



Review Article

Mesenchymal stromal cells for bone sarcoma treatment: Roadmap to clinical practice



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ABSTRACT

Over the past few decades, there has been growing interest in understanding the molecular mechanisms of cancer pathogenesis and progression, as it is still associated with high morbidity and mortality. Current management of large bone sarcomas typically includes the complex therapeutic approach of limb salvage or sacrifice combined with pre- and postoperative multidrug chemotherapy and/or radiotherapy, and is still associated with high recurrence rates. The development of cellular strategies against specific characteristics of tumour cells appears to be promising, as they can target cancer cells selectively. Recently, Mesenchymal Stromal Cells (MSCs) have been the subject of significant research in orthopaedic clinical practice through their use in regenerative medicine. Further research has been directed at the use of MSCs for more personalized bone sarcoma treatments, taking advantage of their wide range of potential biological functions, which can be augmented by using tissue engineering approaches to promote healing of large defects. In this review, we explore the use of MSCs in bone sarcoma treatment, by analyzing MSCs and tumour cell interactions, transduction of MSCs to target sarcoma, and their clinical applications on humans concerning bone regeneration after bone sarcoma extraction.

Abbreviations: AAT, a1-antitrypsin; Abs, antibodies; Ang1, angiopoietin-1; APCs, antigen presenting cells; ASC, adipose-derived stromal/stem cells; BD, bone defect; BMSCs, bone marrow-derived mesenchymal stromal cells; CAM, cell adhesion molecules; CCL5, chemokine ligand 5; CCR2, chemokine receptor 2; CD, cytosine deaminase; CD, classification determinants; CLUAP1, clusterin associated protein 1; CSPG4, Chondroitin sulfate proteoglycan 4; CXCL12/CXCR4, C-X-C chemokine ligand 12/ C-X-C chemokine receptor 4; CXCL12/CXCR7, C-X-C chemokine ligand 12/ C-X-C chemokine receptor 7; CXCR4, chemokine receptor type 4; CX3CL1, chemokine (C-X3-C motif) ligand 1; DBM, Demineralized Bone Marrow; DKK1, dickkopf-related protein 1; ECM, extracellular matrix; EMT, epithelial-mesenchymal transition; FGF-2, fibroblast growth factors-2; FGF-7, fibroblast growth factors-7; GD2, disialoganglioside 2; HER2, human epidermal growth factor receptor 2; HGF, hepatocyte growth factor; HMGB1/RACE, high mobility group box-1 protein/ receptor for advanced glycation end-products; hMSCs, human mesenchymal stromal cells; IDO, indoleamine 2,3-dioxygenase; IFN- α , interferon alpha; IFN- β , interferon beta; IFN- γ , interferon gamma; IGF-1R, insulin-like growth factor 1 receptor; IL-1b, interleukin-1b; IL-2a, interleukin-2a; IL-6, interleukin-6; IL-8, interleukin-8; IL-10, interleukin-10; IL11RA, Interleukin 11 Receptor Subunit Alpha; IL-12, interleukin-12; IL-18, interleukin-18; IL-21, interleukin-21; MAGE, melanoma antigen gene; MCP-1, monocyte chemoattractant protein-1; MMP-2, matrix metalloproteinase-2; MMP2/9, matrix metalloproteinase-2/9; MRP, multidrug resistance protein; MSCs, mesenchymal stem/stromal cells; NF- κ B, nuclear factor kappa-light-chain-enhancer of activated B cells; OPG, osteoprotegerin; PBS, phosphate-buffered saline; PDGF, platelet-derived growth factor; PDX, patient derived xenograft; PEDF, pigment epithelium-derived factor; PGE2, prostaglandin E2; PI3K/Akt, phosphoinositide 3-kinase/protein kinase B; PTX, paclitaxel; RANK, receptor activator of nuclear factor kappa-B; RANKL, receptor activator of nuclear factor kappa-B ligand; RBCs, red blood cells; RES, reticuloendothelial system; rh-TRAIL, recombinant human tumour necrosis factor related apoptosis-inducing ligand; RNA, ribonucleic acid; SC, stem cells; SCF, stem cells factor; SDF-1, stromal cell-derived factor 1; STAT-3, signal transducer and activator of transcription 3; TAAs, tumour-associated antigens; TCR, T cell receptor; TGF- β 1, transforming growth factor beta 1; TGF- β , transforming growth factor beta; TNF- α , tumour necrosis factor alpha; TNF, tumour necrosis factor; TRAIL, tumour necrosis factor related apoptosis-inducing ligand; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor; WBCs, white blood cell; 5-FC, 5-fluorocytosine

