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Therapeutic Strategies Targeting Cancer Stem Cells

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1. Introduction

The classical clonal evolution theory of neoplastic development supports the notion that cellular transformation results from random mutations and subsequent clonal selection. However, recent advancements in identification of the malignant populations responsible for tumor maintenance and recurrence have lent support to the cancer stem cell (CSC) hypothesis as a model of carcinogenesis, and posit that tumor growth is driven by a rare subpopulation of cells with stem cell-like properties. Cancer stem cells are commonly thought of as derivatives of a normal tissue stem cell that undergoes genetic alterations, which allow for sustained aggressive and clonal characteristics, self-renewal capacity and the ability to differentiate into all populations within a malignancy. Cancer stem cells alone, as compared to the bulk of cells in a tumor, are considered to be responsible for tumor initiation, metastasis and resistance to treatment. Moreover, CSCs are believed to share many properties with normal stem cells providing them with an overall insensitivity to conventional radio- and chemotherapy. Therefore, successful targeting of such a highly tumorigenic yet rare population must be considered in order to improve the therapeutic efficacy of the currently available anti-cancer therapy. Here, we provide a summary of recent progress towards development of biomarkers that identify CSCs, the molecular mechanisms behind the conventional anti-cancer therapy resistance, and the development of therapeutic strategies to selectively target CSC populations.

2. Normal stem/progenitor cells and CSCs

In the developing embryo, stem cells are located in the inner mass of the blastocyst where they are known as the embryonic stem cells and can give rise to the majority of cell types in the body, a characteristic referred to as pluripotency. At later developmental stages, embryonic stem cells differentiate into adult stem cells, which are multipotent (i.e., they can give rise to a restricted number of cell types) and form different tissues and organs (Fuchs and Segre 2000). One of the most important features of stem cells is their ability to undergo asymmetric cell division, a process whereby a progenitor cell gives rise to a new stem cell that can maintain its own progeny through self-renewal.

CSCs reportedly share many properties with normal stem cells. It is still not clear whether CSCs derive from mutated tissue specific stem cells or more differentiated cells that have re-

initiated a self-renewal program as part of or following transformation. Regardless of their origin, CSCs have been found to resemble the normal stem or progenitor cells of their tumor's derivative tissue (Calabrese et al. 2007). Microscopic analysis of many malignancies reveals a complex heterogeneous picture composed of significant phenotypic diversity. Even though CSCs make up only a minor fraction of a tumor, they are defined by their ability to self-renew, producing tumorigenic daughter cells, and their ability to give rise to different nontumorigenic cancer cell phenotypes. Collectively, CSC-descendants contribute to the cellular heterogeneity of the tumor.

3. Molecular signature for cancer stem cell

Cancer stem cells are commonly characterized on the basis of the expression of specific- or combinations of molecules (e.g. CD133 and CD44), but they can also be distinguished from their progeny by functional attributes such as high expression of cytoprotective enzymes (e.g. aldehyde dehydrogenase, ALDH) and drug-efflux pumps (e.g. ABC transporters). Advancements in cell sorting technology via flow cytometry and fluorescent antibodies have enabled researchers to reproducibly isolate phenotypically defined rare cell populations. Utilizing these tools, John Dick's laboratory first isolated CSCs from acute myeloid leukemia (AML) as early as 1997 (Bonnet and Dick 1997). In this pioneering work, Dick and colleagues showed that in human AML, a rare subset of tumor cells with the CD34⁺/CD38⁻ signature possessed the ability to recapitulate the entire original disease over several transplantations. These findings suggest that self-renewal and pluripotency are characteristic of this small subpopulation, and are absent within the broader CD34⁺/CD38⁺ population (Lapidot et al. 1994; Bonnet and Dick 1997). The consensus view of hematological malignancies is that the CD34⁺/CD38⁻ signature does not identify most CSCs (Alison et al., 2011). However, it should be noted that other markers have also been used to characterize CSCs in these cancers (Alison et al. 2011). In contrast, there is little agreement regarding the molecular identity of CSCs in solid tumors. The first solid tumor associated CSCs were isolated from breast cancer in 2003 (Al-Hajj et al. 2003). Since then, CSCs have been identified in brain- (Hemmati et al. 2003; Singh et al. 2003), colon- (O'Brien et al. 2007), melanoma- (Fang et al. 2005), pancreatic- (Hermann et al. 2007), prostate- (Collins et al. 2005), ovarian (Bapat et al. 2005), lung- (Eramo et al. 2008) and gastric-cancers (Fukuda et al. 2009). The isolation of many solid CSCs has been carried out using a number of adhesion markers including CD44 and CD24, or other CSC- associated functional markers such as multidrug efflux proteins ABC transporter and Prominin1 (CD133), an apical plasma membrane protein predominantly found on embryonal epithelial structures. In glioblastoma and medulloblastoma, CD133 is routinely used to enrich for CSCs (Singh et al. 2003). CD133 expression has also been used as a CSC phenotypic marker for colon cancer (O'Brien et al. 2007). However, although CD133 has continued to identify tumor cells with self-renewal capacity in a number of other solid tumors, there is an ongoing debate as to how robust a universal marker it actually is within the solid tumor CSCs (Wu and Wu 2009). Most of the cell surface markers used to distinguish stem cells in normal and cancerous tissues have thus far not been expressed exclusively by stem cells alone. Additionally, the same markers used for isolation of CSCs in one organ cannot directly be used for identification in other organs. Such situations underlie the importance of combining phenotypic markers with functional markers as a signature to identify tissue specific CSCs.

