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Cancer Stem Cells and Its Therapeutic Implication

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ABSTRACT: The recent concept of 'cancer stem cells' has directed scientific communities towards a different wide new area of research field and possible potential future treatment modalities for the cancer. Stem cells have certain features like unlimited proliferation potential, which give rise to cancer and are called cancer stem cells. Cancer stem cells (CSCs) play crucial roles in tumor progression, chemo- and radiotherapy resistance, and recurrence. Recent studies on CSCs have advanced understanding of molecular oncology and development of novel therapeutic strategies. Strategies aimed at efficient targeting of CSCs are becoming important for monitoring the progress of cancer therapy and for evaluating new therapeutic approaches. In this review, we primarily focuses on the recent developments in the cancer stem cells, now considered as backbone in the development of the cancer; and their role in carcinogenesis and their implications in the development of possible new cancer treatment options in future. Rapid advances in the cancer stem cell (CSC) field have provided cause for optimism for the development of more reliable cancer therapies in the future and discussed about new diagnostic and therapeutic opportunities.

KEYWORDS: Cancer Stem Cell, Chemo resistance, Target Therapy, apoptotic death pathways

I. INTRODUCTION

Cancer is the most common cause of mortality and morbidity in all over the world.Cancer cells are cells having unlimited proliferation potential which is dividing at a fast rate in an unregulated manner. In the transformation of the normal cell into cancer cell, the genes which regulate the cell growth and differentiation will be altered. The development of cancer is a complex multistep process that requires the accumulation of mutations resulting in a cell acquiring the essential hallmarks of cancer: evasion of apoptosis, self-sufficiency in growth signals, and insensitivity to antigrowth signals, invasive and metastatic abilities, limitless replicative potential, and sustained angiogenesis.The cancer stem cell (CSC) theory has given a broad view about tumor development and progression.CSCs, also called as, cancer initiating cells, are defined as the fraction of cells within a tumor that are long lived, possess the potential to proliferate indefinitely.CSCs have some character which are commonly found in stem cell populations such as differential metabolic activity, specific signaling pathway activity, and regulation of cell cycling characteristics.The CSCs have the capability of both self-renewal and multi-lineage differentiation into diverse cancer cells, which plays an important role in malignantproliferation, invasion, metastasis, and tumorrecurrence.CSCs, also termed tumor initiating cells (TICs) or cancer metastasis-initiating cells (CMICs), are known to exhibit aggressive phenotype.Cancer cell dormancy, host immune insult due to tumors or high dose chemotherapy, radiotherapy and surgical operation may lead to treatment failure and tumor recurrence. However, recent studies suggest that the few cells that exist in the tumor and have the characteristics of stem cells may be causative of cancer metastasis, recurrence, and drug resistance. This current review discusses the new breakthroughs and discoveries in the CSCs and provides a theoretical basis for developing therapies that target the minority CSC population and presents a new perspective for the treatment of cancer.

A.ORIGIN OF CANCER STEM CELLS

In 1875 Julius Cohnheim introduced a theory, that tumors may arise from stem cells which are left over from embryonic development [1].Thereafter; leukemia stem cells were first isolated in 1997 [2]; and CSCs were isolated and characterized from solid tumors in breast cancer in 2003 [3]. From the consensus of an American Association for Cancer Research (AACR) workshop in 2006, CSCs are defined as a kind of cell that posses stem cell-like properties, *i.e.*, self-renewal and pluripotency [4]. CSCs usually account for 1–4 in 100 leukemia cells [5,6] or 1 in 1000–5000 cells in lung; ovarian; and breast cancers [7]; but have strong tumorigenicity; metastaticity and resistance to radio- and chemotherapy; playing critical roles in cancer progression and therapeutic response [8,9].

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The cancer stem cells reveal many mysteries related to a cancer growth, however origin of the cancer stem cells is yet to be defined. The origin of the cancer stem cells are recognized by two important factors, first one is a number of mutations that required for a cell to be cancerous[10] and a stem cell needs to overcome any genetic constraints on both self-renewal and proliferation capabilities[11]. It is unlikely that all the mutations could occur in the lifespan of a progenitor/ mature cell. Therefore, cancer stem cells should be derived from either the self-renewing normal stem cells or from the progenitor cells that have acquired the ability of selfrenewal due to mutations which [12] is shown in figure1. The hypothesis that cancer stem cells are derived from normal stem cells rather than more committed progenitorcells have been addressed in the cases of AML where leukaemia initiating cells (LIC) from various subtypes of AML with different stages of differentiation have been shown to share the same cell-surface markers with normal haematopoietic stem cells [13,14]. However, from different studiesit was suggested that cancer stem cells can be derived from the normal stem cells, as well as from the committed short-lived progenitors, giving rise to the tumors with comparable latencies, phenotypes and gene expression profiles[15-25] Lack of the markers in the solid tumors, has made it difficult to study and characterize the origins of the cancer stem cells, however there have been identification of cell-surface markers in the brain[26], lung[27-32] and prostate[33] which may allow the separation of the stem or progenitor cells with the tumour initiating function.

