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Review Article

Cancer stem cells or aberrant stem cells: The targetable target of cancer

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ABSTRACT

A new kind of cells known as cancer stem cells (CSCs) is making their presence among the different types of cancer cells. Endowed with the properties of self-renewal and differentiation, they abet the development, growth, metastasis and heterogeneity of cancer cells. Increasingly making their presence by way of resisting the action of chemo and radiotherapy, they are proving havoc in the management of cancer. Great amount of work is going on to deal with them.

Keywords: Cancer stem cells; division; source; targeting; resistance; therapy; chemotherapy.

INTRODUCTION

Normally body cells divide to generate, maintain, and repair tissue. Body cells divide when they get signals from neighboring cells or growth hormones or chemicals such as cyclins etc. But in cancer, cells go on dividing irrespective of presence or absence of growth factors (Microscope imaging station, 2010). Further, cancer cells migrate from their original site and form new masses at distant sites of the body. Basically, cancers originate from normal cells that gain the ability to proliferate abnormally and finally turn malignant. Afterwards, these malignant cells grow clonally into tumors and finally have the ability to metastasize (Dayem AA et al., 2010). Hence cancer can be viewed as a group of diseases that are characterized by uncontrolled cellular growth, cellular invasion into adjacent tissues, and the potential to metastasize if not treated at a sufficiently early stage (Are stem cells involved in cancer, 2010). Cancer cell populations are heterogeneous in nature; exhibit hierarchies of cellular populations with a range of differentiation phenotypes with specific morphologies and lineage markers. Broadly, cancer cells are characterized by two cell types' tumorigenic cells and non tumorigenic cells. The tumorigenic cells are a specific type of cells with pivotal role in cancer initiation, relapse and progression (Rich JN et al., 2007, Ghosh N et al., 2009) tumorigenic potential are termed as Cancer Stem Cells (CSCs).

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CANCER STEM CELLS: KEY CELLS OF CANCER

Cancer tissue is compiled by various types of cells, at different stages of differentiation and with different phenotypes (Sukowati CHC et al., 2010). Cancer Stem Cells have been identified and isolated in cancer cells of the hematopoietic system, breast, brain, prostate, colon, head and neck, and pancreas. CSCs is a predetermined cell population with the ''stem cells'' phenotype, enable this cell to flourish the cancer, while other cells of the same cancer are incapable of self-renewal (Zou GM et al., 2008).CSCs are able to self-renew, differentiate, able to initiate tumor and are resistant to conventional chemotherapy or radiation therapy (Tang C et al., 2007, Sell, S 2009).

The defining characteristic of normal stem cells are proliferation, self renewal, differentiation, expression of stem cell markers, decreased rate of apoptotic death, active telomerase expression. However the particular group of stem cells found in tumors is found to display aberrant patterns of proliferation (extensive), self -renewal (unlimited) and differentiation (abnormal multipotency) (Sukowati CHC et al., 2010, Zou GM et al., 2007, Zou GM et al., 2008, Zhu Z et al., 2010, Mimeault M et al., 2006, Singh N et al., 2010, Fujii H et al., 2009, Wicha MS et al., 2006).Since these are found in cancerous tissues these have been termed as Cancer Stem Cells or can be called as Aberrant Stem Cells. CSCs are present in small numbers in tumors. CSCs constitute about 1% of the tumor cells making them difficult to study and analyze (Lou H et al., 2007). Cancer is now increasingly being recognized as a stem cell disease (Vermeulen L et al., 2008, Macingova Z et al., 2008).