4. Cancer stem cell and patient prognosis

According to the CSC hypothesis, these cells are not only responsible for the unlimited growth of a tumor, but also for the maintenance of the minimal residual disease and constitutive recurrences following therapy and metastasis. Therefore, quantification of the presence of this rare population within a disease burden may serve as a prognostic indicator. Generally, it is believed that a high proportion of stem cells signify a worse prognosis. For example, in breast cancer, the most poorly differentiated tumors have the highest burden of CSCs (Pece et al. 2010). Similarly, elevated immunoreactivity of nestin and CD133 in tumor specimens is associated with a poor prognosis in patients with brain tumors (Laks et al. 2009). Furthermore, others have reported that high CD133 expression in brain tumors is a dismal prognostic marker for progression free- and overall-survival (Zhang et al. 2008). Contrary to these findings, Kim and colleagues recently examined the three established stem cell markers, nestin, CD133 and CD15 in 88 cases of glioblastoma by immunohistochemical analysis and reported that there was no correlation between stem cell marker expression and the clinical outcome of these patients (Kim et al. 2011). Elevated expression of CD133 in colon cancer is also an independent marker of poor prognosis and is associated with liver metastasis (Horst et al. 2009). In pancreatic cancer, high CD133 expression is an independent adverse prognostic factor for 5-years survival and is associated with lymph node metastasis (Maeda et al. 2008). Furthermore, the expression of the CSC specific functional markers, such as ALDH, is directly correlated with a poor prognosis in a number of tumors including AML (Cheung et al. 2007), breast (Morimoto et al. 2009), head and neck squamous cell carcinoma (Chen et al. 2009) and prostate cancer (Rasheed et al. 2010). Another potential CSC associated marker is the ABC transporter, which has also been reported to be a sign of poor prognosis in AML patients, whereby there is a reduced overall 4-year survival associated with elevated expression of ABCC11 (Guo et al. 2009). In summary, patients with tumors that express elevated levels of molecular markers related to CSCs tend to have a poorer prognosis than patients with tumors that express low levels of these makers. However, considering the inconsistency between individual stem cell markers, there is a need to define a CSC signature more precisely before it can be considered as a predictor of clinical outcome.

5. Mechanisms of resistance and stem cell biology

Like normal stem cells, CSCs are considered to be relatively quiescent. This characteristic leads to their relative resistance towards conventional radio- and chemotherapy, which predominantly targets rapidly dividing cells (Rich and Bao 2007). During therapy, the tumor burden may decrease significantly following treatment with the superficial appearance of tumor regression. However, quiescent CSCs can survive this therapy and eventually give rise to new daughter tumor cells and thereby re-initiate disease resulting in recurrence. In chronic myeloid leukemia (CML), a rare population of cells with the hematopoietic stem cell (HSC)-like phenotype harbor the definitive genetic aberration, t(9;22)(q34;q11) - the Philadelphia chromosome. This fusion product, a tyrosine kinase, is sufficient to initiate CML. Despite the immense success of Imatinib, a tyrosine kinase inhibitor, in controlling disease burden, a subpopulation of quiescent stem cells remains inherently resistant to therapy (Elrick et al. 2005).

DNA damage repair pathways are considered to be the guardians of genomic and chromosomal stability. Because stem cells are at the basis of tissue homeostasis, they appear

to have a very efficient DNA repair capacity (Maynard et al. 2008). Moreover, it has been demonstrated that central nervous system (Smith et al. 2000) and hematopoietic stem cells contain lower levels of reactive oxygen species (ROS) as compared to their mature counterparts due to increased antioxidant defenses (Ito et al. 2004). In glioblastoma, increased DNA repair capacity in CD133⁺ CSCs appears to be related to the resistance to treatment (Bao et al. 2006). Other contributions to CSC radioresistance may arise from the fact that they may reside in hypoxic niches (Baumann et al. 2008). An increased expression of drug transporters, such as the ABC transporters, has been reported in many different types of normal stem cells (Zhou et al. 2001) and also in CSCs (Ginestier et al. 2007). Some studies suggest that the expression of such pumps on the cell surface represents a class of CSCs with high drug efflux capacity and an inherently increased resistance to chemotherapeutic agents (Hirschmann-Jax et al. 2004). Thus, it seems that CSCs may resist standard anti-cancer therapies via a combination of molecular mechanisms associated with normal stem cell biology. It is widely believed that in order to prevent relapse, effective targeting of CSCs is likely to be essential.

6. Therapeutic strategies targeting cancer stem cells

Most currently available cancer therapies are designed to target cells that are highly mitotic and rapidly dividing. However, nearly all malignancies are heterogeneous in nature. Many different types of cells have been shown to be present in tumors, including CSCs. These cells, which appear to provide the tumor initiating capacity in many cancers, are further capable of evading conventional chemo- and/or radiotherapy due to their inherent stem cell characteristics. After therapy, tumors have a higher population of therapy resistant stem cells; therefore specific targeting of this population is of utmost importance. Here, we highlight the latest strategies to successfully target and eliminate CSCs, the roots of cancer.

6.1 Pharmacological targeting

Small molecule inhibitors have shown promising results when used alone or in combination to target slow growing chemo- and radio-resistant CSCs. Several strategies have been employed including targeting signaling pathways that impart chemo- and radio-resistance to CSCs, thereby increasing their susceptibility to conventional therapy. Examples include targeting protective vascular niches that shield CSCs from environmental insults (Gilbertson and Rich 2007) and directly targeting apoptotic pathways, hence inducing programmed cell death in CSCs.