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1. Introduction

Sarcomas are malignant neoplasms of mesenchymal tissue that are classified as bone or soft tissue in origin [1]. Osteosarcomas and chondrosarcomas are the most common malignant bone tumours, followed by Ewing sarcomas [2]. Osteosarcomas and Ewing sarcomas primarily affect children and adolescents, while chondrosarcoma incidence increases with age [1]. Osteosarcoma and Ewing sarcoma represent 2.4% and 1.4% of childhood cancers, respectively [3]. Ewing sarcoma is a small, round blue cell tumour that in children arises in bone in 80% of the cases, whereas in adults, 75% of primary tumours arise in soft tissue [4]. Osteosarcoma is characterized by the presence of malignant osteoid and occurs primarily in the metaphysis of long tubular bones of young patients with a median age of diagnosis of 15 to 19 years [4,5]. Following osteosarcoma, chondrosarcoma is the second most frequent primary malignant bone tumour and is characterized by the production of cartilage matrix [6]. The treatment of bone sarcoma is challenging [7]. Intermediate and high-grade sarcomas are more frequently treated with a combination of surgery, chemotherapy and/or radiation therapy. Tumour resection depends on the cancer size and grade, staging and sensitivity to neoadjuvant chemotherapy; it typically requires wide tumour excision along with a margin of healthy tissue around it. Multidrug chemotherapy and radiotherapy are adjuvant treatments which reduce the risk of local and distant relapse, but with major shortcomings including associated morbidity and poor targeting efficiency to a tumour [8].

During the last 30 years, many new approaches to the treatment of bone sarcomas have been developed; however, these have failed to improve 5-year overall survival [8]. Targeting techniques aim to achieve greater accumulation of antineoplastic agents in the tumour whilst maintaining a non-toxic concentration in non-target organs and tissues. Mesenchymal stromal cells (MSCs) may offer an advantage through the delivery of antineoplastic agents or factors such as interferons, interleukins, TNF and antibodies selectively to tumour cells.

The emerging therapeutic role of SCs follows exponential progress in understanding their natural behaviour and characteristics. Stem cells interact with other cell types and are involved in tissue development, regeneration, homeostasis, and evolution by natural selection [9]. Four major categories of stem cells are currently encountered; embryonic, fetal, adult and induced pluripotent SCs [10]. Although all types of SCs can be used for medical research, adult SCs are usually utilized for cellular therapies as they can be easily collected from patients, show high multiplication capability in vitro and can migrate to target tissues of the host [11]. On the other hand, the use of embryonic SCs face legal and ethical restrictions in some countries and could be restricted as they are available in limited quantities [10]. When it comes to SCs isolation from fetus there are practical restrictions as it could harm the fetus and is possible only during the early stages of life [11]. Mesenchymal stromal cells are mainly obtained from adult tissues and are extensively studied for their regenerative capacity through multipotent differentiation [12] and antitumor activity [13]. Although MSCs are usually isolated from the bone marrow, adipose tissue, and cord blood, they can also be obtained from other tissues such as smooth, skeletal and cardiac muscle, spleen, liver, pancreas, lung, testes, menstrual blood, periosteum, dermis, pericytes, trabecular bone, placenta, amniotic fluid, dental pulp, hair follicle and peripheral blood [14]. Moreover, they differentiate into mesodermal, endodermal and ectodermal lineage cells [14]. Currently, two major categories are most widely studied among MSCs; bone marrow MSCs (BMMSCs) and adipose tissue MSCs (ADMSCs) [10]. Mesenchymal stromal cell populations are established in niches; specialized microenvironments that play a central role in the interaction between MSCs and adjacent cells to maintain tissue homeostasis through balancing self-renewal and differentiation [15]. In these microenvironments, MSCs exhibit posterity, produce multiple heterologous cell types and, through those multiple cell types, establish an ECM specific for the niche [16]. The niche protects MSCs not only from

differentiation or apoptotic stimulus but also from overproduction that may lead to carcinogenesis [17]. Cancer cells exploit similar mechanisms of the MSCs as the tumour sites share common functional features with MSCs niches [18].

The mechanisms of tumour stroma generation and wound healing appear to be contiguous. Mesenchymal stromal cells are attracted to the site of the tumour by tumour-associated inflammatory signals [19,20]. Several studies have examined cell-cell and paracrine interactions between MSCs and tumour-cells, demonstrating a complicated relationship between them, with MSCs potentially promoting or suspending tumour progression even within the same cancer model [21]. In this review, we explore the feasible therapeutic roles of MSCs in bone sarcoma, analyzing MSCs and tumour interactions, transduction of MSCs to target sarcoma, and clinical applications of MSCs in humans concerning bone regeneration after bone sarcoma extraction.

2. Can we safely place MSCs near tumour cells?

2.1. MSCs and tumour cell interactions

Several factors can influence the interaction between MSCs and cancer cells: the origin and pre-treatment of MSCs, the cancer type and various in vitro and in vivo system-related factors (the ratio of MSCs and cancer cells, simultaneous or sequential injection of MSCs and cancer cells, local versus systemic MSC delivery or kinetics of carcinogenesis) [22].

In vivo and in vitro studies have confirmed that numerous factors such as monocyte chemoattractant protein-1 (MCP-1 or CCL2) in breast cancer or stromal cell-derived factor-1 (SDF-1) in prostate, colorectal and breast cancer that are produced by tumour and inflammatory cells promote the homing and migration of MSCs into the tumour microenvironment [23]. The homing and fate of mesenchymal stromal cells have been related to cell to cell interactions that occur between MSCs and tumour cells through cytokine/receptor pairs including stem cell factor (SCF)/c-Kit; monocyte chemoattractant protein-1 (MCP-1)/chemokine receptor 2 (CCR2); hepatocyte growth factor (HGF)/c-Met; vascular endothelial growth factor/receptor (VEGF/VEGFR); stromal cell-derived factor 1(SDF-1)/CXCR4; and high mobility group box-1 protein/ receptor for advanced glycation end-products (HMGB1/RACE) [24–30]. Other inflammatory cytokines, growth and angiogenic factors, also enhance migration of MSCs to the tumour site (Table 1).