MULTIPLICATION OF NORMAL vs CANCER TISSUE

The CSC theory proposes that tumors have a cellular hierarchy similar to their normal tissue counterpart

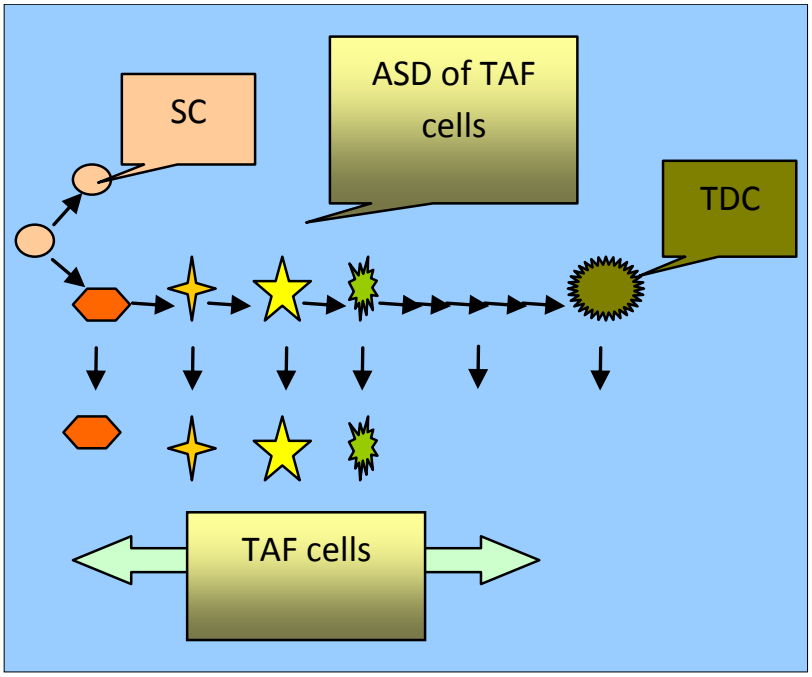

Figure 1: Asymmetric division of Normal stem cells: The normal asymmetric cell division of TAF cells to ultimately form TDC. SC-Stem Cells, TAF-Transit Amplifying Cell, TDC-Terminally Differentiated Cells, ASD-Asymmetric Division of cells

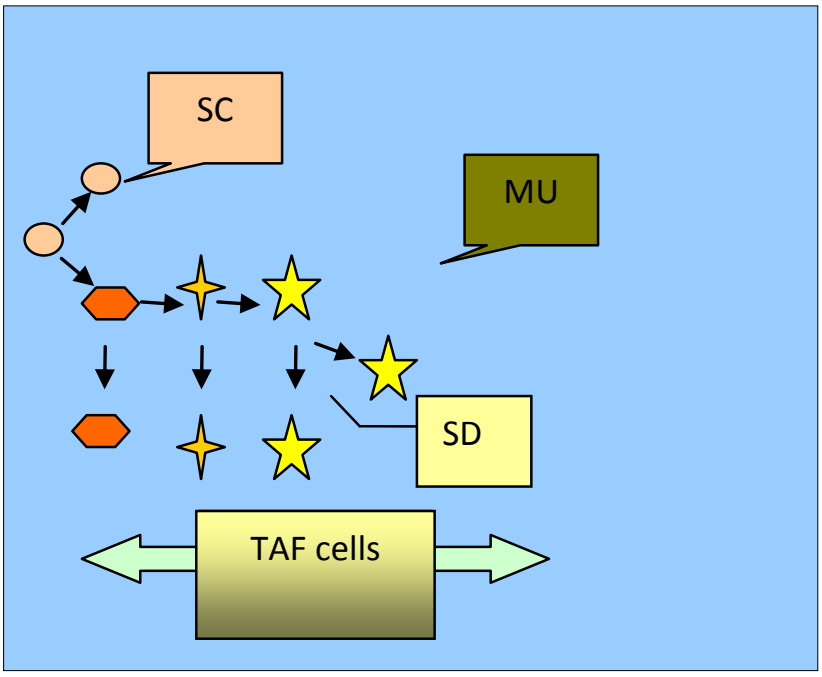

Figure 2: Symmetric division of CSCs: After mutation, TAF cells undergo symmetric division instead of asymmetric division. Hence, there is no formation of TDCs. SC-Stem Cells TAF-Transit Amplifying cell, MU- Mutation of TAF cells SD-symmetric division of cells

(Lobo NA et al., 2007).Cancers, like normal organs, are maintained by a hierarchical organization that includes slowly dividing stem cells, rapidly dividing Transit Amplifying Cells (TAF or precursor cells or progenitor cells), and differentiated cells or mature cells (Kondo T et al., 2004).

