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**An overview of the role of cancer stem cells in spine tumors with special focus on chordoma**

Safari M *et al*. Cancer stem cells in spine tumors

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**Abstract**

Primary malignant tumors of the spine are relatively rare, including less than 5% of all spinal column tumors. However, these lesions are often among the most difficult to treat and encompass challenging pathologies such as chordoma and a variety of invasive sarcoma**s**. The mechanisms of tumor recurrence after surgical intervention as well as resistance to radiation and chemotherapy remain a pervasive and costly problem. Recent evidence has emerged supporting the hypothesis that solid tumors contain a sub-population of cancer cells that possess characteristics normally associated with stem cells. Particularly, the potential for long-term proliferation appears to be restricted to subpopulations of cancer stem cells (CSCs) functionally defined by their capacity to self-renew and give rise to differentiated cells that phenotypically recapitulate the original tumor, thereby causing relapse and patient death. These cancer stem cells present a unique opportunity to better understand the biology of solid tumors in general, as well as targets for future therapeutics. The general objective of the current study is to discuss the fundamental concepts to understanding the role of CSCs with respect to chemoresistance, radioresistance, special cell surface markers, cancer recurrence and metastasis in tumors of the osseous spine. This discussion is followed by a specific review of what is known about the role of CSCs in chordoma, the most common primary malignant osseous tumor of the spine.

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**Key words:** Spine tumor; Chordoma; Cancer stem cell; Stem cell marker; Chemoresistance

**Core tip:** Primary malignant tumors of the spine are relatively rare, including less than 5% of all spinal column tumors. However, these lesions are often among the most difficult to treat and encompass challenging pathologies such as chordoma and a variety of invasive sarcoma**s**. The mechanisms of tumor recurrence after surgical intervention as well as resistance to radiation and chemotherapy remain a pervasive and costly problem. Recent evidence has emerged supporting the hypothesis that solid tumors contain a sub-population of cancer cells that possess characteristics normally associated with stem cells. These cancer stem cells could be targets for future therapeutics.

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**INTRODUCTION**

The concept of cancer stem cells that is sufficient for the initiationand maintenance of tumors and underlies treatment resistance hasreceived significant attention in many areas ofoncology[1,2]. Recent studies have provided evidence that cancer stem cells (CSCs) exist in a variety of human tumors, including brain and thyroid tumors, melanoma, breast cancer, prostate tumors and gastroenterological cancers[3,4]. It should be noted that CSCs from different cancers, leukemia and solid tumors, might be different in their phenotypic properties and self-renewal pathways, thus these cells will need to be defined for each disease[5]. Cancer stem cells are typically recognized by virtue of the expression of cell surface markers. CD133, nestin and recently CD90 have been considered the putative markers of CSCs in malignant cancers, including glioblastoma multiform (GBM). Unlike non-tumor stem cells, tumor stem cells lack the normal mechanisms that regulate proliferation and differentiation, resulting in uncontrolled production and incomplete differentiation of cancer cells[6]. These cells are considered to be tumorigenic in contrast to the bulk of cancer cells, which are thought to be non-tumorigenic and also responsible for progression, metastasis and relapse after treatments[5]. The presence of such cells has also been demonstrated in spine tumors[7]. Spinal tumors are uncommon lesions and affect only a minority of the population but can cause significant morbidity in terms of limb dysfunction and mortality as well[8,9]. The current theory implies that stem cells may play an important role in tumors of the osseous spine. In support of this hypothesis, there is increasing evidence pointing to the existence of a subset of tumor cells with high tumorigenic potential in many spine tumors[7]. It has been recently investigated that chordoma cells and cancer stem cells exhibit similar characteristics, including self-renewal, differentiation, metastasis, therapeutic resistance and recurrence of cancer[10,11]. In studies of chordoma stem cells, the most promising findings concern how stem cells may offer a reasonable explanation of why this tumor is so difficult to eradicate and suggest how new therapies might be targeted. In this review we present current evidence regarding the role of cancer stem cells in spine tumors, highlighting new insights and unresolved issues in the identification of this elusive population in chordoma.

