Available online at www.scholarsresearchlibrary.com

Scholars Research Library

Der Pharmacia Lettre, 2015, 7 (2):136-141
(http://scholarsresearchlibrary.com/archive.html)

ISSN 0975-5071
USA CODEN: DPLEB4

Monoclonal antibodies as therapeutic targets in cancer stem cells

Sina Pakdel[1], Farzaneh Pakdel[2]*, Firouz Pouralibaba[2], Reza Khorshidi Khiyavi[3], Parisa Falsafi[2], Hosein Eslami[2], Vahid Fakhrzadeh[4] and Shiva Solahaye Kahnamouii[5]

[1]Legal Medicine Organization, Tabriz, Iran
[2]Department of Oral Medicine, School of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[3]Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Tabriz University of Medical Sciences, Tabriz, Iran
[4]Department of Protedentics, School of Dentistry, Tabriz University of Medical Science, Tabriz, Iran
[5]Neuroscience Research Center, Department of Maxillofacial Surgery, Cardiovascular Research Center, and Drug Applied Research Center, Tabriz University of Medical Science, Tabriz, Iran

---

ABSTRACT

Cancer stem cells (CSCs) composes a different subpopulation of tumor cells that exhibit self-renewal and tumor beginning capacity and the ability to give rise to the heterogeneous lineages of cancer cells that encompass the tumor. Since current cancer therapies fail to eliminate CSCs, ultimately leading to cancer recurrence and progression, selective targeting of CSCs with mAbs and antibody constructs reviewed here in may represent a novel and promising therapeutic strategy to eradicate cancer. CSCs have been recognized from many human tumors and share many of the characteristics of normal stem cells. Targeting CSCs could be a strategy to improve the effect of cancer therapy but this is not as simple as it seems. Targets such as CD133 could confine CSCs from normal cells enabling specific interference but indirect strategies such as interfering with the establishment of a supportive niche through anti-antigenic or anti-stoma therapy could be more effective. This review will outline the recent discoveries of mAB targeting for CSCs.

INTRODUCTION

Monoclonal antibodies are clinically and commercially-established therapeutics. A great deal of progress has been made over the last years in overcoming problems and translating the phenomenal amount of laboratory research into clinical products[1-4]. According to a consensus definition, these CSCs are cells within a tumor that possess the capacity to self-renew and to give rise to the heterogeneous lineages of cancer cells that comprise the tumor. CSCs can be clear experimentally by their ability to recapitulate the generation of an incessantly growing tumor in serial xenotransplantation settings[5-8]. CSCs harbor numerous inherent mechanisms of confrontation to conventional chemotherapeutic drugs. Seminal studies show that CSCs can even be enriched by conventional chemotherapeutic drug, as demonstrated in breast cancer patients receiving systemic chemotherapy comprising conventional cytotoxic drugs[6,7] .Moreover, many novel tumor-targeted drugs, including tyrosine kinase inhibitors and some established monoclonal antibodies (mAbs) fail to eliminate CSCs, so that there is an critical need for novel agents and strategies that efficiently target CSCs for the use in elaborated clinical settings, preferably in combination with conventional cytostatic drugs, novel tumor-targeted agents, and radiation therapy[9-12]. In contrast to conservative gyrostatic drugs, radiotherapy and novel tumor-targeted drugs, mobs raised against cancer cell-specific or CSCs-specific cell surface proteins exploit the host´s immune system to eliminate the cells targeted by the mob by using classical

humeral and cellular immune mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity[13-15]. Then, targeting of cancer cells and CSCs with specific mAbs and antibody constructs shows not as a single job seen with conventional cytostatic and radiation therapy, but is substantially supported by the host´s immune system. In the last few years, several mAbs and antibody constructs that selectively target CSCs have been developed and validated[16-19].