Stem cells are characterized by two main properties. Self-renewal and differentiation (Rubio D et al., 2005). This is accomplished by means of asymmetric divisions where by two daughter cells are formed. Out of the two daughter cells formed, one is the replica copy of stem cell while the other is little more differentiated in nature i.e. tissue determined cell or the progenitor cell. This tissue determined cell is Transit Amplifying Cell

(TAF) or the progenitor cell. TAF undergoes more rounds of asymmetric divisions whereby they give rise to more differentiated cell at each end of each asymmetric division as well as maintaining their own replica copies. Ultimately the result of these asymmetric divisions is a progeny of cells, which are well differentiated but are no longer capable of proliferating i.e. undergoing divisions. These are the Terminally Differentiated Cells (TDCs) or the mature cells of the tissue, which ultimately die. These worn off cells are replaced by more TDCs by the divisions of TAFs (Figure 1). The stem cells of the normal tissue usually remain dormant but they are called into action if there is requirement to replace lost tissue or to increase the number of cells in response to stress such as loss of blood or injury to blood vessel (Sell S 2007). Cancer as a cellular process is caused by a failure of the cells in the adult tissues to mature normally, so they instead of terminally differentiating to mature tissue cells, they retain the proliferation potential of embryonic transit-amplifying cells (Sell S 2009).

CSCs like normal stem cells, retain both features of self-renewal and differentiation, but have lost homeostatic mechanisms, which maintain normal cell number (Zhang H et al., 2008). In cancer tissue, stem cells undergo symmetric divisions rather than asymmetric ones i.e. undergo divisions in such a manner that more CSCs are formed. During symmetric divisions the two daughter cells formed are replica copies of one another i.e. stem cells only. This results in the expansion of stem cells resulting in tumorigenisis (Liu S et al., 2005). In cancer due to certain mutations some TAFs switch over from asymmetric divisions to symmetric pattern of divisions. In symmetric divisions the TAFs form two identical copies of themselves while differentiated cell is not formed. Due to this there occurs a maturation block in the tissue concerned where no more differentiated cells or TDCs are generated. This phenomenon is known as Maturation arrest. The outcome is an accumulation of undifferentiated or poorly differentiated cancer transit-amplifying cells (Sell S et al., 1994, Sell S 2007). Depending upon the level of TAFs at which maturation block occur the tumor acquires the heterogeneity of cells. That is why it is said that the tumors are heterogeneous with respect to the cellular lineages (Morrison SJ et al., 2006). Due to mutations TDCs are no longer able to form depending upon the level of tissue where mutations have occurred; the type of cells in the tumor varies (Figure 2).

Self-renewal drives tumorigenesis, whereas differentiation (aberrant in tumors) contributes to tumor phenotypic heterogeneity (Wicha MS et al., 2006). All these factors lead to increase in number of cells in cancer tissue. Thus, cancer can be viewed as disease of deregulated self-renewal (Costa FF et al., 2007). Often the shrinkage in size of tumor is considered as a response to the treatment. Tumor response is usually taken in the clinic as the shrinkage of a tumor by at least 50% (Wicha MS et al., 2006). However, tumor often shrinks in response to the treatment to recur again. This happens because the therapies usually do not target CSCs. Due to this the lost number of cells in tumor mass is again replenished by symmetric and asymmetric mode of divisions of CSCs and TAFs (Sagar J et al., 2007).

SOURCES OF CANCER STEM CELLS

The origin of the CSCs is still not clear. There seems to be wide array of possibilities for the origin of CSCs in the body. Some of the different possibilities are:

1) From S*omatic Cell*: A normal somatic cell can acquire stem cell like properties through mutations in their genes like oncogenes or tumor suppressor genes. Mutations make them go awry. They display altered response towards growth, antigrowth, apoptotic signals. They evade the constraints of replication and start dividing uncontrollably. Due to changes in genetic composition they can undergo metastasis and expand their influence (Li Linheng et al., 2006, Jamil K 2009).