**THEORY OF CANCER STEM CELLS**

The cancer stem cell theory was first postulated about 50 years ago, whereas it is only in the last 10 years that advances in stem cell biology have provided direct evidence supporting this hypothesis[11,12]. It has been proposed that tumors are organized by a hierarchy of heterogeneous cell populations with different proliferation potentials in which the capability to initiate tumor formation and promote tumor growth exclusively resides in a small subpopulation of cancer cells (< 1%) termed cancer stem cells or tumor- initiating cells (Figure 1)[13,14]. In general, the most important criteria to define CSCs are: cancer-initiating ability on orthotopic implantation, genetic alterations, aberrant differentiation properties, capacity to generate non-tumorigenic end cells and multi lineage differentiation ability[15,16]. Numerous investigations have suggested that the introduction of key mutations known to cause aberrations in key signaling pathways can transform normal stem cells into tumor- initiating cells[7,17]. Nevertheless, other experimental evidence have manifested that the introduction of certain oncogenes can transform more differentiated cell types into cancer cells that result in tumors[18]. Moreover, current studies have considered the role of hypoxia in cancer by demonstrating different responses to hypoxia between heterogenic subpopulations within the tumor[19,20]. This sensitivity of tumor structure to oxygen status is driven by the hypoxia inducible factors (HIF) proteins in the CSCs population. The HIFs have been determined to be expressed in the cancer stem cell, possibly promoting the stem-like phenotype and driving tumor growth. Notch signaling has also a significant role in the formation of numerous malignancies; therefore, hypoxia may promote Notch signaling in cancer stem cells and maintain them in an undifferentiated state[21]. Since the presence of cancer-initiating cells within a cancerous mass greatly impairs long-term survival after therapy, it is imperative to understand the characteristics of these cells, including their specific markers and the molecular mechanism for their resistance to conventional therapies[22].

**CANCER STEM CELL MARKERS**

Certain barriers complicate the characterization and isolation of CSCs within tumor bulk, particularly chordoma. Among these obstacles are the facts that stem cells are relatively rare and lack a unique morphology that is easily distinguished from its progeny *in vivo*[23,24]. In an effort to identify specific markers to enrich this population, many groups have used assays based on cell-surface proteins such as CD20,CD24, CD34, CD90, CD44, CD133, stage-specific embryonic antigen 1 (SSEA-1), nestin, integrin α6, epithelial-specific antigen (ESA), efflux activity (side-population cells), and more recently, label-retention (Table 1)[25-27]. It is highly noticeable that the expression of CSC surface markers is tissue type-specific, even tumor subtype-specific[28]. In addition, aldehyde dehydrogenase (ALDH1) is a marker used initially for the enrichment of normal stem cells and has recently been used to identify CSC in colon, breast, and lung cancers[14,29,30]. Noticeably, one of the biggest challenges of using ALDH as a marker of CSC is the arbitrary nature of the 2 or 3% cut-off of cells with the highest and lowest ALDH activity[31]. Expression of stem cell genes such as (sex determining region Y)-box2 (SOX2), octamer-binding transcription factor 4 (OCT4) and NANOG is also used as a marker of tumor-initiating cells (TICs). These genes are found in embryonic stem cells and appear to be essential for maintenance of an undifferentiated state, pluripotency, and self-renewal [32].

**ROLE OF CSCS IN CANCER METASTASIS**

Metastasis, frequently a final and fatal step in the progression of solid malignancies, encompasses several fundamental biological events: cancer initiation, breach of the basement membrane barrier, vascularization, invasion, detachment, embolization, survival in the circulation, arrest, extravasation, evasion of the host defense and progressive growth[33,34].