Cancer stem cells

Cancer stem cells are cancer cells that possess characteristics associated with normal stem cells, specifically the ability to give rise to all cell types found in a particular cancer sample. It is often considered to be associated with chemo- resistance and radio-resistance that lead to the failure of traditional therapy [20]. There show to be several sources from which cancer stem cells may happen. They may happen from normal ASCs (adipose-derived stromal cells), from more restricted progenitor cells or even from differentiated cells [21]. Normal stem cells are more likely to be the targets of mutants and leading to the formation of CSCs for they already possess active self-renewal pathways. It is also possible for progenitors and other differentiated cells to give rise to CSCs, though they would have to acquire more genetic mutations, especially in self-renewal genes. Cancer stem cells can represent approximately 0.1–10% of all tumor cells and their antigens are typically expressed at lower levels than the 'established' tumor-associated antigens. Unlike these, the discovery of CSC antigens was not based on their over-expression but due to their presence on populations of cells which had stem cell-like properties. However, it has been hypotheses that CSCs arising from normal stem cells are more aggressive than those from progenitor cells, though this remains to be proven [22]. The first CSC was identified in human acute myeloid leukemia (AML), showed that a rare malignant cell with the ability to repopulate the entire original disease over several transplantations, implying self-renewal and capacity to differentiate, was only found within the immature CD34+CD38-, but not the CD34+CD38+ sub-population [23]. After that, cancer stem cells were found in some solid tumors subsequently. The first solid CSCs were identified in breast tumors in 2003 [8], and then CSCs were isolated from brain [24], colon [25], melanoma [26], pancreatic [27], prostate [13], ovarian [14], lung [15] and gastric [16] cancers. The emerging picture on CSCs is creating significant excitement and interest in the cancer field. It is believe that the targeting of CSCs offers important and revolutionary advances in the targeting of cancer. Eradicating cancer stem cells, the root of cancer origin and recurrence, has thought as a promising approach to improve cancer survival or even to cure cancer[28-30]. In the research of killing cancer stem cells, many possible ways were developed to achieve this objective, including molecular targeted therapy, target molecular signaling pathways, natural compounds and their potent to target CSCs, the use of mesenchymal stem cells, and differentiation therapy. Though great progresses have been made in recent year, the accurate mechanism of cancer stem cell is still not clear and the really effective therapy is still not found[31-35].

Target signal pathways

Based on the research of the regulation mechanism of the cancer stem cell, cancer stem cells relied highly on the signal path ways' stability if they want to maintain the ability to self-renewal and differentiate. Some researchers have suggested that signal path ways' disorder or excessive activation may lead to the tumorigenicity. Understanding the mechanisms that underlie the self-renewal behavior of CSCs is of greatest importance for discovery and development of anticancer drugs targeting CSCs[36-38]. During those pathways, Wnt, Notch (figure 1) and Hedgehog signaling pathways may play an important role in the recurrence and maintenance of cancer stem cell. The signaling pathways that govern normal SC proliferation are also those promoting carcinogenesis, by initiating CSC proliferation. Deregulation of signaling pathways, such as p53/p21, Notch, Sonic hedgehog (Shh) Wnt/-catenin, Bmi-1 and Hox gene family products, can lead to transformation of SCs into CSCs A lot of efforts have been made to identify small molecules capable of disrupting aberrant Wnt/β-Catenin pathway responses induced by loss of APC, which promise such agents would be therapeutically effective against colorectal cancer and other tumors[39]. A broad spectrum of compounds seems useful to specifically modulate Wnt/β-Catenin signals. Those drugs may also help to eliminate drugs-resistant CSC, which is thought to be responsible for tumor relapse and metastasis. For instance, NSAID interferes with Wnt signaling by directly inhibiting the Wnt target COX2 (e.g. aspirin and sulindac) or by promoting degradation of TCF (Celecoxib) [34]. The compound XAV939 antagonizes Wnt signaling via stimulation of β-catenin degradation and stabilization of axin [35]. Notch signaling pathway is a highly conserved developmental pathway, which plays a critical role in cell-fate decision, tissue patterning and morphogenesis [36]. There are four human Notch receptors that consist of an extracellular peptide containing epidermal growth factor receptor-like repeats and a transmembrane pep tide. The Notch pathway functions in determining a diverse array of cell fates and regulates many cellular processes during embryonic development and throughout adulthood. It has been associated with several human cancers, including cervical, lung, breast carcinoma