2) From S*omatic Stem Cells*: The malignant transformation of a somatic stem cells into CSCs may arise due to the accumulation of mutations in oncogenes, tumor suppressor genes (TSG) and miss-match repair genes, or genetic modifications such as deletions, amplifications, chromosomal rearrangements and epigenetic alterations like change in DNA methylation pattern, histone modification etc. These might result in the aberrant activation of distinct developmental cascades in somatic stem cells. These activated cells may generate CSCs (Mimeault M et al., 2006, Gil J et al., 2008).

3) From *Embryonic Stem Cells*: Some cancers or some of the pediatric sarcomas (*e.g*., ephroblastoma) or teratocarcinomas are found to develop from very early embryonic stem cell (ESC). These ESCs are "aberrantly" left in the tissues during ontogenesis (Ratazczak MZ et al., 2005).

4) From *Tissue committed stem cells or Pluripotent stem cells* of Bone Marrow: Bone marrow has got mobile pool of Tissue committed stem cells/Pluripotet stem cells. During certain conditions they migrate to other tissues e.g. during chronic inflammation these cells march towards damaged tissue e.g. during chronic inflammation; in an attempt to regenerate the tissue. However, sometimes instead of forming tissue cells, they get revert to a kind of stem cell like cells called CSCs (Ponomaryov T et al., 2000). A mutation that enhances nuclear β-catenin in granulocyte-macrophage progenitor cells causes a blast crisis in some patients with chronic myeloid leukemia It seems these mutated progenitor cells have acquired the ability to self-renew, a feature thought to be specific to stem cells, and to undergo unlimited growth as cancer cells (Jamieson CH et al., 2004, Al-Hajj M et al., 2004, Pardal R et al., 2003, Li Linheng et al., 2006)

5) From D*ifferentiated cells*: Sometimes the differentiated cells of the tissue due to accumulation of mutations may dedifferentiate to become in certain situations CSC. This has been common in some patients who have a family history of cancer and who carry predisposing inborn mutations and chromosomal abnormalities (Ratazczak MZ et al., 2005).

6) From *Deregulated signaling pathways*: Tissue stem cells use multiple signaling pathways to control normal stem cell self-renewal. It has been observed that deregulation of these pathways may lead to extensive proliferation with the development of a CSC Table1. Numerous signaling pathways have been implicated in this process (Spillane JB et al., 2007).

Table 1: Different signaling pathways and associated cancers

Defected Signaling Pathway	Corresponding Cancer
HedgeHog (HH)	Pancreatic, gastric, prostrate, breast (Karhadkar SS et al., 2004, Olsen Cl et al., 2004)
B-catenin/APC gene (adenomatosis polyposis coli)	Colon Cancer (Kolligs FT et al., 2009)
Notch	Cervical cancer , human T-cell acute lymphoblastic leukemia, (Nam Y et al., 2005, Dievart A et al., 1999, Nockoloff BJ et al., 2003, Benson RA et al., 2004)
Bmi-1	Pediatric brain tumors. (Hemmati, H.D et al., 2003)
TGF-β and IL-6	Liver cancer (Tang Y et al., 2008)
PTEN/Akt/PI3K	Prostate cancer stem (Dubrovska A et al., 2009)
Hox gene family	Acute myeloid leukemia (Fischbach NA et al., 2005)

7) From *Dysfunctional Niche*: Stem cells reside in a specialized cellular location known as a niche. The niche provides a microenvironment that maintains the balance between quiescence and self-renewal of the stem cell population. Damage to this niche may lead to malignant transformation of cells. In the mammary gland sustained expression of matrix metalloproteinase-3 (MMP3), a stromal enzyme that destroys basement membrane, can lead to epithelial tumorigenesis It has been revealed that damage of the stromal cells can influence the corresponding epithelial cells toward a neoplastic state. Thus the factors in microenvironment have profound impact on the stem cells status. An imbalance in the control of the niche may lead to malignant transformation of stem cells (Sneddon JB, 2007, Hill RP 2006, Lang SH et al., 2009).

8) From *Mutated Somatic Cells*: It has been recognized that one of the source of CSCs are the fused products of mutated somatic cells with normal stem cells (Schatton T et al., 2007).