According to cancer stem cell theory, CSCs are favorable seeds of metastasis. Brabletz *et al*[35] firstly proposed the hypothesis of migrating CSCs, which possess both an element of stemness and mobility[36]. Evidence has been offered that EMT (epithelial-to mesenchymal transition) represents a crucial step towards invasiveness and metastasis, and is strongly associated with poor clinical outcome in a variety of tumors[37]. Importantly, EMT endows human mammary epithelial cells with CSCs-like properties which characterized by their CD44high/CD24low phenotype through up-regulating Mena, member of the Ena/VASP family which plays a significant role in tumor metastasis[38,36]. In fact, induction of EMT in immortalized human mammary epithelial cells led to the expression of stem cell markers, gain of mesenchymal characteristics, and phenotypes associated with CSCs[39]. These observations established a direct link between EMT and the acquirement of properties of migratory stem cells. Moreover, it has been found that up regulation of some micro RNAs and down regulation or absence of some of them have been observed in metastatic CSCs. For instance, over-expression of miR-30 in breast CSCs xenograft reduced lung metastasis, whereas blocking miR-30 expression increased metastasis *in vivo*[40]. Target genes with an established role in tumor cell invasion, migration, and other steps in the metastatic process have been identified for many miRNAs, including MMPs, HER receptors, BMPs, PTEN, ZEB1, ZEB2, or E-cadherin[41]. Additional evidence demonstrated that a subpopulation of migrating CD133+ CXCR4+ cancer stem cells is essential for tumor metastasis. Hermann *et al*[42] have also shown that CD133 +CXCR4+ subsets determined the migrating phenotype of pancreatic cancer, although both CD133+CXCR4+ and CD133+CXCR4- pancreatic cancer stem cells were able to form pancreatic cancer when transplanted into athymic mice [33]. In addition, the CXCR4/SDF-1 axis could mediate metastasis of the distinct subpopulation of CSCs. On the basis of the provided histological evidence for the existence of CXCR4+ CSC in the invasive front of human tumor specimens, it has been hypothesized that a specific subset of CXCR4+ CD133+ CSC plays an important role in tumor metastasis[43].

**MECHANISMS OF CSCS RESISTANCE TO THERAPY**

***Chemoresistence***

It has become increasingly evident that CSCs are uniquely resistant to standard chemotherapeutic agents compared with their non–stem cell. There are several criteria attributed to the role of CSCs in Chemoresistance: (1) Entrance into a long-term latent state; (2) CSCs activate DNA damage response; (3) Dormant CSCs are concealed in vascular niche with lower concentrations of reactive oxygen species.

CSCs highly express multi-drug resistance due to up-regulation of cellular efflux pumps[5,44,45]. Although there is a growing body of literature considering the role of CSCs in the Chemoresistance for different malignancies including breast, lung, glioblastoma multiforme (GBM), head and neck, and pancreatic cancer, there is a paucity of literature focusing specifically on this subject for spine tumors[46-50]. For instance, Jiang *et al*[31] investigated the expression of CD133 in primary Ewing’s tumors and cell lines to see if there was a correlation between CD133 expression and chemoresistance. Similarly, functional studies of CD133+ and CD133- fractions derived from Ewing’s sarcoma family tumors (ESFT) cell lines demonstrated that, although CD133+ cells could be isolated from all ESFT cell lines, only CD133+ cells isolated from the STA-ET-8.2 cell line displayed evidence of stem cell characteristics and chemo-resistance[51]. Noticeably**,** CD133+ glioblastoma cells chemoresistance may be caused by an over expression of genes important in drug resistance such as BCRP1, DNA-mismatch repair (MGMT), and inhibition to cell apoptosis (FLIP, BCL-2, BCLXL)[52,53]. Bleau *et al*[54] reported that down-regulation of autophagy-related proteins play a significant role in the resistance of CD133 glioma cells to temozolomide (TMZ). The role of CSCs in chemoresistance has also been investigated in tumors (most natably breast and lung cancer) that commonly metastasize to the spine[55,56]. For example, it is well established that tumorigenic breast cancer cells expressing high levels of CD44 and low or undetectable levels of CD24 may be resistant to standard dose chemotherapy (docetaxel, doxorubicin, cyclophosphamide and trastuzumab) and therefore responsible for cancer relapse[28,57]. Moreover, several studies implicate ATP-binding cassette super family as one type of multi drug resistant proteins, which can pump chemotherapy drugs out of the cell and lead to chemoresistance[33,58]. ABCG2 is one of the most important member of this family and represents a purified marker of cancer stem cells transporters and its substrates include many commonly used drugs in cancer chemotherapy[59]. Despite these finding demonstrating the relationship between cancer stem cells and chemoresistance, further studies are essential to provide direct evidence supporting the existence of chemotherapy-resistant CSCs in order to develop alternative strategy for targeted therapy**.**