and neuroblastoma. Ligand binding via the Jagged or Delta-like family of membrane proteins leads to cleavage of the receptor by members of the A Disinterring and Metalloprotease (ADAM) and γ-secretase families of proteases. The Notch pathway plays an important role in maintenance of the stem cell in glioblastoma, breast cancer stem cells and some other tumor stem cells. Since the activation of Notch signaling can up regulate several factors that in turn transmit bidirectional signals among cancer cells expressing both legends and receptors and it can also transmit signals among cancer, stroma and endothelium cells [37]. In a study learned about Notch signaling pathway in glioblastoma suggested Notch inhibition can lead to a decrease of cancer stem cells in glioblastoma via an endothelial cell intermediate [38]. In the experiment, Notch inhibition depletes CD133+ in glioblastoma and promotes increased responsiveness to radiation. Notch inhibition can be achieved in different level. 1, Inhibition of γ-secretes mediated notch cleavage.

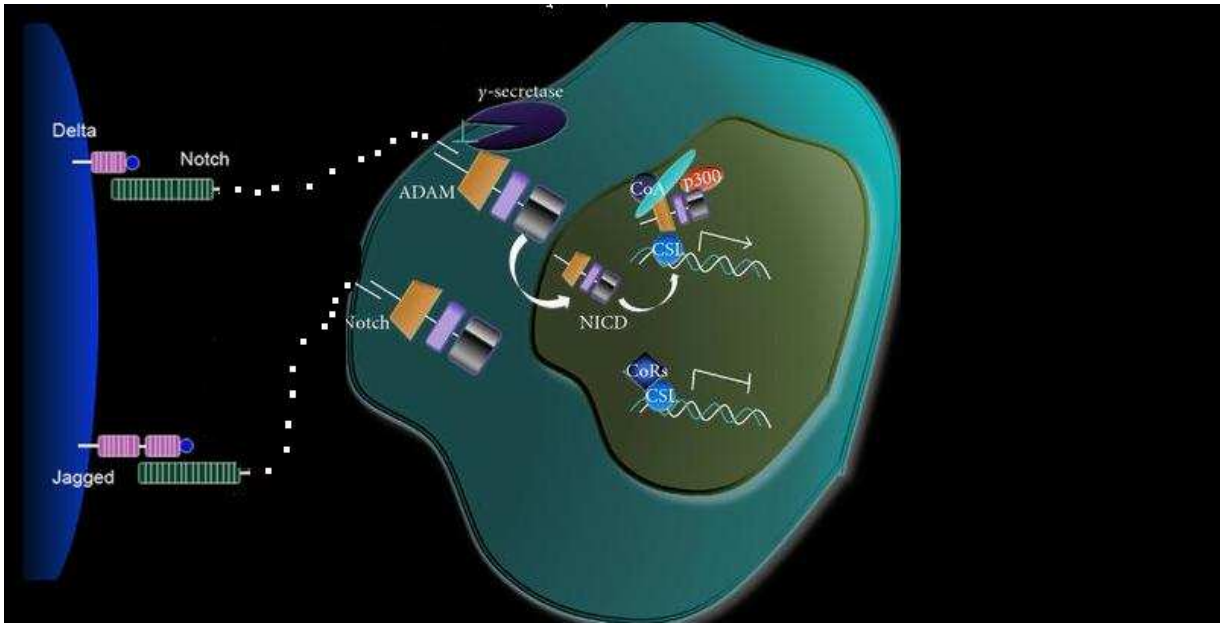

Figure 1: notch signaling pathway in cancer

Differentiation therapy

Differentiation therapy is an approach to the treatment of advanced or aggressive malignancies so that they can resume the process of maturation and differentiation into mature cells. It aims to force the cancer cell to resume the process of maturation. Differentiation therapy may use either known differentiation inducing agents and/or newly designed differentiation-inducing agents. Vitamin A and its analogue (retinoid) can reverse the malignant progression process through signal modulations mediated by nuclear retinoid receptors and altars retinoic acid leads to frequent remission of acute promyelocytic leukemia by inducing promyelocyte differentiation [39]. There has been a lot of progress in the development of small molecule drug intervention of CSC pathways. Most of drugs target the renewal pathways and still require research before they can use in a truly CSC-specific way. The potent NFκB inhibitor. The new differentiation-inducing agents are rep-resented by those legends that can normally induce stem cells to undergo asymmetric mitosis. Those agents can be delivered to the cancer stem cells to force them to switch from a symmetric to an asymmetric mitotic program. Such agents would include gene products of Want, Hedgehog, TGF, and EGF. On the other hand, using inhibitors such as antisense or ribosome agents that block specific factors, which usually either inhibit asymmetric mitosis or activate symmetric mitosis, could cause asymmetric cancer stem line mitosis [40]. Therefore, it has been shown that starvation can lead cells to become growth quiescent and at times differentiate or undergo apoptosis if their mitotic program is changed such as c-myc deregulation. Indeed, inhibitors of Wnt signaling, such as ICG-001 showed promising in vitro and in vivo efficacy without toxicity, due to its benefit of differentia-tion of colon cancer cells [41].