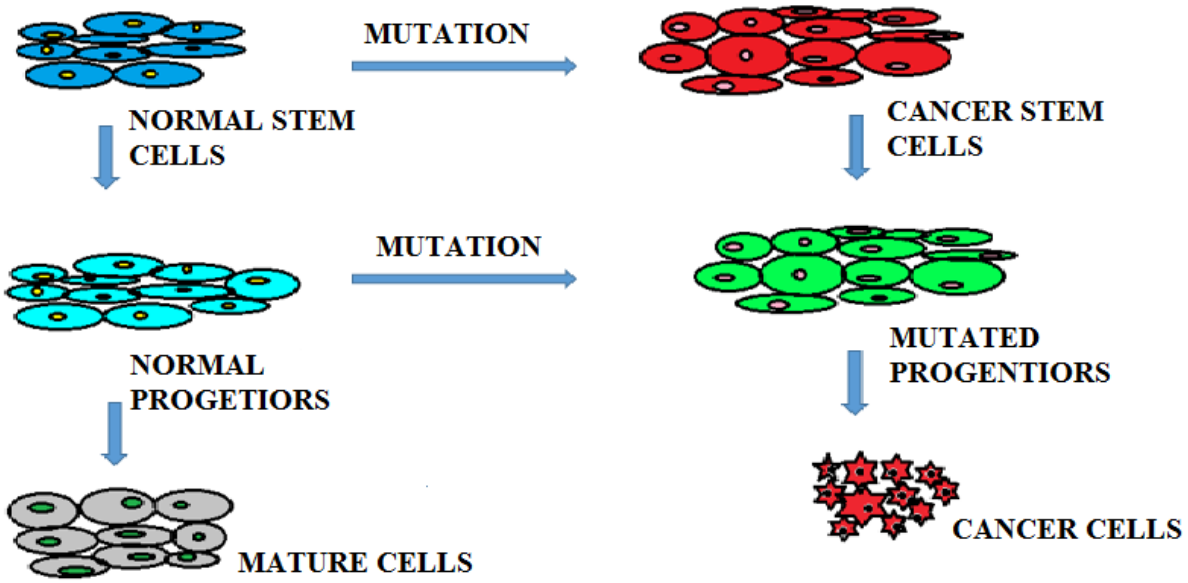

FIGURE 1: A SIMPLE MODEL OF ORIGIN OF CANCER STEM CELLS

Understanding of CSCs has advanced in the past decade. CSCs and normal stem cells exist in a dynamic equilibrium and could interconvert [34,35].Normal stem cells could acquire the properties and tumor formation ability of CSCs by reprogramming [36,37]. If CSCs are a fixed cell population, after progressive proliferation of the ratio of cancer cells should be reduced, but it is clearly not the case. The proportions of CSCs in cancer cell lines remain about 0.1% in the constant culture [38,39]. Hypoxia-inducible factor (HIF2α) promotes the self-renewal of the stem cells and enhances a more stem-like phenotype in the non-stem population [40-45]. The CSCs may also develop *de novo* from differentiated cancer cells (*i.e.*, reprogramming) by the induction of microenvironment.

II. BIOMARKERS OF CANCER STEM CELLS

Cancer stem cells are the small aggressive thing within the entire population of cancer cells and it is important to identifysuch population of CSC and to target it for the successful cancer therapies. CSCs of various origins have been known to express different marker proteins like ABCG2, ALDH1,CD44, CD24 and CD133, Thy-1, Sca-1 [46-54]. Such marker proteins, hence, have an aggressive effect to be harnessed as biomarkers for CSCs. These marker molecules are also known to play roles in various biological processes. A list of common marker proteins of CSCs, is

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represented in Table1. Novel antigen profiles emerge with CD117+, CD133+ hepatic precursors in regenerating liver tissue[55]and with a resident CD45–, CD90+ subpopulation of tumor cells in hepatocellular carcinoma (HCC), both of which might selected as hepatic CSCs .The CD90+ cells are not present in the normal liver cells and, when injected into immune deficient mice, create tumors[56].In human HCC and HCC cell lines, specifically CD133+ cells, not CD133– cells, has the ability to do self-renewal, create differentiated progenies and form tumors[57]. Pancreatic adenocarcinoma is the fourth most common cause of cancer death in the USA, displays extensive local destruction and early metastasis and has the worst prognosis of all human tumors (3% five-year survival). Pancreatic CSCs represent less than 1% of all pancreatic cancer cells and express the surface markers CD44+, CD24+ and epithelial specific antigen (ESA)+. Colorectal cancer is the third most frequent cancer and the second leading cause of cancer-related death in the Western world[58]. Current anticancer therapies fails to target colorectal cancer cells. Colorectal carcinoma develops as a result of successive mutations during clonal expansion of a single stem cell located at the bottom of the colorectal crypt. Colorectal CSCs express CD133+, ESA+ (EpCAM+) but are devoid of differentiation markers such as CK20 CD133+ [59]colorectal CSCs grow exponentially in vitro as undifferentiated spheres under serum-free conditions and generate tumors in NOD/SCID mice with morphological and antigenic profiles similar to their tumor of origin. Breast cancer is the major cause of death among women worldwide, and more than 40,000 breast cancer fatalities occur annually in the USA alone. MCF-7 breast cancer cells expresses the luminal epithelial marker MUC-1, and this SP produced MUC+ tumors in vivo[60] thus identifying MUC-1 as a new potential stem/progenitor cell marker. Recently, the cellsurface receptor PROCR (protein C receptor, CD201), CD44+ and CD24 is found to be present on 100% of breast cancer cells, and CD44+, CD24, PROCR+ cells were enriched for genes involved in cell motility, chemotaxis, hemostasis and angiogenesis.In prostate cancer, the basal cell marker profile CD44+[61] CD133+ collagen receptor [62] was observed.

TABLE 1: A LIST OF MARKERS IN CANCER STEM CELLS

CANCER TYPES	MARKERS	REFERENCE
Glioma/Medulloblastoma, head and Neck cancers, Lung, Prostate,Melanoma, Osteosarcoma	ABCG2 (ATP-binding cassette transporter)	Guo et al.
Breast, Pancreas, Bladder, Prostate	A1/ALDH1A1 (Aldehyde Dehydrogenase 1)	de Beca et al.
Glioma/Medulloblastoma, Head and neck cancers, Breast, Pancreas, Bladder, Prostate,Ovarian, Osteosarcoma, Leukemia	CD44	deBeça et al. [46], Wang et al.
Breast, Pancreas, Liver, Oesophagus, Gastric	CD24	Wang et al.
Glioblastomas, Prostate, Gastric, and Breast	CD133/Prominin1	Yasuda et al. [49], Brescia et al. [50]
Breast and Prostate	Stem Cell Antigen (Sca-1)	Xin et al. [53], Witz IP. [54], Miles et al. [55]
Osteosarcomas, Leukemia, ovarian cancers, Melanomas, Laryngeal cancers	CD105/Endoglin	Taskiran et al. [51], Marioni et al. [52]

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III.IMPLICATIONS FOR THERAPEUTIC APPLICATIONS

If there is cancer stem cells in the tumors there exists three possibilities to takes place. First one is the mutation of normal stem cells or progenitor cells into cancer stem cells which leads to the development of the primary tumour. Second one is, during chemotherapy, most of the primary tumour cells may be destroyed but if cancer stem cells are not eradicated, they become refractory cancer stem cells and may lead to recurrence of tumour. Third, the cancer stem cells will migrate from one place to another thus causing metastasis.Theoretically, identification of the cancer stem cells may allow the development of treatment modalities that target the cancer stem cells rather than rapidly dividing cells in the cancer.The cancer stem cells are relatively quiescent compared to other cancer cells and do not appear to have the hyper-proliferation signals activated such as tyrosine kinase. These make the cancer stem cells resistant to the toxicity of the anti-cancer drugs, which traditionally target the rapidly dividing cells. In addition, the tumour suppressor gene *PTEN*[63], polycomb gene *Bmi1* [64] and the signal transduction pathways such as the Sonic Hedgehog (Shh), Notch and Wnt that are crucial for normal stem cell regulation, have been shown to be deregulated in the process of cancinogenesis[65]. These deregulated signalling pathways and gene expressions may have impact on response to cancer therapy.