***Radioresistance***

Radiation therapy is crucial in the treatment of the majority of spine tumors, whether in combination with chemotherapy and/or surgical resection[60]. There is considerable evidence to suggest the role of CSCs in the resistance of a wide panel of tumors to radiation therapy[61]. Diehn *et al*[62] suggested that human and mouse cancer stem cells contained lower levels of reactive oxygen species (ROS), compared with their non-tumorigenic progeny. Thus, the heterogeneity of (ROS) levels in a subsets of CSCs may contribute to their radioresistance[33,63]. Based on this evidence**,** it is possible that the poor tumor control associated with chordoma may be due to hypoxic effects and/or cancer stem cells which are resistant to ionizing radiation and chemical agents[64,65]. Recent clinical data suggest that the combination with topoisomerase II inhibitor razoxane improve the effectiveness of chordoma radiotherapy[64,66]. Bao *et al*[67] have recently shown that CD133+positive glioma cells survive ionizing radiation by preferentially activating DNA damage response and also inhibiting the cell cycle checkpoint kinases Ch1 and Ch2 sensitised the resistant cells to radiotherapy[68]. As a result, CD133+ positive cell fraction seems to be responsible for acquiring radioresistance and presumably is one of the main source of tumor recurrence after radiotherapy[69]. More importantly, in CD133 positive glioma stem cells the expression of the autophagy-related proteins LC3, ATG5 and ATG12 was increased as a response to radiation[70]. Noticeably, other stem cell mechanisms, including notch, hedgehog, PTEN and EGFR may also have a role in CSCs radioresistanc[71-75].

**ROLE OF CSCS IN PRIMARY SPINE TUMORS**

***Chondrosarcoma***

Chondrosarcoma is the most common primary malignant bone tumor of chondrogenic origin, typically occurring in the fourth and fifth decades of life [76,77]. Molecular lesions and aberrant oncogene expression in the p16INK4a/pRb pathway may be characteristic of this tumor[78]. Chondrosarcoma is most commonly observed in the petrous portion of the temporal bone as well as in petrooccipital, spheno-occipital, and sphenopetrosal synchondroses areas [79]. The treatment of chondrosarcoma is usually limited to wide-margin surgical resection and conventional radiation therapy and chemotherapy have not been proven to be effective[80,81]. Recent studies demonstrated that resistance to chemotherapy may be attributed to multidrug resistance-1 and to P-glycoprotein expression[82]. Based on histopathology, chondrosarcoma is able to divide into primary subtypes: conventional, dedifferentiated, clear cell, and mesenchymal and only 12% of all skull base chondrosarcomas show mesenchymal characteristics[83,84]. Importantly, chondrosarcomas with mesenchymal features are associated with an approximately tenfold increase in 5-year mortality, compared to those with conventional histopathologic traits[79]. The novel findings suggest that this tumor differentiates along the chondrocytic lineage and normal differentiation of mesenchymal stem cells into chondrocytes is accompanied by sequential production of characteristic extracellular matrix proteins[85,86]. Transcription factor SOX9 is also involved in the activation of chondrogenesis from mesenchymal chondroprogenitor cells in an adult organism during fracture repair. Furthermore, increased expression of SOX9 and the prechondrogenic splice variant type IIA collagen in chondrosarcomas provides further evidence that these tumors may originate from a multipotent stem cell committed to differentiation along the chondrogenic pathway[7,87].