Once MSCs are recruited by cancer cells, they enhance the production of factors like TGF- β , VEGF, SDF-1, and CCL5 or microparticles like exosomes that can either induce or inhibit tumour growth; owing to this bimodal interaction, MSCs have been described as a "double-edged sword" [23]. The pro- or anti-tumorigenic effect of MSCs on tumour progression depends mainly on the MSC source and the tumour model used [31]. The pro-tumorigenic effect of MSCs includes four main pathways: immunosuppression, tumour angiogenesis and epithelial-mesenchymal transition (EMT)-mediated supplementation of tumour [32](Fig. 1).

3. Pro-tumorigenic effect

3.1. MSC-mediated immunosuppression

The immunosuppression caused by MSCs promotes immunotolerance and tumour progression [33]. A prerequisite for the immunomodulatory function of MSCs in the tumour microenvironment is their activation by immune cells producing IFN- γ , TNF- α , IL-2 α or IL-1 β [34–36]. Once MSCs are activated, they produce a number of molecules (namely TGF- β 1, HGF, IDO, PGE2) that inhibit lymphocyte proliferation and suppress the immune function of T lymphocytes, dendritic cell maturation/differentiation, and NK and B-cell activation; simultaneously, MSCs increase the production of regulatory T-cells using a contact-dependent mechanism or by secreting IL-10 and TGF- β ,

Table 1
Inflammatory cytokines, growth and angiogenic factors that enhance MSC migration to the tumour site.

Tumour released chemotactic factors	Tumour model	Stem Cell type	Mechanism of action
Epidermal growth factor (EGF)	Glioma [194]	hBMMSCs	Migration of SCs into the established human glioma although they were injected at the opposite cerebral hemisphere
	Pancreatic carcinoma [195]	hBMMSCs	Migration of SCs to tumour blood vessels due to a tumour hypoxia-induced secretion of GFs including EGF
	Melanoma, Mouse mammary carcinoma [196]	BMPCs	Migration of SCs to tumour site and recruitment to the growing vasculature
Vascular endothelial growth factor-A (VEGF-A)	Glioma [197]	hMSCs	Enhancement of the migration and invasion of SCs to the tumour
	Pancreatic carcinoma [195]	hBMMSCs	Migration of SCs from bone marrow to tumour blood vessels mainly due to tumour hypoxia-induced secretion of VEGF
Platelet-derived growth factor (PDGF)	Pancreatic carcinoma [195]	hBMMSCs	Migration of SCs to tumour blood vessels due to tumour hypoxia-induced secretion of PDGF
Stromal-derived growth factor-1 (SDF-1)	Osteosarcoma [92]	hMSCs	Enhancement of SCs migration to the tumour site and promotion of growth and metastasis
	Prostate tumour [198]	ADSCs	Migration of SCs to tumour site is possibly mediated by homing factor SDF-1 (CXCL12)
Interleukin-8 (IL-8)	Hec1a endometrial carcinoma [199]	O-ASC	Recruitment of SCs and possible tumour progression
C–C motif chemokine ligand 25 (CCL25)	Multiple Myeloma (MM) [200]	hBMMSCs	Attraction of SCs to MM through the CCL25/CCR9 axis and supportive role in MM cell growth
Hematoma-derived growth factor (HDGF)	Breast carcinoma [201]	hBMMSCs	Promotion of SCs chemotaxis to the tumour site
Monocyte chemoattractant protein-1 (MCP-1)	Primary & metastatic breast tumours [202]	hMSCs	<i>In vivo</i> and <i>in vitro</i> stimulation of SCs migration to tumour site
Urokinase plasminogen activator (uPA)- Urokinase plasminogen activator receptor (uPAR)	Malignant solid tumour (brain, lung, prostate, breast) [203]	NSCs and MSCs	Significantly greater migration of SCs to the tumour expressing high levels of uPA and uPAR
Transforming growth factor beta-1 (TGF-β1)	Breast cancer [204]	hBMMSCs	Attraction of SCs in the tumour site
C-X-C motif chemokine-1 (CXCL1)	Hec1a endometrial carcinoma [199]	O-ASC	Recruitment of SCs to the tumour and possible tumour progression
Neurotrophin-3	Malignant Glioma [205]	MSC	Combined with IL-8, TGF-beta1 overexpression, mediate tropism of SCs to the tumour site
Tissue Inhibitor of Metalloproteinase-1 (TIMP-1)	Glioma [206]	hNSC	Regulation of CD63 and β1 integrin-mediated signalling and enhancement of SCs adhesion and migration

Factors:

GF: growth factor, EGF: Epidermal growth factor, **VEGF-A:** Vascular endothelial growth factor-A, **PDGF:** Platelet-derived growth factor, **SDF-1:** Stromal-derived growth factor-1, **IL-8:** Interleukin-8, **CCL25:** C–C motif chemokine ligand 25, **HDGF:** Hematoma-derived growth factor, **MCP-1:** Monocyte chemoattractant protein-1, **uPA:** Urokinase plasminogen activator, **uPAR:** Urokinase plasminogen activator receptor, **TGF-β1:** Transforming growth factor beta-1, **CXCL1:** C-X-C motif chemokine-1, **Neurotrophin-3, TIMP-1:** Tissue Inhibitor of Metalloproteinase-1.