IV.DIFFERENTIATION THERAPY WITH CANCER STEM CELLS

Even though, many new drugs are designed for the treatment of CSCs which target cellular mechanisms that regulate cell proliferation, including Bmi-1, Notch, Sonic hedgehog and Wntsignaling pathways. Nonetheless, these attempts are generally quite tissue-specific, making it difficult to extensively target CSCs across tumors to achieve broad therapeutic efficacy. Cancer develops when there is a block during the maturation scheme, thus termed maturation arrest, resulting in retention of the property of symmetric division in both daughter cells.The maturation arrest should occur in self-renewing progenitor cells, for they do not undergo typical turnover like mature cells and remain present before proliferative stimulus is given. The concept of this model also explains the differentiation state of the cancer that develops will depend on the stage of differentiation at which maturation arrest occurs. To this point, differentiation therapy has been proposed to induce terminal differentiation of the cancer stem or progenitor cellsso thatactive proliferation and chemoresistance can be suppressed. The therapy has been encouraged by some preclinical and clinical outcomes including inhibiting glioblastoma expansion with BMP- 4 [66], and in treating acute promyelocyticleukemia with retinoic acids (vitamin A analogs) to remove the maturation block [67]. The proposed study is aimed at preliminarily validating the concept described above. Our recent reports also demonstrated that the malignant potential ofOsteosarcoma is reflective of the level of retained stem cell attributes and aldehyde dehydrogenase (ALDH) enzymatic activity [68,69]. When these putative CSCs were exposed to BMP-2, they were induced to express osteogenic phenotypes without stimulating proliferation, thereby drastically attenuating tumorformation and expansion. Moreover, the heterogenous progenies associated with low ALDH expression were induced to generate structured, calcified bone tissue *in vivo* [70]. Recently, inhibition of aldehyde dehydrogenase (ALDH) activity was shown to reduce chemotherapy and radiation resistance of stem-like ALDHhiCD44+ human breast cancer cells through their differentiation [71-73].

V. THERAUPUTIC APPROACH BY INHIBITING SIGNALLING PATHWAY AND IMMUNO BASED THERAPHY

These new therapeutic strategies target signaling pathways that are involved in the self-renewal processes of cancer stem/progenitor populations and block the growth of differentiated tumor cells. Thus, novel small molecules and specific antibodies have the potential not only to reduce tumor mass but also to eradicate the self-renewable source of CSCs[74-80]. Examples include the reduction of the SP fraction of metastaticUMSCC10B and HN12 head and neck cancer cell lines by (i) the targeting or inhibiting of membraneanchoredtyrosine kinase receptor signaling by EGFR and Her2/Neu and (ii) the supra-additive combinatorialtreatment of prostate cancer cell PC-3 xenographs in mice, which combines docetaxel or the anti-EGFR antibody cetuximab with sunitinib malate (SU11248), an oral multi-tyrosine kinase receptor block targeting vascular endothelial growth factor (VEGF)-1, -2 and -3/plateletderived growth factor

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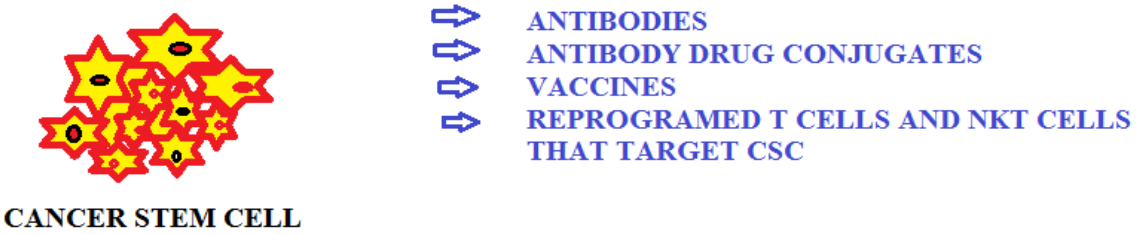
(PDGF)-a and -b/KIT/FLT-3.A new class of peptide molecules, apoptin, brevinin-2R, E4orf4 and hamlet, are emerging that have the capacity to (semi)specifically kill cancer cells .Some of them even appear to 'hijack' signaling pathways thatnormally promote cell survival and proliferation and redirect them to promote cell death[81-85]. Elucidating the mechanisms by which these promising anticancer peptides might kill CSCs could provide the basis for new gene- and peptide-based therapies.

The second element of a therapy against cancer stem cells, along with the appropriate target, is represented by the therapeutic platform which could be a biological or a small molecule capable to affect the viability or biological properties of such cells (Figure 2). Immune interventions are of particular interest as cancer stem cells or tumor initiating cells have a recognizedrefractoriness to conventional therapies (chemotherapy, radiotherapy) and small molecule targeted therapies.

Dr. Richard Morgan from the National Cancer Institute had designed the genetically engineered Tcells encompassing chimeric antigen receptors (CARs) against antigens such as EGFRvIII and CSPG4. Such CARs are endowed with co-stimulatory signalling domains that provide the engineered T cells with supra-physiological capabilities. Dr. Morgan discussed their results obtained in a glioblastoma model, with cancer stem cells in the neurosphere assay as targets for an EGFRvIII-directed CAR engineered T cell approach. These newer CARs complement a growing pipeline that includes anti-CD19 CAR that showed objective clinical responsesin leukemia and lymphoma. A third generation CAR against EGFRvIII, encompassing 4-1BB, CD28, CD3z as signalling domains, is currently undergoing phase 1 clinical testing in patients with relapsed glioblastomamultiformae.