In malignant brain tumor models, Bao et al. demonstrated that following conventional radiation therapy, a fraction of CD133⁺ brain tumor stem cells is enriched, which essentially contributes to the resistance of glioma through preferential activation of the DNA damage checkpoint response and to an increase in DNA repair capacity. Using specific pharmacological inhibitors of the Chk1 and Chk2 DNA checkpoint kinases, the radioresistance of CD133⁺ brain tumor stem cells can be reversed, making them susceptible to ionizing radiation (Bao et al. 2006). Reactive oxygen species (ROS), critical mediators of ionizing radiation-induced cell killing, are shown to be present at lower levels in some subsets of the CSC population in breast cancer. Lower ROS levels in CSCs are associated with an increased expression of free radical scavenging systems predisposing CSCs to develop less DNA damage and preferential sparing after irradiation. Pharmacological depletion of ROS scavengers in CSCs significantly decreases their clonogenicity and results

in radiosensitization (Diehn et al. 2009). Similarly, several pharmacological agents have shown promising results in the reversal of chemoresistance to the CSC population. In the setting of malignant glioma, the therapeutic efficacy of temozolomide (TMZ), an alkylating agent, on chemoresistant glioma stem cells was shown to be enhanced by Notch and SHH pathway inhibition with GSI-I and Cyclopamine (Ulasov et al. 2011). In CML, the combination of tyrosine kinase inhibitors (TKIs), i.e., imatinib, nilotinib, and/or dasatinib, with inhibitors of autophagy resulted in a near complete elimination of phenotypically and functionally defined CML stem cells (Bellodi et al. 2009). Pharmacological inhibition of Hedgehog (Hh) signaling, an essential stem cell maintenance pathway, has been found to impair not only the propagation of CML driven by wild type BCR-ABL1, but also the growth of imatinib-resistant CML in both mouse models and in humans (Zhao et al. 2009). BMS-214662, a cytotoxic farnesyltransferase inhibitor, alone or in combination with the tyrosine kinase inhibitors, imatinib mesylate and/or dasatinib, induces a selective apoptosis of proliferating and quiescent CML stem/progenitor cells while sparing normal stem/progenitor cells. BMS-214662 was also found to be cytotoxic even against CML blast crisis stem/progenitor cells, particularly in combination with a tyrosine kinase inhibitor and equally effective in cell lines harboring wild-type vs. mutant BCR-ABL (Copland et al. 2008). In AML, Zeng et al. demonstrated that SDF-1 α /CXCR4 interactions contribute to the resistance of leukemic cells to signal transduction inhibitors and chemotherapy-induced apoptosis (Zeng et al. 2009). Therefore, it is not surprising that the disruption of these interactions with pharmacological inhibitors of CXCR4 is an effective strategy for sensitizing these leukemic stem cells to chemotherapy, thus targeting CSCs within the protective bone marrow microenvironment (Zeng et al. 2009).

CSCs are situated in vascular niches or microenvironments that tightly regulate the supply of oxygen and nutrients to CSCs and thus control their self renewal and differentiation of CSCs (Gilbertson and Rich 2007). In glioma xenograft models, the depletion of vascular endothelial cells by ERBB2 inhibitors (erythroblastic leukemia viral homolog 2, also known as human epidermal growth factor receptor 2) or VEGF signaling inhibitor has been shown to ablate self-renewing cells (Calabrese et al. 2007). Various small molecules have been shown to directly induce apoptosis in CSCs. In leukemia, TDZD-8 (4-benzyl, 2-methyl, 1,2,4-thiadiazolidine, 3,5 dione) induces cell death by rapid loss of membrane integrity, depletion of free thiols and inhibition of both the PKC and FLT3 signaling pathways in phenotypically primitive cells, *in vitro* colony-forming progenitors, and leukemia stem cells, while sparing the physiology in the hematopoietic stem cell compartment (Guzman et al. 2007). The mTOR inhibitor rapamycin also effectively targets leukemia stem cells via modulation of the phosphoinositide 3-kinase/phosphatase and tensin homolog (PI3K/PTEN) pathway (Yilmaz et al. 2006). In AML, combinational treatment with the proteasome inhibitors carbobenzoxy-l-leucyl-l-leucyl-l-leucinal (MG-132) and anthracycline idarubicin produces rapid and extensive apoptosis in the CSC population via inhibition of nuclear factor kappaB (NF- κ B) and activation of p53-regulated genes, while leaving the normal hematopoietic stem cells viable (Guzman et al. 2007). In the setting of prostate cancer, inhibition of PI3K activity by the dual PI3K/mTOR inhibitor, NVP-BEZ235, inhibited the growth of CD133⁺/CD44⁺ prostate cancer progenitors (Dubrovska et al. 2009). Treatment with Lapatinib, an epidermal growth factor receptor [EGFR]/HER2 pathway inhibitor, in conjunction with conventional therapy, decreases the relative frequency of chemoresistant CD44⁺/CD24^{-/low} breast cancer stem cells (Li and Ren 2008). In a phase III randomized trial for metastatic breast cancer using doxorubicin with or without N,N-Diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine

(DPPE; tesmilifene), apoptosis was preferentially induced in CD44⁺/CD24^{-/low} breast cancer stem cells. The increase in apoptosis attributed to the addition of the latter agent resulted in a significant improvement in the overall survival and a trend towards progression-free survival (Deng et al. 2009).

Most of the anti-cancer drugs target proliferating tumor cells, which dramatically reduce tumor burden but to achieve durable cures may require successful elimination of CSCs that are proven to be responsible for tumor initiation, metastases and relapse. In the search for drugs that selectively target CSCs, we need to make sure that identified compounds do not affect normal stem cells with which CSCs share many properties.

6.2 Immunotherapy

Cancer stem cells (CSCs) have been associated with immunosuppressive properties (Di Tomaso et al. 2010), which are likely a critical part of the mechanism which endows the cells with tumor-promoting and immunomodulatory characteristics. CSC lines have also been shown to be deficient or expressing low levels of MHC-I, MHC-II, antigen processing machinery and NKG2D. Accordingly, recent work has demonstrated that the culture supernatant of adipose tissue stem cells isolated from breast cancer tissues upregulates the immunosuppressive cytokines (IL-10, TGF- β and induces conversion of conventional T cells into FoxP3-expressing regulatory T cells (Razmkhah et al. 2011), a potentially immunosuppressive cell type of the adaptive immune system. Furthermore, CD200 has recently been recognized to be expressed by CSCs (Kawasaki et al. 2007). CD200-deficient mice exhibit gross autoimmune pathology when challenged in various models of experimental autoimmune encephalomyelitis and collagen-induced arthritis (Hoek et al. 2000), implicating the important contribution of CD200 to normal tolerance and immunosuppression.