Cell types:

hBMMSCs: Human Bone Marrow-derived Mesenchymal Stromal Cells, **hMSCs:** Human Mesenchymal Stromal Cells, **ADSC:** Adipose Tissue-derived Stem Cells, **O-ASC:** Omental Adipose Tissue Stromal Cells, **NSCs:** Neural Stem Cells, **MSCs:** Mesenchymal Stromal Cells, **MSC:** Bone Marrow Stromal Cells, **hNSC:** Human Neural Stem Cells, **MSC:** Bone Marrow Stromal Cells, **BMPCs:** Bone Marrow-derived Perivascular Cells.

[37–41]. Regarding specifically T cells, MSCs suppress their activity by inhibiting their proliferation or, by causing apoptosis of already activated T lymphocytes [5].

3.2. Tumour angiogenesis

MSCs promote tumour angiogenesis either by their differentiation into fibroblasts, pericytes, and myofibroblasts or by producing specific growth factors [23]. Proangiogenic factors and chemokines expressed by MSCs, including angiopoietin-1 (Ang1), fibroblast growth factors-2 (FGF-2) and -7 (FGF-7), platelet-derived growth factor (PDGF), stromal-derived factor-1 (SDF-1), IL-8 and vascular endothelial growth factor (VEGF) act synergistically on endothelial cells to promote tumour angiogenesis [42,43,44]. Other factors with potential pro-angiogenic effect are angiogenin and CCL2 in lymphoma and hepatocyte growth factor, cyclooxygenase, IGF-1 and transforming growth factor-α in pancreatic carcinoma [45]. However, in some studies, MSCs suppressed the production of the tumour angiogenic network by inhibiting the growth of endothelial cell-derived capillaries through the production of reactive oxygen species [5].

3.3. EMT-mediated supplementation of a tumour

Epithelial to mesenchymal transition (EMT) has a crucial role in organogenesis, wound healing, tumour progression and metastasis. MSCs facilitate and modulate EMT through the production of regulatory

molecules, namely TGF-β, E-cadherin and micro-RNA, resulting in more invasive phenotype [46,47]. This theory was supported by the upregulation of EMT-specific markers such as N-cadherin, vimentin, Twist and Snail, and the decrease in E-cadherin when breast cancer cells and MSCs were co-cultured [48].

3.4. Metastasis and Anti-apoptotic effects

Based on the type of tumour and MSC status, MSCs and their products can regulate the apoptosis of cancer cells [49–52]. MSC-induced factors cause vascular formation and secretion of growth factors, promoting invasion of cancer cells and the development of early tumour metastasis [53]. The pro-metastatic effect of MSCs has been proven in breast cancer (CCL5 and IL-17B), hepatocellular carcinoma (MMP2) and osteosarcoma (CXCR4/VEGF axis) [23]. On the other hand, the intravenous injection of UC-MSCs or ADMSCs in mice with mammary tumours reduced the formation of lung metastases [50]. Thus, the role of MSCs in the development of distant metastasis is controversial.

4. Antitumorigenic effect: the role of NF-κB, Akt and Wnt pathways

MSCs and cancer cells are thought to use similar signaling pathways regulating self-renewal and differentiation, namely the Wnt/β-catenin, Notch, Shh and BMP pathways [23,54]. Although the anti-tumorigenic mechanisms of MSCs are not fully understood, it is presumed that they are related to the downregulation of NF-κB, PI3K/Akt, and Wnt pathways [55]. Uneven activation of the Wnt/β-catenin pathway has led to