Dr. Elaine Hurt from Medimmune described an in vitro high throughput assay utilized in their laboratory to discover novel targets associated with cancer stem cells, applicable to breast cancer and other tumor types. These targets are amenable to antibody based immunotherapy and related approaches, as they are expressed on the cell membrane. She discussed the rationalesupporting EZH2, a novel target associated with the Wnt/Notch pathway, and thus closely related to stemness. This assay and screening methodology carries the promise of leading to identification of numerous membrane borne targets associated with tumor initiating cells.



VI. APOPTOTIC MEDIATED THERAPHY

Apoptosis is a characterization of antitumor drugs and it's regulated by several molecular phenomena, such as the expression of Bm-1 and the loss of p53. Bmi-1, a member of the polycomb group (PcG) family, which is responsible for the self-renewal and maintenance of CSCs. Being, Bmi-1as an oncogene, it could enable cancer cells to escape apoptosis by modulating multiple growth signaling pathways [86]. Thus, its overexpression in cancer cells could be used as a survival marker. The role of Bmi-1 in chemoresistance has been addressed recently.Silencing of Bmi- 1 gene could promote sensitivity to cisplatin and induction of apoptosis.

A. Apoptotic Signaling in CSCs

Apoptosis is an active, strictly regulated, and energy-dependent cell death process. In mammalian cells, apoptosis is regulated via two different pathways, *i.e.*, the extrinsic and intrinsicpathways. Caspases play important roles in apoptosis. The activation of caspase family proteinstriggered by these two signaling pathways results in a series of

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cellular substrate excision and changes, such as chromatin condensation, DNA fragmentation, membrane blebbing, and cell shrinkage. The extrinsic pathway is triggered through the binding of extracellular proapoptotic ligands to cell surface receptors, known as death receptors, such as CD95, nerve growth factor receptor (NGFR), and TNF-related apoptosis-inducing ligand (TRAIL) receptors. After binding to the receptor, a death-inducing signaling complex (DISC) composed of the Fas associated death domain (FADD) and procaspase-8 and -10 is formed, and this protein complex activates procaspase-8 and -10 inside itself, and then cleaves procaspase-3 and initiates the apoptosis process. In theextrinsic pathway, the downregulation of cellular FLICE inhibitory protein long isoform (c-FLIPL) by ubiquitination at lysine residue (K) 195 occurs. The intrinsic pathway, also known as the mitochondrial pathway, is induced by a variety of stress signals that trigger cellular and DNA damage, such as ionizing radiation, cytotoxic agents, and growth factor withdrawal. They lead to mitochondrial outer membrane permeabilization (MOMP) and transcription or post-translational activation of BH3-only proapoptotic B-cell leukemia/lymphoma 2 (Bcl-2) family proteins. The mitochondrial permeability is a key step in the apoptosis cascade and mediated by Bcl-2 family proteins. The mitochondrial permeability allows the release of apoptotic proteins, such as cytochrome c and second mitochondria-derived activator of caspase (Smac), from the intermembrane space into cytosol. The assembly of cytochrome c and apoptotic protease-activating factor-1 (Apaf-1) activates caspase-9 which in turn activates the effectors caspase-3, -6, and -7, leading to apoptosis. Inhibitors of apoptosis protein (IAP) prevent both intrinsic and extrinsic apoptosis by inhibiting caspase activity, which represents the last protective measure against apoptosis . Death signaling can also be activated by c-Jun *N*-terminal kinase (JNK) signaling which leads to phosphorylation of Bcl-xL at Ser62, decreasing its anti-apoptotic activity in the intrinsic pathway. Intrinsic and extrinsic apoptosis pathways are both disordered in cancer cells; and apoptosis evasion is one of the hallmarks in cancer cells. Apoptotic signaling pathways, including extrinsic and intrinsic pathways, are also deregulated in CSCs. In glioblastoma and lung CSCs, the death receptors (DR) mediating the extrinsic pathway are expressed at a high level, and the upregulation of DR4 in colon CSCs leads to chemo-resistance. The FLICE-like inhibitory proteins (cFLIP) are a negative modulator of death receptor-induced apoptosis, consisting of two subtypes: long cFLIP (cFLIPL) and short Cflip (cFLIPS) . In CD133+ glioblastoma, breast cancer, and T-cell acute leukemia cells, the cFLIPs are up regulated. Silencing of cFLIPs by siRNA restores cell sensitivity to death stimuli, suppressing CSC self-renewal and tumor metastasis. It was reported that insufficientexpression of death receptors and up expression of c-FLIPs leads to CSCs-enriched neurosphere resistance to trail.

Dysregulation of the intrinsic pathway in CSCs is mainly reflected in Bcl-2 family proteins and the DNA damage response. Bcl-2 family proteins are composed of anti-apoptotic proteins (Bcl-2, Bcl-XL and Mcl-1) and pro-apoptotic molecules (Bax, Bak, Bid, Bim, Bik, Noxa and Puma. It is the imbalance of anti- to pro-apoptotic protein ratio rather than a specific molecule expression level that tips the balance to cell survival and regulates sensitivity to apoptotic stimuli . In most tumors, anti-apoptotic Bcl-2 family proteins are overexpressed in CSCs. For instance, CD133+ glioma CSCs express a high level of anti-apoptotic proteins Bcl-2 and Bcl-XL and high expression of Mcl-1 correlates with resistance to the Bcl-2 inhibitor ABT-737 in glioma CSCs. In colon CSCs, Bcl-2 is increased and inhibits apoptosis and autophagy. Downregulation of Bcl-2 or upregulation of Bax induces apoptosis of CSCs . Therefore, inhibition of the mitochondrial death cascade has been attractive for CSC-targeted therapeutic intervention of cancers.[87]

CSC differentiation is reversible, *i.e.*, the mature tumor cells or precursor cells can obtain CSCproperties by dedifferentiation. Understanding of CSCs has explained the heterogeneity, metastasis recurrence and chemo-/radiotherapy resistance of tumors, and the evasion of apoptosis of CSCs is considered a main mechanism of recurrence and chemoresistance of cancers, representing novel therapeutic potentials. The apoptosis is mediated by complex networks composed of many death and survival signaling molecules and pathways. Manipulating the apoptotic machinery, including activation of pro-apoptotic pathways and inactivation of anti-apoptotic pathways to eradicate CSCs, displays great potentials. Selective induction of CSC differentiation, suppression of their self-renewal, or triggering of their apoptosis by targeting key signaling molecules and microenvironment factors, are certainly attractive explorations to cancer researchers. Combined applications of agents targeting CSC apoptosis are an important advantage improving their antitumor efficacy.

