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Targeting Signal Pathways Active in Leukemic Stem Cells to Overcome Drug Resistance

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1. Introduction

Acute myeloid leukemia (AML) is a serious and often lethal disease. Over the last several decades, although there have been advances in the treatment of AML, however, the survival of patients with AML has not changed significantly[1-3]. Most of patients will relapse within two years and ultimately died of the disease[4]. The scarce efficacy of current treatments indicates the resistance of leukemia cells to cytotoxic agents and even immunotherapy and survival from the treatment without major injure. Thus, there is a desperate need for new effective therapies for AML patients.

The hematopoietic system is thought to originate from pluripotent hematopoietic stem cells (HSC) capable of producing a hierarchy of downstream multilineage and unilineage progenitor cells that differentiate into mature cells[5]. HSCs have self-renewal and can differentiate into multiple lineages[6]. HSC self-renewal is either symmetrical, producing two daughter HSCs, or asymmetrical, producing an identical HSC and a progenitor with diminished self-renewal capacity but with the ability to enact clonal expansion[7]. It is also believed that leukemia is initiated and maintained by a rare population of leukemia cells with stem cell properties similar to those of normal HSCs known as leukemic stem cell (LSC). The concept that a rare population of the tissue stem cell maybe the cellular origin of cancer was proposed almost 150 years ago. Approximately 50 years ago the concept that only a small subpopulation of so-called LSCs may be connected to the maintenance and evolution of myeloid leukemia emerged. Conclusive evidences for the existence of LSCs come from the function assay using SCID-leukemia and NOD/SCID-leukemia xenotransplantation models in which mice were transplanted with leukemic cells from the bone marrow and peripheral blood of AML patients. These studies demonstrated that the leukemic grafts were highly representative of the original patients disease and the SCID/leukemia initiating cell presented at a frequency of 0.2-100/10^6 mononuclear cells[8]. More recently, this principle has also been extended to other tumors, such as breast, brain, prostate, pancreas, colon, lung, liver, and head and neck tumors[9-15]. Due to a high degree of phenotypic and functional similarity, it has been hypothesized that most human leukemias arise from transformation of HSCs. However, other studies have shown that transduction of the MLL-ENL or MOZ-TIF2 fusion genes into HSCs, common myeloid progenitors, and granulocyte-macrophage progenitors resulted in the identical leukemia. These results indicate that committed progenitors may acquire self-renewal capability and transform into LSCs[16,17].

LSCs have been reported to be the only tumorigenic population and play a central role in relapse because of the failure of current chemotherapy to eradicate them. The existence of LSC highlights the critical need for the new therapeutic strategies to directly target the LSC population for ultimately curing leukemia.

Basing on the solid evidences that leukemia is stem cell disease, the view of drug resistance changes. It is believed that LSCs are naturally resistant to conventional chemotherapy and serve as the main mediators of drug resistance[18-22]. Moreover, it is accepted that drug resistance is governed by the mutations that confer protection mechanism through modulation of cell survival factors. To that end, a number of signal pathways involved in LSCs viability and survival, namely the Hedgehog, Ras, FLT3, PI3K/AKT, NF-κB, mTOR are aberrantly regulated in LSCs. Because of their wide-ranging biological effects, deregulation one or more of these pathways may give rise to a failure of current chemotherapy. Others and we have long been interested in exploring the mechanisms of drug resistance of LSCs influenced by these cell survival pathways and molecular interaction networks. Thus we can determine the critical elements and the general rules driving the network to guide the use of specific inhibitors of a given pathway. This review will focus on the drug resistance of LSCs and the signal pathway and their potential cross-talk. (Figure1).