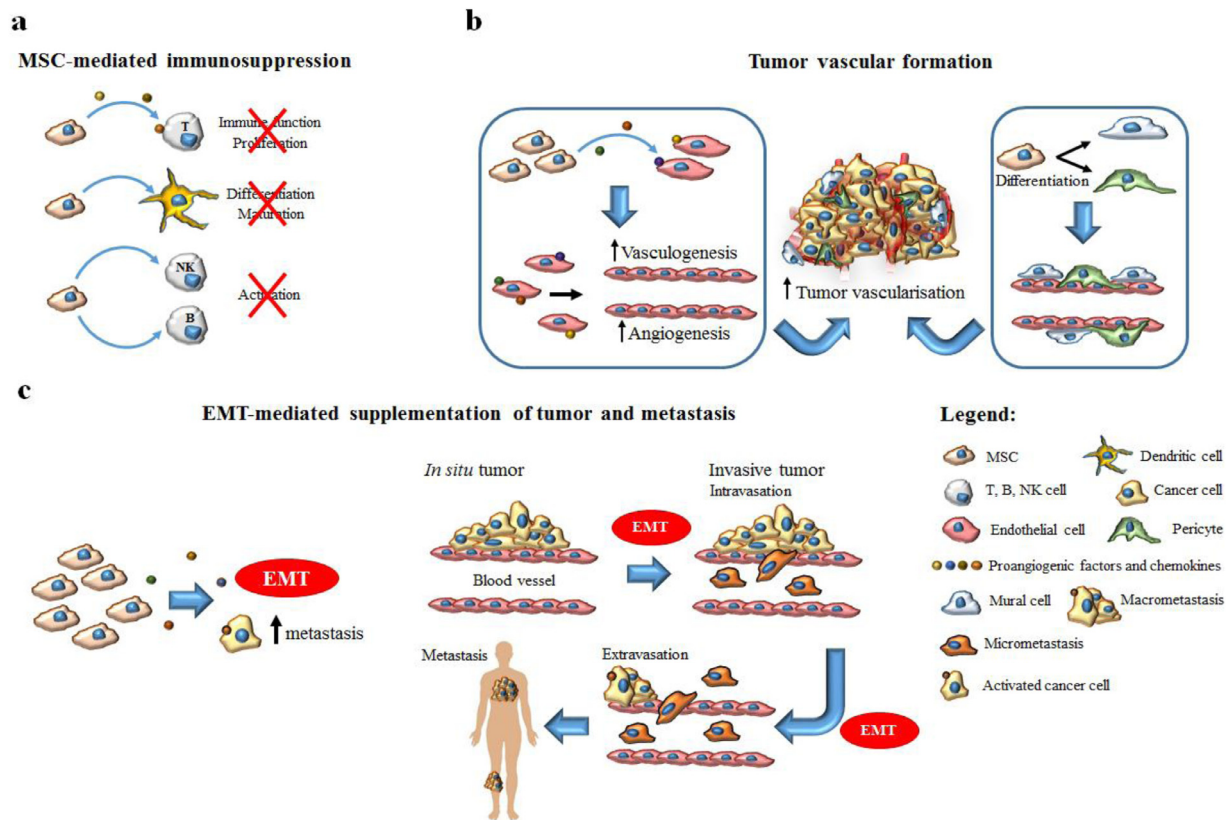


Fig. 1. MSC pro-tumorigenic effect main pathways.

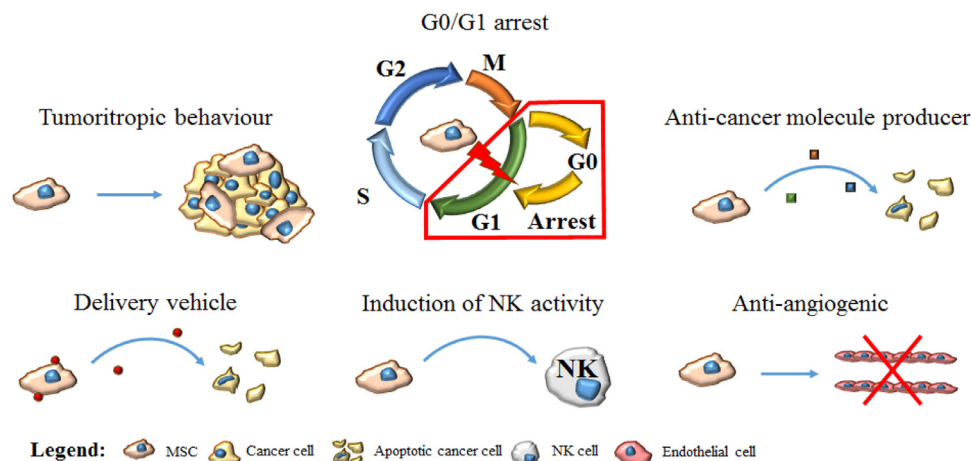


Fig. 2. MSC anti-tumorigenic and pro-apoptotic effect.

the development of a variety of human tumours [56,57]. Human umbilical cord-derived MSCs (hUC-MSCs) co-cultured with glioma cells downregulate β -catenin expression in glioma cell lines and increase the levels of secreted DKK1 which is an inhibitor of the Wnt pathway [58]. The anti-tumorigenic and pro-apoptotic effect of MSCs results from the suppression of the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) signaling pathway in some cancer types [59]. However, many factors secreted by MSCs activate the PI3K/Akt pathway in other cancer types and this effect may depend on the metabolic or genetic profile of cancer cells [60]. Existing data from pre-clinical studies regarding the pro-apoptotic effect of MSCs on cancer cells through the down-regulation of PI3K/Akt pathway support this antitumor potential in hepatocellular carcinoma, glioma cells, Kaposi's sarcoma, and prostate and breast cancer [61–65]. Other possible mechanisms that contribute

to the anti-tumour potential of MSCs include apoptosis caused by up-regulation of TRAIL, G1 arrest, and expression of tumour suppressor genes [23] (Fig. 2).

4.1. Safety of use of MSCs in proximity to a tumour

The unique characteristics of MSCs (self-renewal, differentiation, and tropism to the tumour site) raised expectations of possible therapeutic applications in cancer patients. Major safety issues and knowledge gaps, however, remain to be explored [66].