IDENTIFICATION OF CANCER STEM CELLS

According to CSCs hypothesis, CSCs are defined by their capacity to self-renew, differentiate, and to initiate tumors in vivo. The first step in eradicating CSCs is their identification and further characterization of CSCs (Behbod F et al., 2004). It will make it possible to study the biological behavior of patient tumors as a function of the CSC paradigm thus allowing a more targeted approach to therapy of individual tumors (Perryman SV et al., 2006).

Many markers in the form of surface antigens and metabolic activities have been identified. Markers for stemness are ascribed in the form of self-renewal pathways, absence of markers of differentiation, elevated levels of detoxifying enzymes, and immortality, which are more or less specific to all stem cells. Thus, a number of markers representing the stemness phenotype are most likely to be employed in identifying and isolating stem cells. CSCs also express similar stem cell markers as normal stem cells (Cheng JX et al., 2009). Stem cells in solid organs can be identified using cell surface markers in the form of cell surface proteins. E.g. specific antibodies directed at these markers have facilitated the isolation of *hematopoietic* stem cells by flow cytometry. Similarly the surface markers of breast CSCs in the form of Lin-CD24-/ESA+ have been elucidated by flow cytometry (Woodward WA et al., 2008).

Various markers useful in the identification of stem cells and CSCs are defined below (Natarajan TG et al., 2007).

i) Markers of stem cells division and immortality: DNA label retention, high telomerase reverse transcriptase expression (TERT), and high telomerase activity.

ii) Protein Markers:

iii) Signaling proteins: WNT, Hedgehog (HH), Notch, Bone Morphogenic Protein (BMP)

iv) Surface antigens in normal CSCs: CD24 (Heat stable antigen), CD29 (Integrin β1), ESA (Ethelial Specific Antigen),CD44, CD49f (integrin α6),CD133(Prominin-1), P63, CD34, NCAM, Thy-1, c-Kit, Flt-3 (Klonisch T et al., 2008).

v) Detoxifying proteins: ABCG2, Aldehyde Dehydrogenase enzyme (ALDH)

a) Communication proteins: Connexin 43and Connexin26 (These are not expressed by stem cells rather are acquired by differentiated cells; thus absent in SCs or CSCs), chemokine receptor protein-CXCR4

b) Transcriptional regulation Proteins: OCT-4, Nanog

Differences in the presence or absence of certain stemness markers may be used to screen one stem cell type from the other or CSC (Natarajan TG et al., 2007).

RESISTANCE OF CANCER STEM CELLS TO CONVENTIONAL CHEMOTHERAPY AND RADIOTHERAPY

The high frequency of relapse following conventional cytotoxic chemotherapy and radiotherapy indicates that CSCs survive standard treatments (Wang JCY et al., 2007). For this purpose, stem cells activate some protective mechanisms that shield them from senescence and cellular stress (Moserle L et al., 2010). Some are discussed below:

1. Quiescent nature: Generally the chemotherapy targets rapidly dividing fraction of tumor cells. But CSCs reminiscent to normal tissue stem cells often exist in a quiescent state for a long time making these cells resistant to conventional chemotherapeutic drugs, which only target dividing cells. Residual CSCs may survive in a quiescent state for many years and result in later tumorigenesis. Therefore, it is conceivable that conventional chemotherapies will only eradicate the bulk of a tumor, sparing the cancer stem or initiating cells. Hence, the focus of the therapies should be targeting of CSC as real root of the problem i.e. cancer (Behbod F et al., 2004).

2. Presence of Drug efflux pumps: Similar to normal stem cells, CSCs express high levels of drug transporter proteins, such as ATP-binding cassette protein family members such as multidrug resistance 1 protein (ABCB1/MDR1/PGY1), multidrug Resistance-associated Protein-1 (ABCC1/MRP1), multidrug resistance-associated protein-3 (ABCC3/MRP3) and breast cancer resistance protein (ABCG2/BCRP/MXR) (Sukowati CHC et al, 2010, Moserle L et al., 2010). The main role of the ABC transporters is to protect the cells from accumulation of toxic compounds since these proteins have the capacity to export drugs and decrease the cell sensitivity to drugs. This explains the close association between ABC transporters proteins and drug resistance (Tang C et al., 2007). This drug-transporting property of stem cells conferred by these ABC transporters is an important marker in the isolation and analysis of haematopoietic stem cells. Because they don't accumulate the fluorescent dyes such as Hoechst 33342 and rhodamine 123, stem cells can be sorted by collecting cells that contain only a low level of fluorescence. These cells are referred to as 'dull cells' or 'side population' (SP) cells (Dean M et al., 2005) as they are found on the side of the distribution of cells on the cell sorter (Lou H et al., 2007).