2. Leukemic stem cells and drug resistance

According to the hierarchy model, Leukemia consists of a heterogeneous population, within which only a rare population of LSCs sustains the disease. LSCs share some properties of normal stem cells, Such as self-renewal potential, proliferation and essential property of self-protection. The whole drug resistance concept has been revised incorporating the LSC paradigm. LSCs play the key role in the drug resistance of leukemia. LSCs present in the original tumour mass and survive chemotherapy, whereas the committed but variably differentiated cells are killed. Several mechanisms make LSCs more resistant to conventional chemotherapeutic agents. For example, LSCs exhibited higher expression of drug resistance proteins, such as lung resistance-related protein (LRP) and multiple resistance-associated proteins (MRP)[23]. Recent work from our group suggests that LSCs are resistance to mitoxantrone and daunorubicin via up-regulation of ABCG2 and MRP. Another group of investigators have demonstrated that LSCs isolated from human leukemia are predominantly in the G0 phase of the cell cycle that made it resistance to cell cycle specific chemotherapeutic agents such as Ara-c[24]. Furthermore, LSCs have capacity for DNA repair. As a result, at least some of LSCs can survive chemotherapy including DNA damage agents such as alkylating agents[25]. Moreover, LSCs are resistant to chemotherapy through impaired apoptosis pathway[26-28]. Our unpublished data show that LSCs up-regulated Bcl2 protein and Bcl2 siRNA enhanced the sensitivity of LSCs to mitoxantrone cytotoxicity. The properties of LSCs suggest that the current chemotherapy drugs will not be curative. Current studies focus on a number of signaling pathways that regulate chemoresistance of LSCs through survival pathway. We will outline some of these pathways and their potential in drug resistance.