The role of MSCs in different cancer types is ambiguous. In vivo animal studies of murine melanoma and renal murine adenocarcinoma (Renca kidney cancer cells) showed that co-implantation of MSCs increased tumour size possibly because of MSC-mediated

immunosuppression [67,68]. The production of trophic factors from MSCs including VEGF, chemokine CCL5 and IL6 (activation STAT-3) has been connected with tumour growth and metastasis in Burkitt's lymphoma, breast cancer, colonic cancer and chronic myeloid leukaemia [69–73]. Rowan et al. investigated the safety of human adipose tissue-derived stromal cells (ADSC) included in fat grafts that were used for reconstruction after surgical resection of a breast tumour. The application of human ADSCs in proximity to breast cancer raised concerns as it was associated with an increase in the migration and metastasis of cancer cells [74]. In an animal study, Zheng et al. scrutinized whether the proximity of breast tumour cells (4T1) and bone marrow-derived mesenchymal stromal cells (BMMSCs) could affect tumour growth. Interestingly, they found that the co-injection of 4T1 cells and BMMSCs accelerated cancer cell proliferation, whereas simultaneous distant injection had the opposite results. When MSCs were injected distantly from cancer cells, they had immunoregulatory action by decreasing the accumulation of myeloid-derived suppressor cells and regulatory T cells at the tumour site [75]. Another mechanism that could increase the aggressiveness of a tumour is the potential differentiation of MSCs to tumour associated fibroblasts that are capable of increasing neovascularization within the tumour stroma and the metastatic rate [76,77].

4.2. MSCs and bone sarcoma interactions

One human and several animal studies have investigated the safety of using MSCs in proximity to bone sarcomas by exploring MSCs and tumour cell interactions [78–93]. Aanstoos et al. evaluated the safety of application of MSCs in mice with osteosarcoma. They used three groups: mice receiving MSCs intravenously or at the surgical site following tumour resection and mice receiving no MSCs; and they evaluated both the development and progression of pulmonary metastasis and local recurrence. Mice that received MSCs intravenously developed the first detectable metastases significantly earlier (2.93 ± 1.90 days) than those that received local injection of MSCs (6.94 ± 6.78 days) and those that received no MSCs (5.93 ± 4.55 days). The recurrence rate and the size of the recurrent tumours, however, were not affected significantly by delivery of the MSCs at the surgical site or intravenously [94].

The co-implantation of rat BMMSCs and COS1NR osteosarcoma cells resulted in the acceleration of non-metastatic cancer settlement and proliferation in a study by Tsukamoto et al. All animals in which MSCs and osteosarcoma cells were co-implanted developed tumour by week 4, compared to those that received only osteosarcoma cells and developed tumour by week 6. However, there was no significant statistical difference in tumour size after six weeks and in the number of metastases between the two groups. On the other hand, intravenous BMMSC injection led to stabilization of the initial tumour size, without altering its histological appearance, and significant enhancement of metastatic lung nodules (17.33 ± 8.39 vs. 2.0 ± 2.0 , $p = 0.03$). The overexpression of the CXCL12/CXCR7 axis was probably involved in osteosarcoma cell-MSCs interaction that led to an increase in pulmonary metastases and tumour progression. Moreover, the elevation of the basement membrane degrading enzymes, MMP-2 and MMP-9 in MSCs, was connected with increased tumour metastasis [95]. The protumorigenic effect of locally administrated MSCs could be correlated with the number of MSCs applied. Lee et al. showed in an animal study that local administration of ADMSCs in low proportions suppress tumour growth, whereas higher proportions show a tumour-promoting effect [88]. In vivo mice studies also indicated that MSCs could promote CXCR-4-mediated osteosarcoma proliferation and pulmonary metastasis through the production of VEGF by MSCs [89]. In vitro co-culture of osteosarcoma cells and BMMSCs showed that SCF-1 secreted from BMMSCs promoted the proliferation and invasion of osteosarcoma cells. In contrast to BMMSCs, osteosarcoma cells expressed higher levels of CXCR4, indicating that the SDF-1/CXCR4 axis plays a pivotal role in osteosarcoma cell proliferation [96]. Another in vivo mice model

indicated that SDF-1 could also be secreted from Saos-2 cells in the conditioned medium and enhance the migration of hMSCs to the tumour site, where osteosarcoma cell growth and pulmonary metastasis are promoted by the secretion of CCL5 from exogenous hMSCs [92]. Moreover, pre-clinical data showed that BMMSCs could promote osteosarcoma growth through PI3K/Akt and Ras/Erk intracellular cascades, and enhance metastasis through CXCR4 signaling [91].

Avril et al. investigated the interaction of human osteosarcoma cells with human adipose tissue-derived stromal cells (ADSCs), MSCs obtained from bone marrow, and pre-osteoclasts when co-injected in immunodeficient mice. Adipose tissue-derived stromal cells constitute a population of MSC-like cells that are used in plastic and reconstructive surgery. They found that ADSCs and MSCs increased tumour size while pre-osteoclasts did not; none of them, however, increased metastasis. The cell cycle of proliferating osteosarcoma cells was accelerated by factors secreted by MSCs, in contrast to the quiescent state of dormant tumour cells that remain stable. They concluded that ADSCs/MSCs could be used for reconstructive surgery after osteosarcoma resection; however, they may not be good candidates for targeted cell therapy as they may enhance tumour cell proliferation [97]. Soluble factors secreted from adipose tissue, such as IL-6 and leptin, induced the activation of osteosarcoma cell cycles from G₁ to mitosis phases and thus increased the local growth of a tumour. However, they do not promote lung metastasis and osteolysis [80].