Considerations for Stem Cell-Mediated Antibody Therapy

Factors that must be measured when evaluate stem cells as a stage for antibody therapy include: (a) potential immunogenicity of stem cells, (b) the optimal stem cell lineage, (c)the preferred source of stem cells, and (d) whether this loom is capable of achieving therapeutic concentrations of antibody at the tumor sites.

Concentration of Antibody at Tumor Site.

A final concern is whether stem cell-mediated antibody delivery can generate a therapeutically effective concentration of antibody at the tumor site. Tumor-localized antibody production is expected to require significantly less antibody to attain therapeutic concentrations at the tumor site than systemic administration of antibodies. However, whether even this concentration can be achieved is not yet known. Factors influencing the concentration of antibody at the tumor site include: (a) the number of stem cells reaching the tumor, (b) the tumor volume covered by stem cells, (c) the amount of antibody produced per stem cell, (d) the duration of stem cell persistence at the tumor site, and (e) antibody pharmacokinetics.The number of stem cells reaching the tumor will depend, at least in part, on the number of cells delivered, strength of tumor tropism and the route of administration. Our data from glioma xenograft models indicate that intracranially injected NSCs can achieve 70%–90% tumor coverage, which may be sufficient to elicit a therapeutic effect [26].

Antibodies against CSC Surface Molecules, Anti-CSC Activity

These mAbs and antibody constructs have been demonstrated to exhibit significant anti-CSCs activity in vitro and in human xenograft mice .Anti-CD44CD44 is a transmembrane glycoprotein and the receptor for hyaloronic acid, osteoponitin, collagens, fibronection, selectin and laminin that mediates adhesive cell to cell and cell to extracellular matrix interactions through binding to hyaloronic acid and its other ligands [42]. Overexpression of CD44 is observed in many tumor cells and is associated with aggressive tumor growth, invasion and metastasis [44]. CD44 was first described as a CSC marker in breast cancer [43] and has subsequently been shown to be expressed on CSCs in bladder, gastric, prostate, pancreatic, ovarian, colorectal and hepatocellular carcinomas and head and neck squamous cell carcinomas [45]. CD44 plays an important role in the regulation of normal and malignant myelopoiesis and is abundantly expressed on leukemic blasts in all human acute myeloid leukemia (AML) subtypes and on AML CSCs [27,68-70]. Moreover, a number of recent studies suggest that CD44 fulfill some of the special properties that are displayed by CSCs, including self renewal, niche preparation, EMT and resistance to apoptosis [46]. Therefore, targeting CD44 by monoclonal antibodies shows as a reasonable strategy to eliminate CSCs [27, 40].H90 is a mouse IgG1 monoclonal antibody (mAb) directed against human CD44 [48]. Ligation of CD44 by H90 activates CD44 signaling, reverses myeloid differentiation blockage and induces myeloid differentiation in AML blasts of subtypes M1 to M5 obtained from different patients [47]. H90 also inhibits proliferation, induces terminal differentiation and mediates apoptosis in human myeloid leukemia cell lines [26]. Notably, H90 is the first mAb that has been shown to target CSCs.