Understanding the many different immunosuppressive pathways in CSCs allows for a more effective design of therapeutic elimination strategies. Among them, a combinatorial approach incorporating immunotherapy has been given serious consideration. One of the tenants of immunotherapy for CSCs is that while chemotherapy, surgical debulking and/or radiotherapy destroy the majority of cancer cells, the survival of small populations of cells with cancer-initiating potential persists, which can be targeted by the activated immune system. Accordingly, recent work has demonstrated that dendritic cells CSCs-fusion resulted in the activation of T cells expressing elevated levels of IFN- γ , with an enhanced killing-property against CSCs (Weng et al. 2010). In glioblastoma, CSCs growth and survival is supported by interleukin 6 (IL6) signaling based on data demonstrating that IL6 blockade contributes to CSC clearance (Wang et al. 2009). In patients with glioblastoma, elevated IL-6 and its receptor expression are associated with reduced survival indicating potential clinical utility of the IL-6 signaling cascade as a target for therapy of primary tumors of the CNS (Wang et al. 2009). Glioma specific CSCs can also be targeted and killed by cytotoxic T lymphocytes (CTL) through a perforin-mediated mechanism. This is supported by recent work by Brown and colleagues demonstrating that CSCs derived from high-grade glioma may be recognized and eliminated by CD8⁺ CTLs (Brown et al. 2009).

6.3 Genetic targeting

6.3.1 miRNA

Given that different types of cancer cells have a specific microRNA expression profile, utilization of microRNA-based therapeutic tools to target CSCs is being increasingly

exploited. The potential for CSCs self-renewal depends on a complex interplay of gene expression and environmental stimuli. Gene expression is controlled at different levels and can also be regulated by small micro-RNA molecules (miRNAs). miRNA are non-coding short nucleotide sequences (≈ 22 nucleotides in length) that block translation of transcripts with complementary mRNA sequences (Bartel 2004). Since miRNAs regulate differentiation and can function as tumor suppressors or oncogenes, the field of miRNA biology has become a subject of great interest for understanding stem cell self-renewal, immunosuppressor status and long lifespan. The number of miRNAs associated with cancer stem cells is continuously expanding. RNA interference strategies are at the frontline of targeting the aberrant expression of different genes utilizing miRNAs. Yu et al. (Yu et al. 2007) using breast cancer stem cell were able to increase the expression of let-7 miRNA, accomplished via a lentiviral vector, leading to reduced proportion of stem cells and resulting in delayed tumor formation and metastasis. Similar results can be achieved not only in solid tumors, but also in leukemia. miRNA-17-92 was found to be up-regulated in leukemia stem cells (Jiang et al. 2010). However, targeting such CSC specific miRNA through RNA interference is yet to be tested in other major types of malignancies.

6.3.2 Oncolytic virus

Virotherapy, a therapeutic approach utilizing conditionally replicative viruses, may hold a potential to directly target self-renewing CSCs. In pre-clinical trials these viruses have demonstrated that these vectors function independent of common resistance pathways that exist for chemotherapeutic agents. Moreover, it is possible to construct viruses that would preferentially target cancer stem cells or other drug-resistant cells. Here, we summarize the recent efforts to develop oncolytic virus in order to target CSCs.

Herpes simplex virus

Attenuated herpes simplex virus (HSV) was used as one of the first gene therapy vectors to target glioma cells. To reduce neurotoxicity, HSV was deleted for RL1, which encodes the ICP34.5 and allows for virus replication even in the presence of the interferon (IFN) response. Later generations of the HSV construct restored the gene under the control of specific enhancers expressed in cancer cells. To preferentially target glioma stem cells that expressed high levels of nestin, the ICP34.5 was restored under the control of nestin, creating rQnestin34.5 (Kambara et al. 2005). Glioma stem cells shown to be resistant to conventional therapies were susceptible to the virus. Interestingly, IFN β treatment inhibited viral replication only in neurospheres, known to be enriched of stem cells (Kurozumi et al. 2008). This is important in light of the general view that cancer cells have a deficient interferon response and viruses such as VSV may not be able to target CSCs.

Adenovirus

Adenoviruses (Ad) are the most commonly used gene therapy vectors. After entry into the cell, the adenoviral early transcription region E1A binds with the cell cycle regulating protein retinoblastoma (Rb). Rb happens to be frequently mutated in various human cancers. Oncolytic adenoviruses were created by deleting a 24 nucleotide ($\Delta 24$)-specific region in E1A that binds Rb: as a result, the virus replicates only in cells that contain mutant Rb cells. Another approach has been to create adenoviruses that express E1A under the regulation of specific promoters found only in cancer cells. Since not all target cells express the necessary coxsackie-adenovirus receptor (CAR) to improve viral entry, adenoviruses

have undergone further surface modifications, such as replacing the fiber with serotype 3 adenovirus (Ad5/3), or by adding polylysine (Ad.pk7) and RGD (Ad.RGD). Breast cancer stem cells were shown by Eriksson et al. to be successfully targeted by mutated Ads, Ad5/3- Δ 24 and Ad5.pk7- Δ 24 (Eriksson et al. 2007). These viruses were able to kill not only CD44⁺/CD24^{-/low} breast cancer stem cells, but also more differentiated cells. By using stem cell specific promoters, Cox-2, hTERT and mdrl, Bauerschmitz et al. (Bauerschmitz et al. 2008) from the same group was able to show a reduction in breast cancer stem cell population after treatment with Ad5/3-mdrl- Δ 24. Adenoviruses have shown similar efficacy in gliomas, esophageal and other CSC models.