***Osteosarcoma***

Osteosarcoma, the most common primary malignant tumor of bone, is among a group of mesenchymal tumors identified by clinical, histologic and molecular heterogeneity, and karyotypes with a high degree of aneuploidy[88]. It is an aggressive bone tumor of osteoblastic origin which primarily affects children and young adults[89,90]. Despite modest advances in surgical resection techniques and chemotherapy regimens, long-term survival rates for osteosarcoma have had no significant improvement, stable at approximately 65%, attributable to the aggressive malignant potential and early metastasis[91]. Lesions frequently occur in the metaphyses of long bones, which express the major pool of mesenchymal stem cells[92]. Recent studies suggest the existence of stem-like cells in primary osteosarcomas and cell lines derived from human osteosaracoma in a subpoplation of cells capable of self-renewal [14, 93]. These cells have been detected in spherical clones under anchorage- independent, serum-starved culture conditions, as side population cells based on efflux of Hoechst 33342 dye or using cancer stem cell markers[94,95]. The identification of CSCs in human osteosarcoma has been more difficult than in tumors originating from other types of tissues[96,97]. Because of differences in mesenchymal origin, the markers that have been characterized and developed for epithelial, hematologic and neural cancers are not necessarily useful for isolation of CSCs from human osteosarcoma[14]. There is preliminary evidence that osteosarcoma stem cells express the mesenchymal stem cell markers CD133, CD117, ABCG2, CXCR4, ICAM-1 and nucleostemin as well as key marker genes Oct3/4 , Nanog, Stat3 and Sox2 [91, 98]. It has been also reported that osteosarcoma stem cells express more anti-apoptotic proteins, including Bcl-2, FLIP, apoptosis inhibitor XIAP, IAP-1, IAP-2 and survivin, than normal osteosarcoma cells[99]. In addition, Wang et all have shown that CSCs could be identified in the established human osteosarcoma OS99-1 cell line based on high aldehyde dehydrogenase (ALDH) activity[90]. More importantly, cells with elevated ALDH activity preferentially represented the stem cell markers Nanog, Oct3/4A and Sox-2 compared with cells with low ALDH1 activity[7]. Mohseny *et al*[100] and Tang *et al*[101] have reported that mesenchymal stem cells or osteoprogenitor cells, because of disruption in the osteoblast differentiation pathway, develop Osteosarcoma. Different pathways, including HH, NOTCH, Wnt/ β-catenin and MAPK, may also be involved in the determination of the fate of osteosarcoma stem cells[11,102,103].

***Ewing sarcoma***

The Ewing’s sarcoma family of tumors (ESFT) is the second most frequent solid bone and soft tissue malignancy of childhood and young adults [104, 105]. Genetically, this tumor is associated with specific chromosomal translocations that result in the formation of fusion genes encoding proteins composed of the transactivation domain of EWS and the DNA binding domain of one of five ETS family transcription factors, including ERG, ETV1, FLI1, FEV, and ETV4[106]. The EWS-FLI1 fusion protein is a favorable candidate for targeted therapy as its expression is limited to tumor cells and is critical for initiation and maintenance of the tumor[107]. Further evidence suggests that the regulation of EWS-FLI1 in hypoxic environments may occur at the posttranscriptional level, which is supported by the observation that HIF-1a-activated genes, such as vascular endothelial growth factor (VEGF), Aldolase-C, GLUT-1, CA9, and IGFBP3, were increased under hypoxia[20]. Interestingly, the histological features of Ewing’s sarcoma suggest that this tumor may arise from a neural crest stem cell exhibiting mesenchymal features or from a mesenchymal stem cell that is neural derived [108]. It has been also investigated that human and mouse bone marrow (BM) mesenchymal stem cells expressing EWS-Fli-1, when engrafted into NOD/SCID mice, induce a malignancy with similar pathologic charactristics as Ewing sarcoma[105,109]. Other evidence implicates a significant role of cancer stem cells in Ewing sarcoma pathogenesis. For instance, it has been reported that the cell surface glycoprotein CD133 is a marker of tumor-initiating cells in ESFT. In fact, functional studies of CD133+ and CD133- fractions derived from ESFT cell lines provide new insight into the biology of these tumors and constitutes the first identification of CSCs in a human sarcoma [110]. Notably, although CD133+ cells could be isolated from all ESFT cell lines, only CD133+ cells isolated from the STA-ET-8.2 cell line exhibited evidence of stem cell features and chemoresistance[51]. Recently, Suva *et al*[111] demonstrated that the cell surface marker CD133/Prominin-1, which has been associated with CSCs in glioblastoma, can also be used to isolate a subpopulation of Ewing sarcoma cells. Awad et all have reported that the subpopulation of ESFT cells that express the highest levels of ALDH have some characteristics of stem cells, including the capacity to generate a heterogeneous population, in vitro clonogenic activity and *in vivo* tumorigenic activity[107]. The current standard treatment for ESFT is chemotherapy with intercalated loco regional management with surgery for patients with localized disease[112]. Accumulating data demonstrated that Ewing sarcoma stem cells (ESSC) are resistant to two of the standard agents used to treat ESFT – doxorubicin and etoposide, suggesting that these cells have relatively higher transport protein activity than the bulk population, and chemoresistance is reversed by verapamil, an inhibitor of ABC transport proteins[107].