VII. CONCLUSION

In conclusion, stem cells and cancer cells share a lot of commonality. However, stem cells are proven be more primitive as compared to cancer and cancer stem cells. Under normal circumstances, stem cells maintain a homeostasis and replenish the adult cell pool while deregulation or imbalances of stem cells can give rise to cancer stem cells and

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eventually full blown cancer. Presently, cancer therapy has entered in to an exciting new era, with traditional therapies such as chemotherapy, radiotherapy and surgery on one side while the stem cells onthe other hand. Apart from their well-known role in immuno-reconstitution, the stem cells have attracted much attention especially with the new gene technologies such as the gene incorporation into the eukaryotic cells allowing more focused delivery of the anti-cancer agents.Now the cancer may be considered as a cancer stem cell disorder rather than that of rapidly growing cells.Although the origin of the cancer stem cells is yet to bedefined, the concept of the cancer stem cells may allow new treatment options in the possible cure of the cancer. However, further research is required to identify and separate the cancer stem cells in various cancers from normal stem cells and other cancer cells. Further work is also required to differentiate the genes and signalling pathways in the process of the carcinogenesis from cancer stem cells for development of new therapies, with the eventual goal of eliminating the residual disease and recurrence.

REFERENCE

1. Knudson AG Jr., Strong LC, Anderson DE: "Heredity and cancer inman", *Prog Med Genet* 1973, 9:113-58:113-158.
2. Morrison SJ, Qian D, Jerabek L, Thiel BA, Park IK, Ford PS, Kiel MJ,Schork NJ, Weissman IL, Clarke MF: "A genetic determinant thatspecifically regulates the frequency of hematopoietic stemcells". *J Immunol*2002, 168:635-642.
3. Al-Hajj M, Becker MW, Wicha M, Weissman I, Clarke MF "Therapeuticimplications of cancer stem cells"*CurrOpin Genet Dev*2004, 14:43-47.
4. Sell S "Stem cell origin of cancer and differentiation therapy" *Crit Rev OncolHematol*2004, 51:1-28.
5. Wang JC, Dick JE "Cancer stem cells: lessons from leukemia"*Trends Cell Biol*2005, 15:494-501.
6. Cozzio A, Passegue E, Ayton PM, Karsunky H, Cleary ML, WeissmanIL "Similar MLL-associated leukemias arising from selfrenewingstem cells and short-lived myeloid progenitors"*Genes Dev*2003, 17:3029-3035.
7. Jamieson CH, Ailles LE, Dylla SJ, Muijtjens M, Jones C, ZehnderJL,Gotlib J, Li K, Manz MG, Keating A, Sawyers CL, Weissman IL "Granulocyte-macrophage progenitors as candidate leukemicstem cells in blast-crisis CML" *N Engl J Med* 2004, 351:657-667.
8. Weissman IL "Normal and neoplastic stem cells" *Novartis FoundSymp*2005, 265:35-50; discussion 50-4, 92-7.:35-50.
9. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, HenkelmanRM, Cusimano MD, Dirks PB: "Identification of human braintumour initiating cells" *Nature* 2004, 432:396-401.
10. Yuan X, Curtin J, Xiong Y, Liu G, Waschsmann-Hogiu S, Farkas DL, Black KL, Yu JS "Isolation ofcancer stem cells from adult glioblastomamultiforme"*Oncogene* 2004, 23:9392-9400.
11. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A, De Vitis S, Fiocco R, Foroni C, Dimeco F, Vescovi A"Isolation and characterizationof tumorigenic, stem-like neural precursors from humanglioblastoma" *Cancer Res* 2004, 64:7011-7021.
12. Xin L, Lawson DA, Witte ON "The Sca-1 cell surface marker enriches for a prostate-regenerating cell sub-population that can initiate prostate tumorigenesis" *ProcNatlAcadSci U S A*2005, 102:6942-6947.
13. Stockler M, Wilcken NR, Ghersi D, Simes RJ "Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer" *Cancer Treat Rev* 2000, 26:151-168.
14. Jordan CT, Guzman ML, Noble M "Cancer stem cells"*N Engl J Med* 2006, 355:1253-1261.
15. Costello RT, Mallet F, Gaugler B, Sainty D, Arnoulet C, Gastaut JA, Olive D "Human acute myeloid leukemia CD34+/CD38- progenitor cells have decreased sensitivity to chemotherapy and Fas-induced apoptosis, reduced immunogenicity, and impaired dendritic cell transformation capacities"*Cancer Res* 2000, 60:4403-4411
16. Park IK, Qian D, Kiel M, Becker MW, Pihalja M, Weissman IL, Morrison SJ, Clarke MF "Bmi-1 is required for maintenance of adult self-renewing haematopoietic stem cells"*Nature* 2003, 423:302-305.
17. Blair A, Hogge DE, Ailles LE, Lansdorp PM, Sutherland HJ "Lack of expression of Thy-1 (CD90) on acute myeloid leukemia cells with long-term proliferative ability in vitro and in vivo" *Blood* 1997, 89:3104-3112 .
18. Blair A, Sutherland HJ "Primitive acute myeloid leukemia cells with long-term proliferative ability in vitro and in vivo lack surface expression of c-kit (CD117)" *ExpHematol*2000, 28:660-671.
19. Druker BJ, Tamura S, Buchdunger E, Ohno S, Segal GM, Fanning S, Zimmermann J, Lydon NB "Effects of a selective inhibitor of the Abl tyrosine kinase on the growth of Bcr-Abl positive cells" *Nat Med* 1996,2:561-566
20. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, Cornelissen JJ, Fischer T, Hochhaus A, Hughes T, Lechner K, Nielsen JL, Rousselot P, Reiffers J, Saglio G, Shepherd J, Simonsson B, Gratwohl A, Goldman JM, Kantarjian H, Taylor K, Verhoef G, BoltonAE, Capdeville R, Druker BJ "Imatinib compared with interferonand low-dose cytarabine for newly diagnosed chronic-phasechronic myeloid leukemia"*N Engl J Med* 2003, 348:994-1004.
21. Branford S, Hughes TP, Rudzki Z "Monitoring chronic myeloidleukaemia therapy by real-time quantitative PCR in blood isa reliable alternative to bone marrow cytogenetics" *Br J Haematol*1999, 107:587-599.
22. Berman DM, Karhadkar SS, Hallahan AR, Pritchard JI, Eberhart CG,Watkins DN, Chen JK, Cooper MK, Taipale J, Olson JM, Beachy PA 'Medulloblastoma growth inhibition by hedgehog pathwayblockade"*Science* 2002, 297:1559-1561.
23. Beachy PA, Karhadkar SS, Berman DM "Tissue repair and stem cell renewal in carcinogenesis" *Nature* 2004, 432:324-331.
24. Oehler VG, Radich JP, Storer B, Blume KG, Chauncey T, Clift R, Snyder DS, Forman SJ, Flowers ME, Martin P, Guthrie KA, NegrinRS,Appelbaum FR, Bensinger W"Randomized trial of allogeneic related bone marrow transplantation versus peripheral blood stem cell transplantation for chronic myeloid leukemia"*Biol Blood Marrow Transplant* 2005, 11:85-92.
25. Heldal D, Brinch L, Tjonnfjord G, Solheim BG, Egeland T, Albrechtsen D, Aamodt G, Evensen SA "Fewer relapses and increased chronic GVHD in patients transplanted with blood stem cells: a 5-year follow-up in a single centre study" *Bone Marrow Transplant* 2003, 32:257-264.
26. Nucci M, Andrade F, Vigorito A, Trabasso P, Aranha JF, Maiolino A, De Souza CA "Infectious complications in patients randomized to receive allogeneic bone marrow or peripheral blood transplantation" *Transpl Infect Dis* 2003, 5:167-173.