Anti-CD133

Human CD133 (prominin-1) is a transmembrane single-chain glycoprotein with two large extracellular loops containing four N-linked glycosylation sites on each extracellular loop, and two small intracellular loops [13,14]. Originally identified as a cell surface antigen present on CD34+ hematopoietic stem cells [13], CD133 has recently been established as marker for the isolation and analysis of CSCs in solid tumors, including brain tumors, and colon, prostate, lung, ovarian, pancreatic and hepatocellular carcinomas [14,15]. CD133 exhibits several splice variants and different poorly characterized glycosylated isoforms, such as CD133-1 and CD133-2, which are bound by the mouse IgG1 mAbs AC133 and AC141, respectively [49]. Although AC133 has been shown to be unsuitable for the detection of CSCs in glioblastoma, because glioblastoma CSCs can solely express non-glycosylated isoforms of CD133 not detectable by AC133 or AC141 [50], colon CSCs selectively express a different CD133 epitope which is bound by AC133 and which is lost upon colon CSC differentiation [51]. Therefore, AC133 can be used for the selective detection and isolation of colon CSCs, whereas its specificity for the detection of CD133+ CSCs in other solid tumors is uncertain [52]. Two mAbs, 32AT1672 (mouse IgG1) and C24B9 (rabbit IgG) that recognize unmodified non-glycosylated epitopes of CD133 are commercially available for research purpose [53]. C24B9 has recently been shown to detect a truncated variant of the CD133 protein expressed by glioblastoma cells that could not be detected by AC133 [54], ultimately indicating that CD133 exhibits numerous variants and epitope modifications detected by different mAb species. Therefore, it is still questionable whether CD133 represents a specific marker for CSCs and a therapeutic target for antibody-mediated elimination of CSCs.