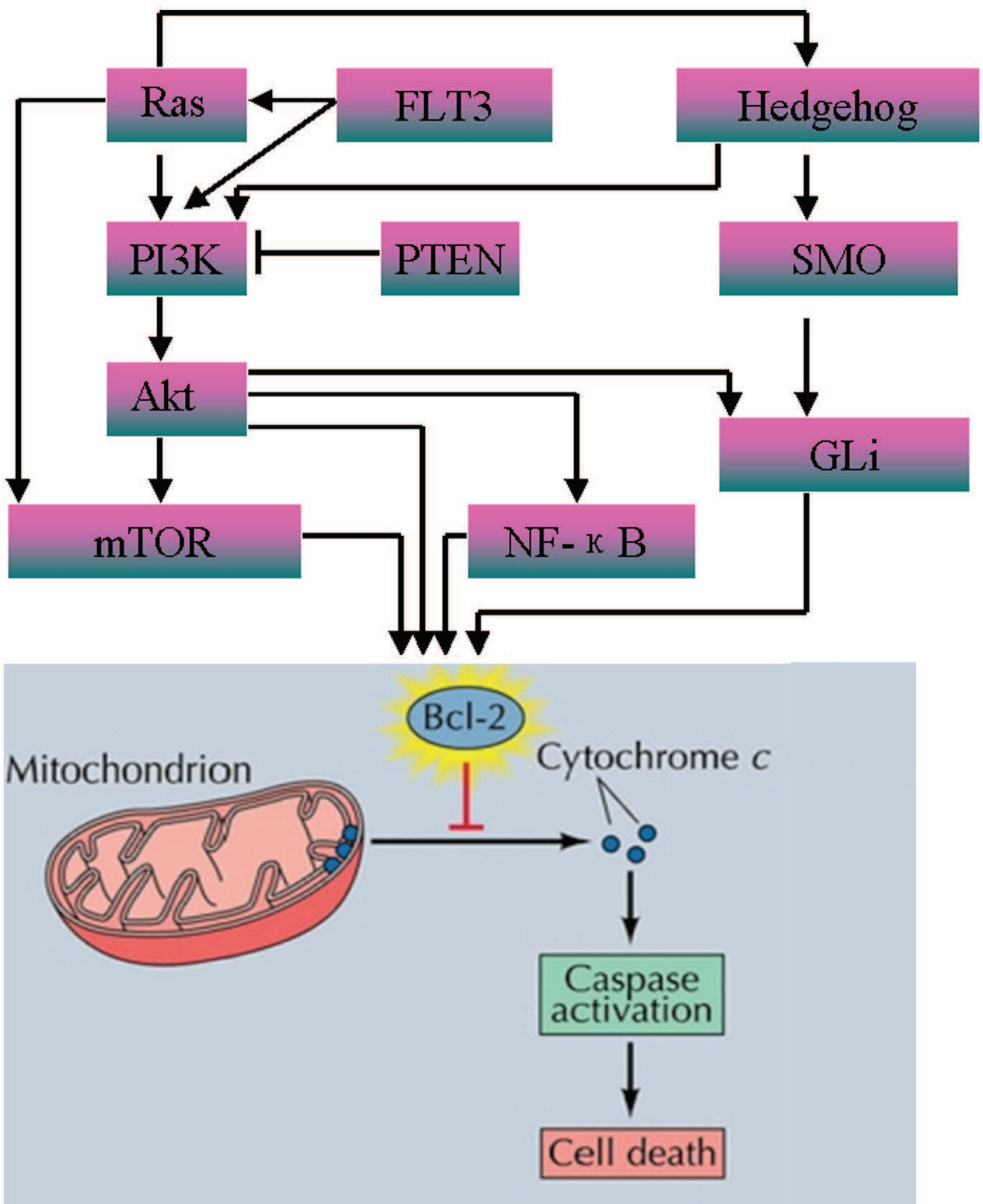

Fig. 1. Signal transduction pathways important in leukemic stem cells

3. Hedgehog pathway

'Hedgehog' (HH) molecules are secretory signaling proteins that were first discovered in Drosophila. Three HH homologs have been identified in humans including Sonic hedgehog (SHH), Indian hedgehog (IHH) and Desert hedgehog (DHH). Secreted hedgehog molecules bind to and inhibit the cell surface receptor Patched 1 protein on target cells. Smoothened is a transmembrane protein primarily located in the membrane endosomes. It is proposed that the endogenous agonist of SMO is a small intracellular molecule transported out of the cell by PTCH1, a mechanism preventing binding to SMO. Upon binding an HH ligand, PTCH1 is internalized and inactivated so that the endogenous agonist of SMO accumulates in cytoplasm and activates SMO. Activated SMO causing release of the Gli family of transcription factors (Gli-1, -2, and -3), which can then translocate into the nucleus and activate gene transcription that control the cell cycle, signal transduction, and apoptosis. HH pathway, which is one of the main pathways that control stem cell fate, self-renewal and maintenance, plays a central role in drug resistance of cancer cells[29-33].

HH pathway makes LSCs more resistance to chemotherapy through several mechanisms. First, HH controls the cell cycle fate during cell proliferation. Activation of the HH pathway may promote tumor repopulation after chemotherapy and contribute to chemotherapy resistance in cancers. Second, HH signaling may act as upstream of other signal pathway that regulate self-renewal of stem cell. The loss of HH signaling by genetically disrupting Smo resulted in the inhibition leukemic stem cells and prolonged survival. Thus, HH pathway activity is required for maintenance of leukemic stem cells and dictates LSC fate decisions[34,35]. It raises the possibility that the drug resistance and disease relapse might be avoided by targeting this essential stem cell maintenance pathway. Furthermore, HH pathway contributes to the survival of tumor progenitor cells by opposing the activation of both intrinsic and extrinsic apoptosis cascades. Gli-1 is considered the positive transcriptional transactivator in the Shh pathway. Gli-1 was also able to induce endogenous Bcl2 expression. Moreover, Hh signal also up-regulats the expression of Bcl2 through activated PI3K and AKT. We have been demonstrated that Bcl2 was high expression via up-regulation Gli in LSCs. These findings suggest that in addition to regulating proliferation of tumor progenitor cells, HH signaling may support the survival of tumor progenitor cells. Moreover, HH pathway regulates the expression of two ABC proteins, multidrug resistance protein-1 and breast cancer resistance protein and leads to the efflux of various chemotherapeutic drugs[36].

4. Ras signaling pathway

Ras, the protein product of the ras proto-oncogenes, is localized to the inner surface of the cell membrane, in which it becomes functional in tranducing the mitogenic signals of tyrosine kinase receptors that regulate diverse signaling pathways involved in cell growth, differentiation and apoptosis. The family of ras includes N-ras, K-ras, and H-ras. Ras mutations are most commonly associated with cancer including leukemia. Transplantation of highly purified hematopoietic stem cells (HSCs) and myeloid progenitors identified HSCs as the primary target for the oncogenic Kras mutation. Karyotypic analysis further indicated that secondary genetic hit(s) target lineage-specific progenitors rather than HSCs for terminal tumor transformation into leukemic stem cells. Thus, the cellular mechanism underlying oncogenic Kras-induced leukemogenesis, with HSCs as the primary target by the oncogenic Kras mutations and lineage-committed progenitors as the final target for cancer stem cell transformation[37]. Once activated, ras is able to trigger several signaling including Raf-Mek-Map kinase pathway[38], FMS-like tyrosine kinase 3 (FLT3) pathway[39], and phosphoinositide 3-kinase (PI3K)/ cytoplasmic protein kinase B (AKT) pathway. The potential relevance of the Raf-MEK-MAP kinase pathway to abnormal hematopoiesis is highlighted by the ability of a constitutively activated mutant Raf to eliminate growth factor dependence of hematopoietic cells. Ras also activates the PI3K pathway, which can result in suppression of apoptosis by directly activating AKT. The PI3K/AKT pathway is important for relaying survival signals in hematopoietic cells by Ras. Mutations of ras in LSCs result in refractory and relapse of leukemia[40].