***Multiple myeloma***

Multiple myeloma (MM) is a clonal B-cell malignancy characterized by clonal expansion of malignant bone marrow cells engaged in the production of a unique monoclonal immunoglobulin(IG)[113]. This tumor has a reported incidence of 5 per 100000 persons and is the cause of 1% of all cancer-induced deaths[114]. More than 70% of multiple myeloma patients may present with bone disease as the onset symptom or develop osteolytic lesions, osteoporosis, or spinal compression fractures during the development of the disease[115]. This is a result of either erosion of bone caused by direct infiltration of plasma cells or secretory factors released by plasma cells resulting in an imbalance in bone metabolism[7]. Analysis of the immunoglobulin gene sequence itself has provided significant insights into the stage of normal B cell development that gives rise to this tumor[116]. Several key observations providing evidence for the role of cancer stem cells in multiple myeloma, and these CSCs have characteristics similar to those of memory B cells[117]. It has been demonstrated that CD138+ multiple myeloma plasma cells cannot undergo long-term proliferation but rather arise from clonogenic CD138neg B cells[118]. It has been investigated that CD138- cells isolated from both established multiple myeloma cells lines as well as from clinical bone marrow (BM) samples give rise to colonies and could be successfully replated, whereas CD138+ cells did not. In contrast to CD138+ cells, CD138- MM cells from human BM were capable of successful engraftment into NOD/SCID mice, indicating their potential for self-renewal[7,119]. In addition, CD138- MM stem cells isolated from cell lines expressed CD19 and CD20 molecules characteristic of B lymphocytes[119]. Ghosh and Matsui investigated the functional role of Hedgehog signaling on multiple myeloma stem cells and found that pathway activation by Hedgehog ligand induced the expansion of less differentiated CD138neg cells, whereas pathway inhibition using a monoclonal neutralizing antibody against Hedgehog ligands or the naturally occurring small molecule inhibitor cyclopamine limited subsequent clonogenic growth[116,119,120]. Moreover, the embryonic stem cell-associated antigen SOX2 may represent another potential antigen expressed by multiple myeloma stem cells[121]. Potentially curative treatment of MM consists of standard chemotherapeutic agents (dexamethasone, lenalidomide, bortezomib, and cyclophosphamide, thalidomide) followed by autologous or allogeneic stem cell transplantation (SCT)[7,114]. Despite the availability of novel therapies, multiple myeloma remains incurable for the vast majority of patients suggesting that cancer stem cells with the growth capacity to mediate relapse are relatively resistant to these clinical strategies. It has been shown that circulating clonotypic B cells may persist following systemic treatment and their frequency increases during clinical relapse[122]. These findings suggest that these cells are drug resistant and mediate tumor regrowth and supports our data that multiple myeloma stem cells are not inhibited by these drugs[123].