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

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27. Canales MA, Arrieta R, Hernandez-Garcia C, Bustos JG, Aguado MJ, Hernandez-Navarro F "A single apheresis to achieve a high number of peripheral blood CD34+ cells in a lithium-treated patient with acute myeloid leukaemia"*Bone Marrow Transplant* 1999, 23:305.
28. Prosper F, Sola C, Hornedo J, Arbona C, Menendez P, Orfao A, Lluch A, Cortes-Funes H, Lopez JJ, Garcia-Conde J "Mobilization of peripheral blood progenitor cells with a combination of cyclophosphamide, r-metHuSCF and filgrastim in patients with breast cancer previously treated with chemotherapy" *Leukemia*2003, 17:437-441.
29. Hernandez-Boluda JC, Carreras E, Cervantes F, Marin P, Arellano-Rodrigo E, Rovira M, Sole F, Lloveras E, Espinet B, Ocejo A, Montserrat E"Collection of Philadelphia-negative stem cells using recombinant human granulocyte colony-stimulating factor in chronic myeloid leukemia patients treated with alphainterferon" *Haematologica*2002, 87:17-22.
30. Ross AA, Cooper BW, Lazarus HM, Mackay W, Moss TJ, CiobanuN,Tallman MS, Kennedy MJ, Davidson NE, Sweet D, "Detection and viability of tumor cells in peripheral blood stem cell collections from breast cancer patients using immunocytochemicaland clonogenic assay techniques"*Blood* 1993, 82:2605-2610.
31. Dal CL, Cottu PH, Lotz JP, Robert I, Extra JM, Miclea JM, Marty M, Marolleau JP "Residual tumor cell contamination in peripheral blood stem cells collections of 117 breast cancer patients evaluated by immunocytochemical technique." *J Hematother Stem Cell Res* 2001, 10:855-862.
32. Kruger W, Togel F, Kroger N, Rossing S, Gieseking F, Gutensohn K,Lindner C, Janicke F, Zander AR "Tumour cell detection in GCSFmobilised stem cell harvests of patients with breast cancer"*Med Oncol*1999, 16:17-22.
33. Passos-Coelho JL, Ross AA, Kahn DJ, Moss TJ, Davis JM, HuelskampAM, Noga SJ, Davidson NE, Kennedy MJ "Similar breast cancercell contamination of single-day peripheral-blood progenitor-cell collections obtained after priming with hematopoieticgrowth factor alone or after cyclophosphamide followedby growth factor" *J ClinOncol*1996, 14:2569-2575.
34. Pedrazzoli P, Battaglia M, Da Prada GA, Lanza A, Cuomo A, BertoliniF, Pavesi L, Robustellidella CG "Role of tumor cells contaminatingthe graft in breast cancer recurrence after high-dosechemotherapy" *Bone Marrow Transplant* 1997, 20:167-169.
35. Cooper BW, Moss TJ, Ross AA, Ybanez J, Lazarus HM "Occulttumor contamination of hematopoietic stem-cell productsdoes not affect clinical outcome of autologous transplantationin patients with metastatic breast cancer" *J ClinOncol*1998, 16:3509-3517.
36. Cagnoni PJ, Jones RB, Bearman SI, Ross M, Hami L, Franklin WA,Capizzi R, Schein PS, Shpall EJ "Use of amifostine in bone marrowpurging"*SeminOncol*1996, 23:44-48.
37. Poloni A, Leoni P, Curzi L, Cantori I, Mancini S, Montanari M, MasiaMC, Olivieri A "Ex vivo pharmacological purging of leukapheresiscollections with nitrogen mustard: amifostinepretreatmentimproves both early and late peripheral bloodprogenitor cell recovery" *ExpHematol*1999, 27:1548-1556.
38. Altes A, Sierra J, Esteve J, Martin-Henao G, Marin P, Sureda A, BrionesJ, Martino R, Villamor N, Colomer D, Carreras E, Garcia J, Brunet S,Montserrat E "CD34+-enriched-CD19+-depleted autologousperipheral blood stem cell transplantation for chronic lymphoproliferativedisorders: high purging efficiency butincreased risk of severe infections" *ExpHematol*2002,30:824-830.
39. Martin-Rendon E, Watt SM "Exploitation of stem cell plasticity" *Transfus Med* 2003, 13:325-349.