5. FMS-like tyrosine kinase 3 signaling

The FLT3 gene, also known as fetal liver tyrosine kinase 2 (PLK2), encodes a membrane-bound receptor tyrosine kinase (RTK). FLT3 have been shown to play a role in leukemogenesis. In most examined patient cohorts, FLT3 is consistently associated with unfavorable prognosis and relapse of AML patients. In recent studies, it was also shown that FLT3 was expressed in LSCs. FLT3 activates special anti-apoptotic signal by up-regulating Bcl2 family. In additionally, FLT3 mediates drug resistance through activating PI3K/AKT survival pathway[41-43]. Interestingly, simultaneous mutations of ras and FLT3 are rare, suggesting functional overlap between the two.

6. The PI3K/AKT cell survival pathway

Oncogenic ras and FLT3 have been shown to activate PI3Ks in AML. Moreover, activating mutations of c-Kit tyrosine kinase receptor, PI3K p110β and/or δ overexpression, low levels of PP2A, autocrine/paracrine secretion of growth factors such as IGF-1 and VEGF also result in PI3K/Akt signaling up-regulation. PI3Ks are heterodimers with separate regulatory (p85) and catalytic (p110) subunits. PI3K activation may be due to the close proximity of p110 to its lipid substrates in the membrane and relief of the inhibitory effect of p85 on p110 kinase activity upon RTK-p85 interaction. Direct binding of p110 to activating ras proteins following growth factor stimulation further stimulates PI3K activity. The increasing evidences have supported that PI3K plays critical roles in the chemotherapy-resistance in LSCs. Furthermore, the downstream effector of PI3K, AKT (a subfamily of the serine/threonine protein kinases), have been associated with the cell growth and survival of cancer stem cell[44-46]. Three AKT isoforms (AKT1, AKT2, and AKT3) have been identified, all of which share an N-terminal PH domain, with central kinase domain, and a serine/threonine-rich C-terminal region. The intermediates of the PI3K/AKT survival pathway are activated in LSCs and high level of PI3K/AKT has been linked to poor prognosis and chemoresistance. Tumor suppressor gene Phosphatase and tensin homolog (PTEN) is negative regulator of AKT pathway. Mutations or losses of PTEN have been found in a large number of cancers including brain, breast, prostate and leukemia[47,48]. Loss of PTEN function results in AKT activating and cancer resistance to conventional therapy and a relapse following initial regression. Shoman etal have reported a strong correlation between down-regulation of PTEN expression and failure to respond to tamoxifen treatment in estrogen receptor-positive tumors[49]. In the hematopoietic system, recently studies show that conditional deletion of PTEN result in leukemia[47]. Thus PI3K/Akt pathway plays the critical role in the LSC resistance to a number of anti-tumor agents. PI3K/AKT pathway controls the expression of the membrane ATP binding cassette (ABC) transporter, multidrug resistance-associated protein 1 to extrude chemotherapeutic drugs. Furthermore, PI3K/AKT activating defect the apoptosis pathway of LSC to protect LSC from chemotherapy.

7. NF-κB signaling pathway

Nuclear factor of kB (NF-κB) is a family of closely related dimeric transcription factors that bind to the kB sites. NF-κB is an inducible and ubiquitously expressed transcription factor that regulates cell survival, inflammation, and differentiation. It is becoming increasingly clear that NF-κB signaling plays critical roles in cancer development and progression. Cancer cells especially poorly differentiated cancer cells show activated NF-κB in the nucleus, suggesting that activated NF-κB regulates its downstream genes to promote cancer cell growth. The exciting results have shown that NF-κB is constitutively activated in LSCs whereas it is strikingly not activated in their normal counterpart, suggesting this transcription factor is preferentially in LSCs[50]. This provides a possible that specific target the LSCs while spare the normal HSCs. More importantly, it has been well known that many chemotherapeutic agents such as neucleoside analogs and anthracyclines induce the activity of NF-κB, which causes drug resistance in cancer cells[51]. Therefore, targeting NF-κB would be promising strategy to overcome the drug resistance of LSCs.