3. Resistance to apoptosis: Importantly, it appears that that CSCs elaborate anti-apoptotic proteins, which can be limited to CSCs initially, but often rapidly acquired by the bulk of tumor cells at relapse, perhaps due to the genetic instability which distinguishes tumor from normal cells. As a result tumors may initially shrink but subsequently become completely resistant to chemotherapy (Moserle L et al., 2010). Genes that participate in apoptosis, such as Bcl2, nuclear transporter κB (NF-κB), mutated p53, and c-myc, have been shown to be involved in drug resistance of tumor cells (Spillane JB et al., 2007).

4. Efficient/Enhanced DNA repair capacity: Highly efficient DNA repair of CSCs is the most important mechanism in the resistance to chemotherapy and radiotherapy. Currently, more than 130 DNA repair related genes have been found in CSCs. CSCs shows an increase in the activity of DNA repair related enzymes. It was found that the increased capacity for DNA damage repair may be an important reason for resistance to chemotherapy and radiotherapy in CSCs (Yu H et al., 2010).

5. Activation of oncogenes and inactivation of tumor suppressor genes: Activation of oncogenes such as Her-2/neu, bcl-2, bcl-XL, c-myc, ras, c-jun, c-fos, and MDM2 as well as inactivation of tumor suppressor genes like p53 can confer resistance to therapy (Michor F et al., 2006).

6. Hypoxic niches of CSCs: stem cell niches are special microenvironments, supplying all signals for stem cell growth, transformation, and the maintenance of self stability. CSCs are usually located in hypoxic niches, which are surrounded by differentiated tumor cells, myofibroblasts, endothelial progenitor cells, and the extracellular matrix in the microenvironment. A three-dimensional niche structure and a developed extracellular matrix act as a shield for CSCs, and letting them away from the effect of chemotherapy drugs and radiations. In addition, DNA damage induced by radiation requires oxygen and CSCs located in a hypoxic niche are not affected by radiotherapy. Hence any changes in cell microenvironments can be the main reasons for delays in stem cell differentiation (Yu H et al., 2010).

TARGETTING CANCER STEM CELLS

Various studies have thrown light on the resistance of CSCs to normal cancer treatments such as chemotherapy, radiotherapy, anti angiogenesis etc. e.g. CSCs from breast, leukemia, colon and pancreas have been found to resistant to chemotherapeutic drugs such as daunorubicin and Ara-C. So, it is becoming clear that the recurrence of cancer is due to the CSCs fraction of cancer cells which tends to evade the action of therapy either due to their resistance mechanisms prevalent in them or due to their location which tends to protect them from the effects of treatment (Marotta LLC et al., 2009). Drug resistance of CSCs is caused by matrix of factors and there are many strategies for overcoming CSC drug resistance. The drug resistance mechanism of every solid tumor is different, and therapy strategies should be different too. During chemotherapy and radiotherapy for patients with cancer, the drug resis-

tance mechanism of each type of CSC should be taken into account and new factors related to tumor drug resistance should be found, thereby, using the most effective therapy to improve the effects of chemotherapy and radiotherapy, enhance patient quality of life, and prolong survival time. Thus an optimal cancer treatment requires a therapy capable of targeting various unique pathways in CSCs responsible for malignant behaviour (Behbod F et al., 2004, Yu H et al., 2010). Some of the studies focusing on targeting cancer stem cells are:

1. Pten is a tumor suppressor gene whose deregulation has been found to be the cause of initiation of several types of tumors e.g. It has been found that the deletion or down regulation of this gene results in generation of leukemic stem cells. Thus pten can be so targeted to prevent its loss of function or restore its function in the hematopoietic stem cells so as to prevent its malignant transformation into leukemic stem cells (Rossi DJ et al., 2006).