**GIANT CELL TUMOR**

Giant cell tumors (GCTs) are the second most common primary sacral tumor after chordomas with a generally benign course and frequently located at the meta-epiphyseal region of long bones including the distal femur, proximal tibia and the radius[124]. Benign GCTs mostly account for expansive osteolytic defects associated with significant bone destruction and represent a high recurrence rate[125]. GCTs are characterized by multinuclear giant cells scattered among a mass of mononuclear cells[126]. The currently favored hypothesis indicates that giant cell tumors of bone contain a subpopulation of cells, localized in the stromal component of the tumor that is spindle shaped and expresses antigens related to the mesenchymal stem cell[127]. Interestingly, this subpopulation has been identified to express mesenchymal stem cell (MSC) markers like CD73, CD105 and CD166 as well as the mesenchymal markers FGFR3 (fibroblast growth factor receptor 3), collagen type IIa and CD34+ antibody[128]. Evidence has also been offered that giant cell tumor stromal cells (GCTSC) show differentiation features of mesenchymal stem cells in the form of CD105 (SH2) and CD73 (SH3, SH4) markers, in addition to expressing markers of early osteoblastic differentiation (Thy 1.1, Stro1)[129]. In support of this hypothesis, Lan *et al*[130] confirmed the heterogeneity in stromal cells (SCs) of GCTB, showing that there were at least two different subsets of cells: Stro-1+ and Stro-1-. Both subpopulations can be further subtyped using additional markers such as CD117, CD133, and CD44. Taking this into account, up-regulation of these markers (CD117, CD113, and CD44) in Stro-1+ SCs further implies that the Stro-1+ subset is enriched with TSCs and may suggest that CD117, CD113, and CD44 may have key roles in the function of tumor stem-like cells in GCTs. Recent clinical studies have used interferon alpha-2b, denosumab, and bisphosphonates to treat inoperable GCTB, but the optimal treatment and medical management of this tumor in the spine and sacrum has not been well established[130,131]. Because these agents mainly inhibit angiogenesis or osteoclast-induced osteolysis in GCTB rather than eliminating the neoplastic SCs.

***Chordoma***

Chordoma is the most common primary malignant bone tumor of the spine that accounts for 1%–4% of all bone malignancies[132]. The median age is 58.5 years, but skull-base presentations affect a younger age, and may even appear in children and adolescents[133]. Chordoma is believed to arise from vestigial notochordal remnants or ectopic notochordal tissue and can occur along the whole length of the spine[134]. chordomas were characterized by their physaliferous

features and immunoreactivity for S-100 and epithelial markers such as epithelial membrane antigen (MUC1) and cytokeratins. In fact, the term chordoma was first introduced by Ribbert in the 1890s, in view of the notochord hypothesis[135]. It has been shown that notochordal cell nests topographically correspond and distribute to the sites of occurrence of chordoma. Perhaps the discovery of brachyury transcription factor in familial chordoma was the most compelling evidence of the notochordal hypothesis[136]. Brachyury is highly expressed in chordoma but not in a wide variety of normal or neoplastic tissue, therefore, could be a novel discriminating biomarker for this tumor [137]. In addition, brachyury regulates several compelling stem-cell genes and has been implicated in promoting epithelial–mesenchymal transition in other human carcinomas[138]. Chordomas are traditionally considered to be slow-growing, radioresistant tumors that are locally aggressive and invasive**)**[10]. Chordomas have the potential for metastases, with extension to the lungs, bone, brain, skin and liver and also the high tendency for local recurrence[139]. Despite advances in radiotherapy techniques, including charged particle (proton beam) radiotherapy for cranial disease, surgery remains the mainstay of chordoma management[140]. Some case studies reported that complete radical resection produces better local control compared with subtotal resection and chemotherapy, however, due to the anatomical location of these tumors, gross total resection can be very challenging[64,134]. It is suggested that PI3K/AKT/TSC1/TSC2/mTOR pathway and epidermal growth factor receptor (EGFR) are potential therapeutic targets for chordoma and the combination with topoisomerase II inhibitor razoxane enhances the effectiveness of radiation therapy in this tumor[141].