Reovirus

Not all oncolytic viruses are affected by stem cell properties of cancer cells or target preferentially a sub-population within the tumor. Reovirus relies on abnormal activation of the Ras signaling pathway and Ras levels are equally upregulated in cancer stem cells and in the more differentiated populations (Marcato et al. 2009). As a result, Reovirus induces rapid oncolysis of colon-, breast-, lymphoma-, brain- and spinal-cancer cells without changing the cancer stem cell frequency. Since it causes a restriction of the cancer stem cell pool, it can also prove of benefit in prolonging remissions.

The major benefit of gene targeting in cancer stem cells is the opportunity it offers in discovering new therapies. Although most of genetic approaches remain to be proven in clinical trials, they appear promising. Their safety profile and no cross-resistance with current therapies make them formidable candidates to combine with the conventional anti-cancer therapy.

7. Conclusion

The identification of CSCs and the recent knowledge about the ability of CSCs to resist conventional chemo- and radiotherapy have prompted a number of novel targeting strategies to attack this rare but extremely important tumor subpopulation in order to eradicate cancer. Functional characterization of CSCs in disease progression and therapeutic resistance has altered our understanding of malignancy, which has led to a re-evaluation of conventional therapies for cancer. Although the jury is still out regarding the molecular signature used for the definitive isolation and characterization of the CSCs as well as defining the exact role that CSCs play in malignant disease progression, there is little doubt regarding the extraordinary capacity of CSCs to promote tumor growth, angiogenesis, invasion, therapeutic resistance and disease relapse post-therapy. These characteristics make CSCs a vital cell population that should be targeted effectively in order to develop successful anti-cancer therapy. Novel and effective therapies directed against CSCs may significantly improve the therapeutic efficacy of the currently available conventional therapies. Recent advancements in stem cell biology have allowed us to gain remarkable insight into the molecular mechanisms or signaling pathways that are differentially present in CSCs and non-stem cell tumor burdens. In this chapter, we have discussed several key molecular and signaling targets that have the potential to be utilized for future development of anti-CSC therapeutics. Most of these targets are still a long way from clinical application. However, the CSC paradigm has provided exciting new venues to improve cancer treatment by reducing recurrence and metastasis, which are considered to be the main cause of most cancer fatalities.

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9. References

- Al-Hajj, M., Wicha, M.S., Benito-Hernandez, A., Morrison, S.J., and Clarke, M.F. 2003. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci U S A* 100(7): 3983-3988.
- Alison, M.R., Lim, S.M., and Nicholson, L.J. 2011. Cancer stem cells: problems for therapy? *J Pathol* 223(2): 147-161.
- Bao, S., Wu, Q., McLendon, R.E., Hao, Y., Shi, Q., Hjelmeland, A.B., Dewhirst, M.W., Bigner, D.D., and Rich, J.N. 2006. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. *Nature* 444(7120): 756-760.
- Bapat, S.A., Mali, A.M., Koppikar, C.B., and Kurrey, N.K. 2005. Stem and progenitor-like cells contribute to the aggressive behavior of human epithelial ovarian cancer. *Cancer Res* 65(8): 3025-3029.
- Bartel, D.P. 2004. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell* 116(2): 281-297.
- Bauerschmitz, G.J., Ranki, T., Kangasniemi, L., Ribacka, C., Eriksson, M., Porten, M., Herrmann, I., Ristimäki, A., Virkkunen, P., Tarkkanen, M., Hakkarainen, T., Kanerva, A., Rein, D., Pesonen, S., and Hemminki, A. 2008. Tissue-specific promoters active in CD44+CD24-/low breast cancer cells. *Cancer Res* 68(14): 5533-5539.
- Baumann, M., Krause, M., and Hill, R. 2008. Exploring the role of cancer stem cells in radioresistance. *Nat Rev Cancer* 8(7): 545-554.
- Bellodi, C., Lidonnici, M.R., Hamilton, A., Helgason, G.V., Soliera, A.R., Ronchetti, M., Galavotti, S., Young, K.W., Selmi, T., Yacobi, R., Van Etten, R.A., Donato, N., Hunter, A., Dinsdale, D., Tirro, E., Vigneri, P., Nicotera, P., Dyer, M.J., Holyoake, T., Salomoni, P., and Calabretta, B. 2009. Targeting autophagy potentiates tyrosine kinase inhibitor-induced cell death in Philadelphia chromosome-positive cells, including primary CML stem cells. *J Clin Invest* 119(5): 1109-1123.
- Bonnet, D. and Dick, J.E. 1997. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med* 3(7): 730-737.
- Brown, C.E., Starr, R., Martinez, C., Aguilar, B., D'Apuzzo, M., Todorov, I., Shih, C.C., Badie, B., Hudecek, M., Riddell, S.R., and Jensen, M.C. 2009. Recognition and killing of brain tumor stem-like initiating cells by CD8+ cytolytic T cells. *Cancer Res* 69(23): 8886-8893.
- Calabrese, C., Poppleton, H., Kocak, M., Hogg, T.L., Fuller, C., Hamner, B., Oh, E.Y., Gaber, M.W., Finklestein, D., Allen, M., Frank, A., Bayazitov, I.T., Zakharenko, S.S., Gajjar, A., and Weissman, I.L. 2009. A self-renewing neural stem cell niche promotes continuous neurogenesis in the adult brain. *Nat Neurosci* 12(12): 1358-1368.