REFERENCES

[1] Heron M. *Natl Vital Stat Rep* **2007**;56:1–95.
[2] Calvocoressi L, Sun A, Kasl SV, et al. *Cancer* **2008**;112:473–480.
[3] Minino AM, Heron MP, Smith BL. *Natl Vital Stat Rep* **2006**;54:1–49.
[4] Martínez-Climent JA, Andreu EJ, Prosper F. *Clin TranslOncol* **2006**;8:647–663.
[5] Graziano A, d'Aquino R, Tirino V, et al. *J Cell Biochem* **2008**;103:408–412.
[6] Wicha MS, Liu S, Dontu G. *Cancer Res* **2006**;66:1883–1890. 1895–1896.
[7] Fukata M, Chen A, Vamadevan AS, Cohen J, Breglio K, Krishnareddy S, et al. *Gastroenterology* **2007**;133: 1869–81.
[8] McCarthy EF. The toxins ofWilliamB. *Iowa Orthop J* **2006**;26:154–8.
[9] Thotathil Z, Jameson MB. *Expert Opin Investig Drugs* **2007**;16:1391–403.
[10] Guan Y, Ranoa DR, Jiang S, Mutha SK, Li X, Baudry J, et al. *J Immunol* **2010**;184:5094–103.
[11] Hasan U, Chaffois C, Gaillard C, Saulnier V,Merck E, Tancredi S, et al. *J Immunol* **2005**;174:2942–50.
[12] Chaturvedi A, Pierce SK. *Traffic* **2009**;10:621–8.
[13] Smits EL, Ponsaerts P, Berneman ZN, Van Tendeloo VF. *Oncologist* **2008**;13:859–75.
[14] Liu L, Botos I, Wang Y, Leonard JN, Shiloach J, Segal DM, et al. *Science* **2008**;320:379–81.
[15] Nicolis SK. *Neurobiol Dis* **2007**;25:217–229.
[16] Dontu G, Wicha MS. *J Mammary Gland Biol Neoplasia* **2005**;10:75–86.
[17] Ginestier C, Hur M, Charafe-Jauffret E, et al. *Cell Stem Cell* **2007**;1:555–567.
[18] Bonnet D, Dick JE. *Nat Med* **1997**;3:730–737.
[19] Al-Hajj M, Wicha MS, Benito-Hernandez A, et al. *Proc Natl Acad Sci U S A* **2003**;100:3983–3988.
[20] Ponti D, Costa A, Zaffaroni N, et al. *Cancer Res* **2005**;65:5506–5511.
[21] Krivtsov AV, Twomey D, Feng Z, et al. *Nature* **2006**;442:818–822.
[22] Park HD, Lee Y, Oh YK, Jung JG, Park YW, Myung K, et al. *Oncogene* **2011**;30:201–11.
[23] Sheyhidin I, Nabi G, Hasim A, Zhang RP, Ainiwaer J, Ma H, et al. *World J Gastroenterol* **2011**;17:3745–51.
[24] Gonzalez-Reyes S, Marin L, Gonzalez L, Gonzalez LO, del Casar JM, LamelasML, et al. *BMC Cancer* **2010**;10:665.
[25] Grimm M, Kim M, Rosenwald A, Heemann U, Germer CT, Waaga- Gasser AM, et al. *Eur J Cancer* **2010**;46:2849–57.
[26] Wang EL, Qian ZR, NakasonoM, Tanahashi T, Yoshimoto K, Bando Y,et al. *Br J Cancer* **2010**;102:908–15.
[27] Zhang JJ, Wu HS, Wang L, Tian Y, Zhang JH, Wu HL. *World J Gastroenterol* **2010**;16:2881–8.
[28] Dvorak HF. Tumors: wounds that do not heal. *N Engl J Med* **1986**;315: 1650–9.
[29] Chen GG, Lee JF, Chan UP, Xu H, Ip PC, LauWY. *Arch Pathol Lab Med* **2002**;126:686–91.
[30] Wang Q, Takei Y, Kobayashi O, Osada T, Watanabe S. *J Clin Biochem Nutr* **2009**;45:163–70.
[31] Glynn SA, Boersma BJ, Dorsey TH, YiM, Yfantis HG, Ridnour LA, et al. *J Clin Invest* **2010**;120:3843–54.
[32] Glynn SA, Prueitt RL, Ridnour LA, Boersma BJ, Dorsey TM, Wink DA, et al. *BMC Cancer* **2010**;10:626.
[33] Russo J, Balogh GA, Heulings R, et al. *Eur J Cancer Prev* **2006**;15:306–342.
[34] Britt K, Ashworth A, Smalley M. *Endocr Relat Cancer* **2007**;14:907–933.
[35] van Garderen E, Schalken JA. *Mol Cell Endocrinol* **2002**;197:153–165.
[36] Foulkes WD. *J Med Genet* **2004**;41:1–5.
[37] Liu S, Ginestier C, Charafe-Jauffret E, et al. *Proc Natl Acad Sci U S A* **2008**;105:1680–1685.
[38] Bendell JC, Domchek SM, Burstein HJ, et al. *Cancer* **2003**;97:2972–2977.
[39] Slamon D, Pegram M. *Semin Oncol* **2001**;28:13–19.
[40] Korkaya H, Paulson A, Iovino F, et al. HER-2 Signaling regulates the mammary stem/progenitor cell population driving tumorigenesis and invasion. Cancer Cell. in press
[41] Panigrahi AR, Pinder SE, Chan SY, et al. *J Pathol* **2004**;204:93–100.
[42] Saal LH, Gruvberger-Saal SK, Persson C, et al. *Nat Genet* **2008**;40:102–107.
[43] Rossi DJ, Weissman IL. *Cell* **2006**;125:229–231.
[44] Li Y, Bu G. *Future Oncol* **2005**;1:673–681.
[45] Turashvili G, Bouchal J, Burkadze G, et al. *Pathobiology* **2006**;73:213–223.
[46] Uyttendaele H, Soriano JV, Montesano R, et al. *Dev Biol* **1998**;196:204–217
[47] Brennan K, Brown AM. *Breast Cancer Res* **2003**;5:69–75.
[48] Miele L, Golde T, Osborne B. *Curr Mol Med* **2006**;6:905–918.
[49] Pece S, Serresi M, Santolini E, et al. *J Cell Biol* **2004**;167:215–221.
[50] Echeverri CJ, Beachy PA, Baum B, et al. *Nat Methods* **2006**;3:777–779.

[51] Dontu G, Jackson KW, McNicholas E, et al. *Breast Cancer Res* **2004**;6:R605–R615.
[52] Nickoloff BJ, Osborne BA, Miele L. *Oncogene* **2003**;22:6598–6608.
[53] Liu S, Dontu G, Mantle ID, et al. *Cancer Res* **2006**;66:6063–6071.
[54] Patocs A, Zhang L, Xu Y, et al. *N Engl J Med* **2007**;357:2543–2551.