8. Strategies to overcome drug resistance through regulating survival signal pathways of LSCs

The concept that leukemia is a stem cell disease has the potential to change the view of drug resistance. As the understanding of the signaling pathway involved in the survival and chemoresistance of LSCs, it is likely to identify new mechanism-based effective therapy directed at LSCs to cure leukemia.

9. Targeting of hedgehog pathway

As indicated above, The HH pathway is activated in LSCs and plays the central role in drug resistance. Cyclopamine is a natural steroidal alkaloid that inhibits the HH pathway by directly binding and suppressing the Smo receptor. Recent studies showed that cyclopamine inhibits various human malignancies including breast, prostate, liver, pancreas, small cell lung cancer, and glioma[52,53]. Importantly, continuous cyclopamine eliminated PC3 cancer-initiating cells. Similarly, cyclopamine treatment also counteracts the expansion of multiple myeloma (MM) stem cell and decrease the number of MM stem cell[54]. Furthermore, blocking the HH signal pathway by Gli siRNA or humanized anti-SHH antibodies has been shown to induce apoptosis in a wide variety of tumors through activation of intrinsic and extrinsic apoptosis cascades and resensitized the chemoresistant CSCs. Recently, Kobune et al showed that HH signaling is active in CD34+ leukemic cells. These CD34+ cells express the downstream effectors glioma-associated oncogene homolog Gli-1 or Gli-2, indicative of active HH signaling. Moreover, inhibition of HH signaling with the naturally derived Smoothened antagonist cyclopamine, endogenous HH inhibitor hedgehog-interacting protein or anti-hedgehog neutralizing antibody induced apoptosis of these CD34+ cells exhibited resistance to cytarabine (Ara-C). Furthermore, combination with cyclopamine significantly reduced drug resistance of CD34+ cells to Ara-C[55]. Taken together, these studies suggest that selective target HH pathway may lead to more effective cancer therapies.

10. Targeting of the ras pathway

The emerging evidences have shown that increase in ras activity may be an early step in the deveplopment of leukemia. The preclinical concept of farnesyltransferase blockade as a targeted therapy against oncogenic Ras has clearly evolved with the recognition that many proteins involved signaling pathways in tumor cells undergo farnesylation. Several farnesyltransferase inhibitors as monotherapy in cancer in vitro or in clinical trial demonstrate encouraging responses and good tolerability. BMS-214662, a cytotoxic farnesyltransferase inhibitor, previously reported to selectively kill nonproliferating subpopulation in tumor cells. Recent studies have also been shown that BMS-214662, alone or in combination with imatinib or dasatinib, effectively induced apoptosis of resistant CML stem cells and potently induced apoptosis of both proliferating and quiescent CML stem/progenitor cells with less than 1% recovery of Philadelphia-positive long-term culture-initiating cells. Normal stem/progenitor cells were relatively spared by BMS-214662[56]. Our unpublished data also showed that manumycin enhanced mitoxantrone-induced apoptosis in LSCs. These data suggest that RAS contribute to drug resistance of LSC and are potential targets for new therapeutic strategies. Farnesyltransferase inhibitor may offer potential for eradication of LSC.