- A., Davidoff, A., and Gilbertson, R.J. 2007. A perivascular niche for brain tumor stem cells. *Cancer Cell* 11(1): 69-82.
- Chen, Y.C., Chen, Y.W., Hsu, H.S., Tseng, L.M., Huang, P.I., Lu, K.H., Chen, D.T., Tai, L.K., Yung, M.C., Chang, S.C., Ku, H.H., Chiou, S.H., and Lo, W.L. 2009. Aldehyde dehydrogenase 1 is a putative marker for cancer stem cells in head and neck squamous cancer. *Biochem Biophys Res Commun* 385(3): 307-313.
- Cheung, A.M., Wan, T.S., Leung, J.C., Chan, L.Y., Huang, H., Kwong, Y.L., Liang, R., and Leung, A.Y. 2007. Aldehyde dehydrogenase activity in leukemic blasts defines a subgroup of acute myeloid leukemia with adverse prognosis and superior NOD/SCID engrafting potential. *Leukemia* 21(7): 1423-1430.
- Collins, A.T., Berry, P.A., Hyde, C., Stower, M.J., and Maitland, N.J. 2005. Prospective identification of tumorigenic prostate cancer stem cells. *Cancer Res* 65(23): 10946-10951.
- Copland, M., Pellicano, F., Richmond, L., Allan, E.K., Hamilton, A., Lee, F.Y., Weinmann, R., and Holyoake, T.L. 2008. BMS-214662 potently induces apoptosis of chronic myeloid leukemia stem and progenitor cells and synergizes with tyrosine kinase inhibitors. *Blood* 111(5): 2843-2853.
- Deng, T., Liu, J.C., Pritchard, K.I., Eisen, A., and Zacksenhaus, E. 2009. Preferential killing of breast tumor initiating cells by N,N-diethyl-2-[4-(phenylmethyl)phenoxy]ethanamine/tesmilifene. *Clin Cancer Res* 15(1): 119-130.
- Di Tomaso, T., Mazzoleni, S., Wang, E., Sovenia, G., Clavenna, D., Franzin, A., Mortini, P., Ferrone, S., Doglioni, C., Marincola, F.M., Galli, R., Parmiani, G., and Maccalli, C. 2010. Immunobiological characterization of cancer stem cells isolated from glioblastoma patients. *Clin Cancer Res* 16(3): 800-813.
- Diehn, M., Cho, R.W., Lobo, N.A., Kalisky, T., Dorie, M.J., Kulp, A.N., Qian, D., Lam, J.S., Ailles, L.E., Wong, M., Joshua, B., Kaplan, M.J., Wapnir, I., Dirbas, F.M., Somlo, G., Garberoglio, C., Paz, B., Shen, J., Lau, S.K., Quake, S.R., Brown, J.M., Weissman, I.L., and Clarke, M.F. 2009. Association of reactive oxygen species levels and radioresistance in cancer stem cells. *Nature* 458(7239): 780-783.
- Dubrovskaya, A., Kim, S., Salamone, R.J., Walker, J.R., Maira, S.M., Garcia-Echeverria, C., Schultz, P.G., and Reddy, V.A. 2009. The role of PTEN/Akt/PI3K signaling in the maintenance and viability of prostate cancer stem-like cell populations. *Proc Natl Acad Sci U S A* 106(1): 268-273.
- Elrick, L.J., Jorgensen, H.G., Mountford, J.C., and Holyoake, T.L. 2005. Punish the parent not the progeny. *Blood* 105(5): 1862-1866.
- Eramo, A., Lotti, F., Sette, G., Pillozzi, E., Biffoni, M., Di Virgilio, A., Conticello, C., Ruco, L., Peschle, C., and De Maria, R. 2008. Identification and expansion of the tumorigenic lung cancer stem cell population. *Cell Death Differ* 15(3): 504-514.
- Eriksson, M., Guse, K., Bauerschmitz, G., Virkkunen, P., Tarkkanen, M., Tanner, M., Hakkarainen, T., Kanerva, A., Desmond, R.A., Pesonen, S., and Hemminki, A. 2007. Oncolytic adenoviruses kill breast cancer initiating CD44+CD24-/low cells. *Mol Ther* 15(12): 2088-2093.