Interleukin-6 (IL-6) seems to play a pivotal role in the bidirectional proliferation of human MSCs (hMSCs) with Saos-2 both in vitro and nude mice models. Interestingly, IL-6 produced from the conditioned medium of Saos-2 could inhibit osteogenic differentiation of hMSCs [98]. A probable explanation for IL-6 mediated promotion of osteosarcomas is through the STAT3 signalling pathway. IL-6 secreted from MSCs activates STAT-3 in adjacent osteosarcoma cells in a concentration-dependent manner, promotes their proliferation, protects them from chemotherapeutic drugs such as cisplatin and enhances their migration and invasion properties [82]. Tu et al. also demonstrated that the co-implantation of Saos-2 and MSCs activated STAT-3 by IL-6 and increased the expression of multidrug resistance protein (MRP) and P-glycoprotein that induced chemoresistance in doxorubicin and cisplatin in mice osteosarcoma samples [99]. The ADMSCs-mediated activation of the STAT-3 pathway in osteosarcoma increased MMP2/9 and decreased E-cadherin expression, promoting tumour progression [83].

In assessing the safety of the use of MSCs for bone healing Hernigou et al. retrospectively evaluated 92 patients with chondrosarcoma (31/92), osteosarcoma (35/92), Ewing's sarcoma (28/92) and other bone tumours (8/92), who received autologous BMMSCs following tumour resection to enhance the healing of the host-to-allograft bone junction. They evaluated the risk of local recurrence after surgical tumour resection at a mean follow-up of 15.4 years. They found no increase in the risk of local recurrence for all cancer types [100]. However, as referred to earlier, there were safety concerns about human adipose-tissue stromal cells (ASC) included in fat grafts that increased migration and metastases of breast tumour and osteosarcoma animal models [74,101]. Autologous fat grafts used in reconstructive surgery have also been related to late local recurrence, 13 years following the onset of osteosarcoma in a female human patient. Successive pre-clinical models showed that MSCs/stromal cells included in the fatty tissue interact with osteosarcoma cells and induce their proliferation [101].

Studies support the hypotheses that the use of MSCs could accelerate pulmonary metastases after resection of the primary osteosarcoma, promote the proliferation of osteosarcoma cells at the tumour site and increase chemoresistance (Table 2). However, current knowledge refers mainly to in vitro and in vivo animal models and has not yet been translated to the clinical setting. It is not clear whether there is a biological reason suggesting that intravenously administrated MSCs have a predilection for locating within the lungs through their interaction with lung metastases or they are likely to be entrapped in the lungs as they are a first pass tissue. Intracardiac or arterial injection of

Table 2
In vitro, in vivo and clinical data on safety of stem cells in proximity to bone sarcomas.

Author/ Year	Model Used	Methods/ Results	Conclusion
Hernigou P/ 2014 [100]	Retrospective cohort study of humans	<ul style="list-style-type: none"> • 92 humans suffering from chondrosarcoma (31 patients), osteosarcoma (35 patients), Ewing's sarcoma (28 patients) and other bone tumors (8 patients) • Risk of local tumor recurrence after surgical resection and autologous BMMSCs for bone defect reconstruction during 15.4 years mean follow-up is not increased 	<ul style="list-style-type: none"> • A longer follow-up period is required as some solid malignant tumors are developed after a 20–40-year latent period • Local recurrence when MSCs are administered beyond the two-year period after bone resection should be investigated
Aanstoos ME/ 2016 [94]	In vivo animal study	<ul style="list-style-type: none"> • Adipose tissue-derived MSCs (ADMSCs) were applied in mice with osteosarcoma • Study included three groups; mice receiving intravenous MSCs, mice receiving MSCs at the surgical site following resection and mice receiving no MSCs • The group of intravenous administered MSCs presented metastases earlier than the other two groups 	<ul style="list-style-type: none"> • Intravenous delivery of MSCs could promote pulmonary micrometastasis • Local application at the surgical site appear to be safe in murine model
Avril P/ 2016 [97]	In vivo animal study	<ul style="list-style-type: none"> • Human MSCs, ADSCs and pre-osteoclasts were co-injected with human MNNG-HOS osteosarcoma cells in mice • MSCs and ADSCs increase MNNG-HOS osteosarcoma growth without exacerbation of osteolytic lesions and lung metastases • ADSCs increase tumor growth in a dose-dependent manner • ADSCs and MSCs produce factors that may accelerate the cell cycle of proliferating osteosarcoma cells 	<ul style="list-style-type: none"> • Further investigation is needed before using MSCs in human with osteosarcoma • ADSCs/ MSCs appear not to increase the risk of local recurrence when used for reconstructive surgery after bone tumor resection • ADSCs/ MSCs when used for tumor-targeted cell therapy can enhance tumor progression
Bian Z-Y/ 2010 [98]	In vivo animal study	<ul style="list-style-type: none"> • Saos-2 with or without co-injection of hMSCs were injected into the proximal tibia of nude mice • exogenous hMSCs target the osteosarcoma site and promote its growth and pulmonary metastases • ALP levels were increased in response to co-injection of Saos-2 and hMSCs • hMSCs and Saos-2 could enhance their own proliferation through IL-6 autocrine 	<ul style="list-style-type: none"> • There is a positive feedback loop of IL-6 in interaction between hMSCs and Saos-2
Perrot P/ 2010 [101]	In vivo animal study	<ul style="list-style-type: none"> • 21 mice were divided in 3 groups: the control Saos-2 group, Saos-2 + fat group and Saos-2 + cannula group • Human adipose tissue-delivered stromal cells (ADSC) included in fat grafts can induce osteosarcoma cells proliferation 	<ul style="list-style-type: none"> • Clinicians must be aware of the possible long term local relapse of osteosarcoma after autologous fat graft
Tu B/ 2016 [99]	In vitro and in vivo animal study	<ul style="list-style-type: none"> • MSCs protect osteosarcoma cells from drug-induced apoptosis • Co-implantation of Saos-2 and MSCs leads to activation of STAT3 by IL-6 and increase not only the expression of multidrug resistance protein (MRP), but also P-glycoprotein 	<ul style="list-style-type: none"> • STAT-3 pathway should be further studied in order to overcome environment-induced chemoresistance

Factors:

ALP: alkaline phosphatase, MRP: multidrug resistance protein.