40. Beccheroni A, Lucarelli E, Donati D, Sangiorgi L, Capponcelli S, GoriniM, Zambon BA, Giardino R, Mercuri M, Ferrari S, Bacci G, Picci P "Recovery of stromal stem cells in bone sarcoma patientsafter chemotherapy: implication for cell-based therapy inbone defect reconstruction" *Oncol Rep* 2003, 10:891-896.
41. Jager M, Schultheis A, Westhoff B, Krauspe R "Osteogenic progenitorcell potency after high-dose chemotherapy (COSS-96)" *Anticancer Res* 2005, 25:947-954.
42. Kang HJ, Kim HS, Koo BK, Kim YJ, Lee D, Sohn DW, Oh BH, ParkYB"Intracoronary infusion of the mobilized peripheral bloodstem cell by G-CSF is better than mobilization alone by GCSFfor improvement of cardiac function and remodeling: 2-year follow-up results of the Myocardial Regeneration andAngiogenesis in Myocardial Infarction with G-CSF and Intra-Coronary Stem Cell Infusion (MAGIC Cell) 1 trial" *Am HeartJ* 2007, 153:237-238.
43. Klein HM, Ghodsizad A, Marktanner R, Poll L, Voelkel T, MohammadHasani MR, Piechaczek C, Feifel N, Stockschlaeder M, Burchardt ER,Kar BJ, Gregoric I, Gams E"Intramyocardial implantation ofCD133+ stem cells improved cardiac function withoutbypass surgery"*Heart Surg Forum* 2007, 10:E66-E69.
44. Engelmann MG, Theiss HD, Hennig-Theiss C, Huber A, WinterspergerBJ, Werle-Ruedinger AE, Schoenberg SO, Steinbeck G, FranzWM "Autologous bone marrow stem cell mobilizationinduced by granulocyte colony-stimulating factor after subacuteST-segment elevation myocardial infarction undergoinglate revascularization: final results from the G-CSFSTEMI(Granulocyte Colony-Stimulating Factor ST-SegmentElevation Myocardial Infarction) trial"*J Am CollCardiol*2006, 48:1712-1721
45. Chawla-Sarkar M, Leaman DW, Borden EC"Preferential inductionof apoptosis by interferon (IFN)-beta compared with IFNalpha2:correlation with TRAIL/Apo2L induction inmelanoma cell lines"*Clin Cancer Res* 2001, 7:1821-1831.
46. Lokshin A, Mayotte JE, Levitt ML "Mechanism of interferon betainducedsquamous differentiation and programmed celldeath in human non-small-cell lung cancer cell lines"*J NatlCancer Inst*1995, 87:206-212.
47. Zhang H, Koty PP, Mayotte J, Levitt ML "Induction of multiple programmedcell death pathways by IFN-beta in human nonsmall-cell lung cancer cell lines" *Exp Cell Res* 1999, 247:133-141.
48. Studeny M, Marini FC, Dembinski JL, Zompetta C, Cabreira-HansenM, Bekele BN, Champlin RE, Andreeff M "Mesenchymal stem cells:potential precursors for tumorstroma and targeted-deliveryvehicles for anticancer agents" *J Natl Cancer Inst*2004,96:1593-1603.
49. Studeny M, Marini FC, Champlin RE, Zompetta C, Fidler IJ, AndreeffM "Bone marrow-derived mesenchymal stem cells as vehiclesfor interferon-beta delivery into tumors"*Cancer Res* 2002,62:3603-3608.
50. Nakamizo A, Marini F, Amano T, Khan A, Studeny M, Gumin J, ChenJ, Hentschel S, Vecil G, Dembinski J, Andreeff M, Lang FF"Humanbone marrow-derived mesenchymal stem cells in the treatmentof gliomas" *Cancer Res* 2005, 65:3307-3318.
51. Muller FJ, Snyder EY, Loring JF "Gene therapy: can neural stemcells deliver?" *Nat Rev Neurosci*2006, 7:75-84.
52. Anderson SA, Glod J, Arbab AS, Noel M, Ashari P, Fine HA, Frank JA"Noninvasive MR imaging of magnetically labeled stem cellsto directly identify neovasculature in a glioma model"*Blood*2005, 105:420-425.Ricci-Vitiani L, Pagliuca A, Palio E, Zeuner A, De Maria R (2008) Colon cancerstem cells. Gut 57: 538-548.
53. Visvader JE, Lindeman GJ"Cancer stem cells in solid tumours:accumulating evidence and unresolved questions" Nat Rev Cancer2008, 8: 755-768.
54. Guo Y, Lübbert M, EngelhardtM "CD34- hematopoietic stem cells:current concepts and controversie" Stem Cells2003, 21: 15-20.