- Fang, D., Nguyen, T.K., Leishear, K., Finko, R., Kulp, A.N., Hotz, S., Van Belle, P.A., Xu, X., Elder, D.E., and Herlyn, M. 2005. A tumorigenic subpopulation with stem cell properties in melanomas. *Cancer Res* 65(20): 9328-9337.
- Fuchs, E. and Segre, J.A. 2000. Stem cells: a new lease on life. *Cell* 100(1): 143-155.
- Fukuda, K., Saikawa, Y., Ohashi, M., Kumagai, K., Kitajima, M., Okano, H., Matsuzaki, Y., and Kitagawa, Y. 2009. Tumor initiating potential of side population cells in human gastric cancer. *Int J Oncol* 34(5): 1201-1207.
- Gilbertson, R.J. and Rich, J.N. 2007. Making a tumour's bed: glioblastoma stem cells and the vascular niche. *Nat Rev Cancer* 7(10): 733-736.
- Ginestier, C., Hur, M.H., Charafe-Jauffret, E., Monville, F., Dutcher, J., Brown, M., Jacquemier, J., Viens, P., Kleer, C.G., Liu, S., Schott, A., Hayes, D., Birnbaum, D., Wicha, M.S., and Dontu, G. 2007. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell* 1(5): 555-567.
- Guo, Y., Kock, K., Ritter, C.A., Chen, Z.S., Grube, M., Jedlitschky, G., Illmer, T., Ayres, M., Beck, J.F., Siegmund, W., Ehninger, G., Gandhi, V., Kroemer, H.K., Kruh, G.D., and Schaich, M. 2009. Expression of ABC-type nucleotide exporters in blasts of adult acute myeloid leukemia: relation to long-term survival. *Clin Cancer Res* 15(5): 1762-1769.
- Guzman, M.L., Li, X., Corbett, C.A., Rossi, R.M., Bushnell, T., Liesveld, J.L., Hebert, J., Young, F., and Jordan, C.T. 2007. Rapid and selective death of leukemia stem and progenitor cells induced by the compound 4-benzyl, 2-methyl, 1,2,4-thiadiazolidine, 3,5 dione (TDZD-8). *Blood* 110(13): 4436-4444.
- Hemmati, H.D., Nakano, I., Lazareff, J.A., Masterman-Smith, M., Geschwind, D.H., Bronner-Fraser, M., and Kornblum, H.I. 2003. Cancerous stem cells can arise from pediatric brain tumors. *Proc Natl Acad Sci U S A* 100(25): 15178-15183.
- Hermann, P.C., Huber, S.L., Herrler, T., Aicher, A., Ellwart, J.W., Guba, M., Bruns, C.J., and Heeschen, C. 2007. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell* 1(3): 313-323.
- Hirschmann-Jax, C., Foster, A.E., Wulf, G.G., Nuchtern, J.G., Jax, T.W., Gobel, U., Goodell, M.A., and Brenner, M.K. 2004. A distinct "side population" of cells with high drug efflux capacity in human tumor cells. *Proc Natl Acad Sci U S A* 101(39): 14228-14233.
- Hoek, R.M., Ruuls, S.R., Murphy, C.A., Wright, G.J., Goddard, R., Zurawski, S.M., Blom, B., Homola, M.E., Streit, W.J., Brown, M.H., Barclay, A.N., and Sedgwick, J.D. 2000. Down-regulation of the macrophage lineage through interaction with OX2 (CD200). *Science* 290(5497): 1768-1771.
- Horst, D., Kriegel, L., Engel, J., Kirchner, T., and Jung, A. 2009. Prognostic significance of the cancer stem cell markers CD133, CD44, and CD166 in colorectal cancer. *Cancer Invest* 27(8): 844-850.
- Ito, K., Hirao, A., Arai, F., Matsuoka, S., Takubo, K., Hamaguchi, I., Nomiyama, K., Hosokawa, K., Sakurada, K., Nakagata, N., Ikeda, Y., Mak, T.W., and Suda, T. 2004.

- Regulation of oxidative stress by ATM is required for self-renewal of haematopoietic stem cells. *Nature* 431(7011): 997-1002.
- Jiang, P., Rao, E.Y., Meng, N., Zhao, Y., and Wang, J.J. 2010. MicroRNA-17-92 significantly enhances radioresistance in human mantle cell lymphoma cells. *Radiat Oncol* 5: 100.
- Kambara, H., Okano, H., Chiocca, E.A., and Saeki, Y. 2005. An oncolytic HSV-1 mutant expressing ICP34.5 under control of a nestin promoter increases survival of animals even when symptomatic from a brain tumor. *Cancer Res* 65(7): 2832-2839.
- Kawasaki, B.T., Mistree, T., Hurt, E.M., Kalathur, M., and Farrar, W.L. 2007. Co-expression of the toleragenic glycoprotein, CD200, with markers for cancer stem cells. *Biochem Biophys Res Commun* 364(4): 778-782.
- Kim, K.J., Lee, K.H., Kim, H.S., Moon, K.S., Jung, T.Y., Jung, S., and Lee, M.C. 2011. The presence of stem cell marker-expressing cells is not prognostically significant in glioblastomas. *Neuropathology*.
- Kurozumi, K., Hardcastle, J., Thakur, R., Shroll, J., Nowicki, M., Otsuki, A., Chiocca, E.A., and Kaur, B. 2008. Oncolytic HSV-1 infection of tumors induces angiogenesis and upregulates CYR61. *Mol Ther* 16(8): 1382-1391.
- Laks, D.R., Masterman-Smith, M., Visnyei, K., Angenieux, B., Orozco, N.M., Foran, I., Yong, W.H., Vinters, H.V., Liao, L.M., Lazareff, J.A., Mischel, P.S., Cloughesy, T.F., Horvath, S., and Kornblum, H.I. 2009. Neurosphere formation is an independent predictor of clinical outcome in malignant glioma. *Stem Cells* 27(4): 980-987.
- Lapidot, T., Sirard, C., Vormoor, J., Murdoch, B., Hoang, T., Caceres-Cortes, J., Minden, M., Paterson, B., Caligiuri, M.A., and Dick, J.E. 1994. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. *Nature* 367(6464): 645-648.
- Li, X. and Ren, J. 2008. [Isolation of CD44+/CD24 -/low and side population cells from MDA-MB-453 cells and the analysis of their activation of Wnt and Notch pathway]. *Beijing Da Xue Xue Bao* 40(5): 471-475.
- Maeda, S., Shintani, H., Kurahara, H., Mataka, Y., Maemura, K., Sato, M., Natsugoe, S., Aikou, T., and Takao, S. 2008. CD133 expression is correlated with lymph node metastasis and vascular endothelial growth factor-C expression in pancreatic cancer. *Br J Cancer* 98(8): 1389-1397.
- Marcato, P., Dean, C.A., Giacomantonio, C.A., and Lee, P.W. 2009. Oncolytic reovirus effectively targets breast cancer stem cells. *Mol Ther* 17(6): 972-979.
- Maynard, S., Swistowska, A.M., Lee, J.W., Liu, Y., Liu, S.T., Da Cruz, A.B., Rao, M., de Souza-Pinto, N.C., Zeng, X., and Bohr, V.A. 2008. Human embryonic stem cells have enhanced repair of multiple forms of DNA damage. *Stem Cells* 26(9): 2266-2274.
- Morimoto, K., Kim, S.J., Tanei, T., Shimazu, K., Tanji, Y., Taguchi, T., Tamaki, Y., Terada, N., and Noguchi, S. 2009. Stem cell marker aldehyde dehydrogenase 1-positive breast cancers are characterized by negative estrogen receptor, positive human epidermal growth factor receptor type 2, and high Ki67 expression. *Cancer Sci* 100(6): 1062-1068.
- O'Brien, C.A., Pollett, A., Gallinger, S., and Dick, J.E. 2007. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature* 445(7123): 106-110.