11. Regulation of the PI3K/AKT pathway

The increasing evidence has shown that activated FLT3, PI3K/AKT pathway is critical for drug resistance of LSCs, therefore, downregulation of FLT3, PI3K, and AKT could sensitize LSCs to chemotherapy and overcome drug resistance. The PI3K/ AKT pathway may be inhibited with PI3K (LY294002, PX-866), PDK1 (OSU-03012, celecoxib), AKT (A-443654, perifosine, tricribine) or downstream mTOR inhibitors such as rapamycin and modified rapamycins (CCI-779 andRAD001). Inhibition of the PI3K/AKT pathway by the specific pathway inhibitors LY294002 leads to a dose-dependent decrease in survival of LSCs[57]. LY294002 also significantly reduced the survival of SP fraction within MCF7 cells and decrease cancer stem-like cells[58]. Wortmannin are able to inhibit CML and AML cell proliferation and to synergize with targeted tyrosine kinase inhibitors. Additionally, dual PI3K/PDK-1 Inhibitor BAG956 have been demonstrated effective against leukemia[59]. Recently, publication by Yilmaz and colleagues demonstrated that mammalian target of rapamycin (mTOR) inhibition with rapamycin not only depleted leukaemia-initiating cells but also restored normal HSC function[47]. In conclusion, inhibition of this pathway leads to an increase in apoptosis in LSCs, and that it potentiates the response to cytotoxic chemotherapy.

12. Targeting of NF-κB Signaling Pathway

Previous studies have demonstrated that NF-κB, a known regulator of growth and survival, is constitutively active in LSCs but not in normal hematopoietic stem cells (HSCs). These suggest that LSC-specific targeted therapy should be feasible using a variety of strategies. Guzman etal have previously shown that a combination of the proteasome inhibitor MG-132 and the anthracycline idarubicin was sufficient to preferentially ablate human LSCs in vitro while sparing normal HSCs[51]. These studies demonstrate that LSC-specific targeting can be achieved. Recently, Guzman etal also demonstrated that the single plant-derived compound parthenolide (PTL) effectively eradicates AML LSCs by inducing robust apoptosis via induce oxidative stress and inhibit NF-κB while sparing normal HSCs[60]. These properties make these compound an attractive agent for clinical evaluation. However, the poor solubility of PTL makes pharmacologic use of the compound difficult. Thus, more recently, orally bioavailable Dimethylamino- parthenolide (DMAPT) induces rapid death of primary human LSCs from both myeloid and lymphoid leukemias, and is also highly cytotoxic to bulk leukemic cell populations[61]. Servida etal also reported that PS-341 induced apoptosis in leukemia progenitor cells[62]. In an effort to expand strategies for selectively targeting LSCs, the recent study has been shown that the compound TDZD-8 (4-benzyl,2-methyl,1,2,4-thiadiazolidine, 3,5 dione), which was originally developed as a non-ATP competitive inhibitor of GSK-3β, was strongly and selectively cytotoxic to multiple types of primary leukemia cells, as well as phenotypically and functionally defined LSCs. The cytotoxicity is associated with a rapid loss of membrane integrity, induction of oxidative stress, and inhibition of several signal transduction pathways including NF-κB and FLT3[63].

13. Conclusions

Altogether, these recent investigations have revealed that leukemia originate from leukemic stem cells. The leukmic stem cells can provide critical functions in leukemic initiation and progression and recurrent disease states. LSCs are often resistant to standard chemotherapy, which make leukemia refractory and relapse. The concept of leukemia as a stem cell disease has the potential to change significantly the view of the problem of drug resistance. Research efforts to discover the specific signal pathway serving to resistance of LSCs should lead to more effective and safe leukemia therapeutic treatments for ultimately curing leukemia. Future studies will focus on the identifying and targeting of critical signal pathway to overcome the drug resistance of LSCs for improvement of the current leukemia treatments.

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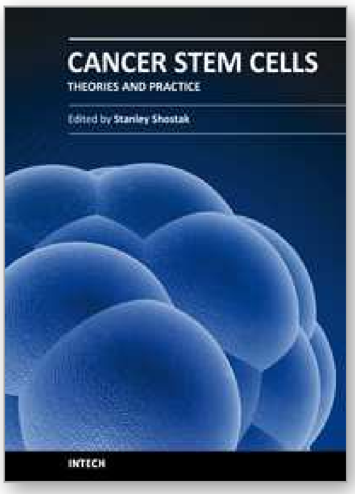

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Cancer Stem Cells Theories and Practice does not 'boldly go where no one has gone before!' Rather, Cancer Stem Cells Theories and Practice boldly goes where the cutting edge of research theory meets the concrete challenges of clinical practice. Cancer Stem Cells Theories and Practice is firmly grounded in the latest results on cancer stem cells (CSCs) from world-class cancer research laboratories, but its twenty-two chapters also tease apart cancer's vulnerabilities and identify opportunities for early detection, targeted therapy, and reducing remission and resistance.