2. One of the promising pathways to induce differentiation potential in CSCs so as to curb their self renewal capacity. One such agent is retinoic acid which has been found to differentiate embryonic stem cells into neuronal stem cells (embryonic stem cells). This strategy of using retinoic acid as a differentiation inducer has been successfully developed for acute promyelocytic leukemia, where retinoic acid has significantly increased the efficacy of chemotherapy (Guan K et al., 2001, Lenz HJ 2008).

3. Polycomb group gene (PcG) is a type of proto oncogene whose expression has deleterious effects on cells e.g. it has been observed that the over expression of Polycomb group gene (PcG) Bmi-1 has a key role in regulating the proliferative activity of normal stem and progenitor cells. BMI-1 promotes self-renewal of stem cells largely by interfering with two central cellular tumor suppressor pathways, p16(Ink4a)/retinoblastoma protein (Rb) and ARF/p53, whose disruption is a hallmark of cancer. Elucidation of the involvement of proto-oncogenes and tumor suppressors in the maintenance of stem cells may be an effective method for eliminating CSCs in variety of cancers (Pardal R et al., 2005, Lessard J et al., 2003, Grienstein E et al., 2007).

4. Vascular niches play an important role in the maintenance and survival of the CSCs. Endothelial cells (ECs) lining the blood vessels promote stem cell survival and cell renewal by releasing certain factors. Studies reveal ECs sought to shelter CSCs from apoptotic stimuli. So any factor which will promote the survival of ECs will in turn support the CSCs e.g. Medulloblastomas over express ERBB2 (Human Epidermal growth factor receptor2), which leads to increased production of vascular endothelial growth factor (VEGF).VEGF is an important regulator of EC survival and proliferation. Consistent with a role for ECs in maintaining CSCs, medulloblastoma cells over expressing ERBB2 formed tumors more rapidly than control cells, and these tumors contained a higher proportion of CSCs. It has been observed that treatment of tumor-bearing mice with inhibitors of either ERBB2 or VEGF signaling depleted blood vessels and caused a dramatic reduction in the number of CSCs and in the growth rate of the tumor. Similar results have been seen with glioblastoma cells, raising the possibility that inhibition of blood vessel growth (Anti-angiogenic therapies) can certainly bear therapeutic implications in various types of cancers (Yang ZJ et al., 2007).

5. Alterations in the apoptotic machinery have been related to chemoresistance in several tumor types. IL-4 (Interleukin 4) promotes resistance to apoptosis in chronic lymphocytic leukemia B cell, enhances anti-apoptotic protein expression in prostate, breast, and bladder tumor cell lines, normal and transformed lymphocytes and enhances proliferation of human pancreatic cancer cells. Blockage of this cytokine is associated with significant growth-inhibitory effect. Experiments have revealed that IL-4 inhibition enhances tumor response to oxaliplatin and 5-FU (Todaro M et al., 2007).

6. Solid tumors are known to contain poorly vascularized regions characterized by nutrient deficit, very low levels of oxygen (hypoxia) and acidic pH (Pouyssegur J et al., 2006, Carmeliet P et al., 2000). Tumor hypoxia has been shown to be with changes in gene expression. The alterations in expression profile are brought about by the transcription factors referred to as hypoxia-inducible factors (HIFs). HIF promotes the activation if certain pathways which are involved in self renewal e.g. Notch pathway and Oct4 (a transcription pathway). As these pathways are also operative in CSCs this suggests that inhibition of HIF activity in the CSCs might block self renewal or may promote differentiation of cells (Keith B et al., 2007).

7. It has been demonstrated that the HSP90 (Heat Shock Protein90) inhibitor 17-DMAG sensitizes breast CSCs to chemotherapy. These *in vitro* experiments have potential clinical implications since HSP90 inhibitors are currently in clinical trials (Wright MH et al., 2008).