- Pece, S., Tosoni, D., Confalonieri, S., Mazzarol, G., Vecchi, M., Ronzoni, S., Bernard, L., Viale, G., Pelicci, P.G., and Di Fiore, P.P. 2010. Biological and molecular heterogeneity of breast cancers correlates with their cancer stem cell content. *Cell* 140(1): 62-73.
- Rasheed, Z.A., Yang, J., Wang, Q., Kowalski, J., Freed, I., Murter, C., Hong, S.M., Koorstra, J.B., Rajeshkumar, N.V., He, X., Goggins, M., Iacobuzio-Donahue, C., Berman, D.M., Laheru, D., Jimeno, A., Hidalgo, M., Maitra, A., and Matsui, W. 2010. Prognostic significance of tumorigenic cells with mesenchymal features in pancreatic adenocarcinoma. *J Natl Cancer Inst* 102(5): 340-351.
- Razmkhah, M., Jaberipour, M., Erfani, N., Habibagahi, M., Talei, A.R., and Ghaderi, A. 2011. Adipose derived stem cells (ASCs) isolated from breast cancer tissue express IL-4, IL-10 and TGF-beta1 and upregulate expression of regulatory molecules on T cells: do they protect breast cancer cells from the immune response? *Cell Immunol* 266(2): 116-122.
- Rich, J.N. and Bao, S. 2007. Chemotherapy and cancer stem cells. *Cell Stem Cell* 1(4): 353-355.
- Singh, S.K., Clarke, I.D., Terasaki, M., Bonn, V.E., Hawkins, C., Squire, J., and Dirks, P.B. 2003. Identification of a cancer stem cell in human brain tumors. *Cancer Res* 63(18): 5821-5828.
- Smith, J., Ladi, E., Mayer-Proschel, M., and Noble, M. 2000. Redox state is a central modulator of the balance between self-renewal and differentiation in a dividing glial precursor cell. *Proc Natl Acad Sci U S A* 97(18): 10032-10037.
- Ulasov, I.V., Nandi, S., Dey, M., Sonabend, A.M., and Lesniak, M.S. 2011. Inhibition of Sonic hedgehog and Notch pathways enhances sensitivity of CD133(+) glioma stem cells to temozolomide therapy. *Mol Med* 17(1-2): 103-112.
- Wang, H., Lathia, J.D., Wu, Q., Wang, J., Li, Z., Heddleston, J.M., Eyler, C.E., Elderbroom, J., Gallagher, J., Schuschu, J., MacSwords, J., Cao, Y., McLendon, R.E., Wang, X.F., Hjelmeland, A.B., and Rich, J.N. 2009. Targeting interleukin 6 signaling suppresses glioma stem cell survival and tumor growth. *Stem Cells* 27(10): 2393-2404.
- Weng, D., Song, B., Durfee, J., Sugiyama, V., Wu, Z., Koido, S., Calderwood, S.K., and Gong, J. 2010. Induction of cytotoxic T lymphocytes against ovarian cancer-initiating cells. *Int J Cancer*.
- Wu, Y. and Wu, P.Y. 2009. CD133 as a marker for cancer stem cells: progresses and concerns. *Stem Cells Dev* 18(8): 1127-1134.
- Yilmaz, O.H., Valdez, R., Theisen, B.K., Guo, W., Ferguson, D.O., Wu, H., and Morrison, S.J. 2006. Pten dependence distinguishes haematopoietic stem cells from leukaemia-initiating cells. *Nature* 441(7092): 475-482.
- Yu, F., Yao, H., Zhu, P., Zhang, X., Pan, Q., Gong, C., Huang, Y., Hu, X., Su, F., Lieberman, J., and Song, E. 2007. let-7 regulates self renewal and tumorigenicity of breast cancer cells. *Cell* 131(6): 1109-1123.
- Zeng, Z., Shi, Y.X., Samudio, I.J., Wang, R.Y., Ling, X., Frolova, O., Levis, M., Rubin, J.B., Negrin, R.R., Estey, E.H., Konoplev, S., Andreeff, M., and Konopleva, M. 2009. Targeting the leukemia microenvironment by CXCR4 inhibition overcomes resistance to kinase inhibitors and chemotherapy in AML. *Blood* 113(24): 6215-6224.

- Zhang, M., Song, T., Yang, L., Chen, R., Wu, L., Yang, Z., and Fang, J. 2008. Nestin and CD133: valuable stem cell-specific markers for determining clinical outcome of glioma patients. *J Exp Clin Cancer Res* 27: 85.
- Zhao, C., Chen, A., Jamieson, C.H., Fereshteh, M., Abrahamsson, A., Blum, J., Kwon, H.Y., Kim, J., Chute, J.P., Rizzieri, D., Munchhof, M., VanArsdale, T., Beachy, P.A., and Reya, T. 2009. Hedgehog signalling is essential for maintenance of cancer stem cells in myeloid leukaemia. *Nature* 458(7239): 776-779.
- Zhou, S., Schuetz, J.D., Bunting, K.D., Colapietro, A.M., Sampath, J., Morris, J.J., Lagutina, I., Grosveld, G.C., Osawa, M., Nakauchi, H., and Sorrentino, B.P. 2001. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. *Nat Med* 7(9): 1028-1034.

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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.

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