).

Breast CSCs Formed by Cell Fusion

Some studies have shown that breast CSCs can be produced in vitro by fusing breast cancer cells with mesenchymal stromal cells or macrophages. Hybrids of bone marrow-derived mesenchymal stem cells (MSCs) and cells from 2 breast cancer cell lines MDA-MB-231 (MDA) and MA11 show increased metastatic capacity. Because MSCs can migrate and localize to breast cancers, formation of MSC-breast cancer cell hybrids maybe a potential mechanism for generating breast CSCs (Rappa, Mercapide, & Lorico, 2012). Fusion of M2 macrophages with cells from breast cancer cell lines MCF-7 and MDA-MB-231 in the presence of polyethylene glycol produces hybrids that show increased migration, invasion, and tumorigenicity and have CD44⁺CD24^{-/low} phenotype (Ding, Jin, Chen, Shao, & Wu, 2012).

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