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55. De Beça FF, Caetano P, Gerhard R, Alvarenga CA, Gomes M, et al. "Cancer stem cells markers CD44, CD24 and ALDH1 in breast cancer specialhistological types" J ClinPathol2013,66: 187-191.
56. Wang KH, Kao AP, Chang CC, Lee JN, Hou MF, et al. (2010) "IncreasingCD44+/CD24(-) tumor stem cells, and upregulation of COX-2 and HDAC6, asmajor functions of HER2 in breast tumorigenesis"Mol Cancer 9: 288.
57. Wang YC, Wang JL, Kong X, Sun TT, Chen HY, et al. "CD24 mediatesgastric carcinogenesis and promotes gastric cancer progression via STAT3activation. Apoptosis",2013.5:254-256.
58. Yasuda H, Tanaka K, Saigusa S, Toiyama Y, Koike Y, et al. "ElevatedCD133, but not VEGF or EGFR, as a predictive marker of distant recurrenceafter preoperative chemoradiotherapy in rectal cancer"Oncol Rep 2009,22: 709-717.
59. Brescia P, Ortensi B, Fornasari L, Levi D, Broggi G, et al. "CD133 isessential for glioblastoma stem cell maintenance. Stem Cells"2013, 31: 857-869.
60. Taskiran C, Erdem O, Onan A, Arisoy O, Acar A, et al. (2006) "The prognosticvalue of endoglin (CD105) expression in ovarian carcinoma"Int J GynecolCancer 16: 1789-1793.
61. Marioni G, Staffieri A, Manzato E, Ralli G, Lionello M, et al."A higherCD105-assessed microvessel density and worse prognosis in elderly patientswith laryngeal carcinoma"Arch Otolaryngol Head Neck Surg.2011,137: 175-180.
62. Xin L, Lawson DA, Witte ON "The Sca-1 cell surface marker enrichesfor a prostate-regenerating cell subpopulation that can initiate prostatetumorigenesis" ProcNatlAcadSci U S A 2013,102: 6942-6947.
63. Witz IP"Differential expression of genes by tumor cells of a low or a highmalignancy phenotype: the case of murine and human Ly-6 proteins" J CellBiochemSuppl 2009,34: 61-66.
64. Miles C, Sanchez MJ, Sinclair A, Dzierzak E"Expression of the Ly-6E.1(Sca-1) transgene in adult hematopoietic stem cells and the developing mouseembryo" Development 2009,124: 537-547.
65. Winquist RJ, Boucher DM, Wood M, Furey BF "Targeting cancer stemcells for more effective therapies: Taking out cancer's locomotive engine"BiochemPharmacol 2008, 78: 326-334.
66. Maugeri-Saccà M, Zeuner A, De Maria R (2011) "Therapeutic targeting ofcancer stem cells" Front Oncol 1: 10.
67. Muller JM, Chevrier L, Cochard S, Meunier AC, Chadeneau C. Hedgehog,(2007) Notch and Wnt "Developmental pathways as targets for anti-cancerdrugs" Drug Discov Today Disease Mechanism.2007, 4: 285-291.
68. Merchant AA, Matsui W "Targeting Hedgehog--a cancer stem cellpathway"Clin Cancer Res 2010,16: 3130-3140.
69. Rappa G, Fodstad O, Lorico A "The stem cell-associated antigen CD133(Prominin-1) is a molecular therapeutic target for metastatic melanom". StemCells 2008, 26: 3008-3017.
70. Smith LM, Nesterova A, Ryan MC, Duniho S, Jonas M, et al. "CD133prominin-1 is a potential therapeutic target for antibody-drug conjugates inhepatocellular and gastric cancer". Br J Cancer 99: 100-109.
71. Croker AK, Allan AL "Inhibition of aldehyde dehydrogenase (ALDH)activity reduces chemotherapy and radiation resistance of stem-likeALDHhiCD44+ human breast cancer cells. Breast Cancer Res Treat 133: 75-Alvi AJ, Clayton H, Joshi C, Enver T, Ashworth A, Vivanco M, Dale TC,Smalley MJ:Functional and molecular characterisation of mammary sidepopulation cells" Breast Cancer Res 2003, 5:R1–R8.
72. Cervello I, Gil-Sanchis C, Mas A, Delgado-Rosas F, Martínez-Conejero JA,Galán A, Martínez-Romero A, Martínez S, Navarro I, Ferro J, Horcajadas JA,Esteban FJ, O'Connor JE, Pellicer A, Simón C "Human endometrial sidepopulation cells exhibit genotypic, phenotypic and functional features ofsomatic stem cells"PLoS One 2010, 5:e10964.
73. Hosonuma S, Kobayashi Y, Kojo S, Wada H, Seino K, Kiguchi K, Ishizuka B "Clinical significance of side population in ovarian cancer cells" Hum Cell2011, 24:9–12.
74. Hu L, McArthur C, Jaffe RB "Ovarian cancer stemlike side-population cellsare tumourigenic and chemoresistant" Br J Cancer 2010, 102:1276–1283.
75. Grivennikov SI, Greten FR, Karin M "Immunity, inflammation, and cancer". Cell 2010, 140:883–899.
76. Kamazawa S, Kigawa J, Kanamori Y, Itamochi H, Sato S, Iba T, Terakawa N "Multidrug resistance gene-1 is a useful predictor of Paclitaxel-basedchemotherapy for patients with ovarian cancer"GynecolOncol 2002,86:171–176.
77. Rodriguez-Antona C "Pharmacogenomics of paclitaxel. Pharmacogenomics"2010, 11:621–623.
78. Anderson ME" Glutathione: an overview of biosynthesis and modulation" ChemBiol Interact 1998, 111–112:1–14.
79. Backos DS, Franklin CC, Reigan P "The role of glutathione in brain tumordrug resistance"BiochemPharmacol 2012, 83(8):1005–1012.
80. Jedlitschky G, Leier I, Buchholz U, Center M, Keppler D "ATP-dependenttransport of glutathione S-conjugates by the multidrugresistance-associated protein" Cancer Res 1994, 54(18):4833–4836.
81. Liu J, Cao L, Chen J, Song S, Lee IH, Quijano C, Liu H, Keyvanfar K, Chen H,Cao LY, Ahn BH, Kumar NG, Rovira II, Xu XL, van Lohuizen M, Motoyama N,Deng CX, Finkel T"Bmi1 regulatesmitochondrial function and the DNAdamage response pathway" Nature 2009, 459(7245):387–392.
82. Li J, Gong LY, Song LB, Jiang LL, Liu LP, Wu J, Yuan J, Cai JC, He M, Wang L,Zeng M, Cheng SY, Li M "Oncoprotein Bmi-1 renders apoptotic resistance toglioma cells through activation of the IKK-nuclear factor-kappaB-pathway"Am J Pathol 2010, 176(2):699–709.
83. Guo BH, Feng Y, Zhang R, Xu LH, Li MZ, Kung HF, Song LB, Zeng MS"Bmi-1promotes invasion and metastasis, and its elevated expression is correlatedwith an advanced stage of breast cancer" Mol Cancer 2011, 10:10.
84. Wang E, Bhattacharyya S, Szabolcs A, Rodriguez-Aguayo C, Jennings NB,Lopez-Berestein G, Mukherjee P, Sood AK, Bhattacharya R "Enhancingchemotherapy response with Bmi-1 silencing in ovarian cancer"PLoS ONE 2011, 6(3):e17918.
85. Fraser M, Bai T, Tsang BK"Akt promotes cisplatin resistance in humanovarian cancer cells through inhibition of p53 phosphorylation andnuclear function"Int J Cancer 2008, 122(3):534–546.
86. Nikolaev AY, Li M, Puskas N, Qin J, Gu W: Parc"A cytoplasmic anchor forp53" Cell 2003, 112(1):29–40.
87. Woo MG, Xue K, Liu J, McBride H, Tsang BK "Calpain-mediated processingof p53-associated parkin-like cytoplasmic protein (PARC) affectschemosensitivity of human ovarian cancer cells by promoting p53subcellular trafficking" J BiolChem 2012, 287(6):3963–3975.
88. Wallace-Brodeur RR, Lowe SW "Clinical implications of p53 mutations" Cell Mol Life Sci 1999, 55:64–75.