There is increasing evidence suggesting that the poor tumor control associated with chordoma may be due to hypoxic effects and/or cancer stem cells which are resistant to ionizing radiation and chemical agents in *in vivo* tumor environment[64]. More recently, a positron emission tomography (PET) study also revealed that a substantial volume of chordoma is hypoxic[142]. Therefore, it is reasonable to consider that chordoma tumors contain a large fraction of hypoxic area. More evidence is now available that cancer stem-like cells may be present in chordoma, contributing to its aggressive nature. Aydemir et al, have shown for the first time that chordoma cells (U-CH1 cells) and tissues express all the common stem cell markers, including oct4, klf4, c-myc, and sox2, and embryonic stem cell markers SSEA-1 and nanog, according to the gene expression analysis[10]. Moreover, they have revealed that chordoma cells are enriched by cancer stem-like cell markers, namely CD133 and CD15, which are able to live in a nonadherent soft agar medium, demonstrating a self-renewal capability. Importantly, these cells could be differentiated into another mesenchymal lineage (an osteogenic lineage) when treated with an osteogenic differentiation agent, indicating that a subpopulation of chordoma cells may possess cancer stem-like characteristics. Further evidence for the existence of a cell population with stem cell properties in human chordoma has been recently reported by Hsu et al. They have established a stable chordoma cell line that is morphologically identical to classic chordoma with expression of brachyury, S100 and keratin. Chordoma sarcospheres were found to be self-perpetuating and exhibited higher expression of the functional stem cell marker ALDH1 compared to typical chordoma cells. Moreover, sarcospheres were able to successfully differentiate into neuroepithelial and mesodermal cell types. The mechanism that controls the formation of chordoma is not clearly understood, however, the resistance of chordoma to chemotherapy and radiation therapy as well as the high rate of recurrence after surgical resection suggests that CSCs may play a role in the pathogenesis of this tumor. Therefore, understanding the molecular pathways that control the maintenance and differentiation ability of normal stem cells and cancer stem cells may contribute to new strategy for treating chordoma.

**CONCLUSION AND FUTURE PERSPECTIVES**

Since the discovery of oncogenes and tumor suppressor genes established the genetic nature of cancer, the cancer stem cell hypothesis is probably the only novel notion that has provided distinct new views in cancer biology in the last decade. Although knowledge of the identification and characterization of CSCs are quickly expanding, little is known about the cellular and molecular mechanisms underlying their distinct functions. Recently, emerging studies have focus on the roles of CSCs in the pathogenesis of many tumors, including spine tumors. However, there have been scarce numbers of publications focusing on the potential role of CSCs in chordoma. Perhaps the rarity of this tumor coupled with a lack of cell lines available to facilitate investigation explains the paucity of literature in this subject.

To sum up, this study is the first of its kind to review further evidence supporting the role of CSCs in spine tumors, specifically in chordoma. Consequently, with a growing appreciation for the essential role of CSCs in tumorigenesis and metastasis, there is significant interest in developing novel therapeutic approaches to effectively target this unique subpopulation.

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Cancer stem cells

Transient amplifying cells

Tumor

**Figure 1 Division model of cancer stem cells.** These cells are a small subpopulation of cancer cells (< 1%).

**Table 1 Cell surface markers and transcription factors potentially associated with cancer stem cells**

|  |  |
| --- | --- |
| Tumor type | Cell surface markers and transcription factors |
| Chondrosarcoma | SOX9 |
| Osteosarcoma | CD133, CD117, CD44, CD105, ABCG2, CXCR4, ICAM-1, STRo-1, OCT 3/4, Nanog, STAT3, SOX2 |
| Ewing sarcoma | CD133/Prominin-1, OCT4, SOX2, Nanog |
| Multiple myeloma | CD19, CD20, CD27+, CD138-, SOX2 |
| Giant cell tumor | CD105, CD37, CD166, CD117, CD113, CD44, CD73, CD166, FGF-R3 |
| Chordoma | CD133, CD15, OCT4, klf4, C-myc, SOX2, SSEA-1, Nanog, Brachyury |