8. Another approach to inhibit CSCs from proliferation is the inhibition of deregulated pathways in CSCs. Some such pathways are:

i) Hedgehog signaling pathway operates during embryogenesis and promotes cellular growth and differentiation. In adult tissues it is normally off. However it becomes active in CSCs leading to an uncontrolled cellular division. Recent studies have found inhibitors of this pathway which can down regulate the unrestrained pathway. One example is steroid like molecule Cyclopamine (Lou H et al., 2007, Hombach-Klonisch S et al., 2008).

ii) In the canonical Wnt pathway, is also involved in the cellular proliferation. The deregulation of this pathway is the major cause of self renewal potential of CSCs. Some molecules which are found to be active against this pathway are PKF118-310, ZTM000990 and anti-Wnt1 and anti-Wnt2 monoclonal antibodies (Hombach-Klonisch S et al., 2008).

iii) Over expression of active form of Notch1 results in the inhibition of tumor-initiating and colony-forming properties when implanted in nude mice and grown in methyl cellulose medium. It suggests that therapies targeting the Notch pathway, such as agents that induce an over-expression of Notch1, provide a unique way of elimination therapy in human CSCs (Hombach-Klonisch S et al., 2008)

iv) STAT3 plays a key role in wide array of processes like cell survival, proliferation, differentiation, oncogenesis, metastasis, immune invasion, and angiogenesis, under both physiological and pathological conditions. So it presents a potential target to suppress the activity of CSCs (Hombach-Klonisch S et al., 2008).

9. A number of groups are using expression profiles of CSCs, in order to identify prospective therapeutic targets. NF-kB is active in AML cells, including the stem cells. It has been shown in a study that i*n vitro* inhibition of NF-kB activity by means of a proteasome inhibitor, in combination with anthracycline, led to apoptosis of AML stem cells, but not of healthy hematopoietic stem cells (Klein S et al., 2006).

10. It has been reported that checkpoint proteins play a crucial role in determining the CSC resistance to radiotherapy. In response to DNA damage the checkpoint proteins are activated and their expression increases. Thus molecules should be found which target these checkpoint proteins and thus enhance the efficacy of radiotherapy (Gil J et al., 2008, Tang C et al., 2007).

11. Telomerase activity is quite upregulated in CSCs due to which after cell division the length of telomeres remains same. This suggests that the cells do not have any aging effect and thus possess infinite replication potential. This implies, inhibition of telomerase activity may represent a valuable therapeutic approach to target CSCs (Huntly BJP et al., 2005). New studies are presently evaluating the effect of GRN163L, a telomerase inhibitor, in NSCLC and multiple myeloma to evaluate its role in both eradicating the CSCs and reducing the rate of tumor relapse (Ciavarella S et al., 2010).

12. It has been shown recently that nuclear factor κB (NF-κB) is activated in quiescent LSC populations. Thus, strategies to inhibit NF-κB, and thereby block growth and survival pathways regulated by NF-κB, may represent a useful approach to more durable AML therapy. One such class of drugs that is being widely explored for cancer therapy is proteasome inhibitors (Guzman ML et al., 2002).

13. Treatment of mice with salinomycin has been found to inhibit mammary tumor growth in vivo and induces increased epithelial differentiation of tumor cells. Thus Salinomycin can come up as effective strategy to control CSCs division (Gupta PB et al., 2009).

CONCLUSION

With the knowledge coming to the fore that cancer stem cells plays a critical role in the development, progression and maintenance of cancer, the course for cancer therapeutics should get a revamp. Instead of focusing on the treatments meant to shrink the size of the tumor, the therapy should target the real offender or the defender of cancer i.e. CSCs. So there is requirement to concentrate more on the targets specific for CSCs and which are absent in normal stem cells or somatic cells. To say more appropriately with the discovery of the role CSCs in the cancer causation, a more rationalized approach should be followed by focusing on drugs hitting CSCs. As a number of targets or cellular pathways are being unveiled which are specific to CSCs, there is a need to discover molecules or drugs specifically targeting these targets. Targeting the key targets of CSCs will help in improving the efficacy and lowering the toxicity often associated with cancer drugs.

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