Cell types:

BMMSCs: Bone Marrow-derived Mesenchymal Stromal Cells, MSCs: Mesenchymal Stromal Cells, ADMSCs: Adipose tissue-derived MSCs, ADSC: Adipose Tissue-derived Stem Cells, MNNG-HOS: human osteosarcoma cell line, Saos-2: osteosarcoma cell line.

MSCs in future studies could help us understand the exact mechanism of presumptive acceleration of pulmonary metastases.

5. Pre-activation and use of transduced MSCs to induce sarcoma cell apoptosis

5.1. Induction of cancer cell death using transduced MSCs

The use of transduced MSCs to express specific anti-cancer proteins selectively to the tumour site offers a promising therapeutic approach. Several proteins, molecules or drug systems have been implicated.

5.1.1. Interferons

Human MSCs genetically engineered to produce interferons have been used to deliver these proteins locally in several cancer models, such as gliomas, metastatic breast, melanoma, endometrial, ovarian, hepatocellular, bronchioloalveolar and prostate models. MSCs expressing IFN- β can reduce tumour size, induce apoptosis and increase survival in the aforementioned cancer types [55,102,103,104,105,106,107,108]. Similarly, IFN- α expressing MSCs were effective in increasing cancer cell apoptosis and suppressing angiogenesis in metastatic melanoma and hepatocellular carcinoma models [109]. IFN- γ -expressing MSCs also inhibited leukemic and lung carcinoma cell proliferation in vitro [35,110,111]. However, when IFN- γ -human BMMSCs were tested

against H460 cells in an animal model, their pro-tumorigenic effect was superior through the promotion of vascularization [112].

5.1.2. Interleukins

Adenovirus-transduced MSCs that expressed interleukin-12 (IL-12), reduced metastases from subcutaneous tumours [113]. A tumour suppressive effect of IL-12 secreted from genetically modified MSCs was also confirmed in a breast carcinoma model [114,115]. MSCs developed to deliver IL-2 and IL-21, when injected into murine gliomas and epithelial ovarian cancer respectively, reduced tumour growth and improved survival [116]. Interestingly, transduced BMMSCs expressing IL-18 and IFN- β promoted apoptosis of cancer cells in an intracranial glioma model [117]. Chemokine CX3CL1 intravenously delivered from transduced MSCs to colon cancer, and melanoma reduced the number of lung metastases [118].

5.1.3. Viruses

MSCs have already been used as vectors of oncolytic adenoviruses in several in vitro and in vivo studies and improved survival in murine ovarian, breast and lung tumour models. Viral replication and invasion to the surrounding tumour tissue induced apoptosis of cancer cells [55]. Komarova et al. studied the impact of MSCs infected by genetically modified coxsackie and adenoviruses against animal ovarian cancer. They showed that MSCs mediated infection of cancer cells had better

Table 3
A list of strategies using transduced MSCs as an anticancer therapy for osteosarcoma.

Anti-cancer agent	Sarcoma model	Therapeutic strategy	Mechanism of action	Study type
<i>TRAIL</i>	Osteosarcoma, Ewing's [140] Ewing's [144]	Cytotoxic agent Cytotoxic agent	Apoptosis, Anti-angiogenic action Apoptosis	<i>In-vitro</i> and <i>In-vivo</i> animal studies <i>In-vitro</i> and <i>In-vivo</i> animal studies
<i>OPG</i>	Osteosarcoma [207]	Cytotoxic agent	Reduction of tumour growth and bone destruction caused by osteosarcoma cells	<i>In-vitro</i> and <i>In-vivo</i> animal studies
<i>CD/5-FC</i>	Osteosarcoma [132]	Gene-directed enzyme-producing therapy	Inhibition of DNA and RNA synthesis of tumour cells	<i>In-vitro</i> and <i>In-vivo</i> animal studies
<i>IL-12</i>	Ewing's [156]	Cytotoxic agent	Inhibition of tumour growth	<i>In-vivo</i> animal studies

Anti-cancer agents:

TRAIL: Tumour necrosis factor related apoptosis-inducing ligand, **OPG:** Osteoprotegerin **CD/5-FC:** Cytosine deaminase/ 5-fluorocytosine **IL-12:** interleukin-12.

results in decreasing tumour size and increasing of survival rate compared with the directly injected adenovirus [119].

5.1.4. TNF

Cancer cell apoptosis mediated by the tumour necrosis factor (TNF) cytokine superfamily was first proposed almost 30 years ago. TNF-α was the first assessed cytokine that proved to be ineffective in triggering cancer cell apoptosis and also had severe adverse events [120]. Attention has now turned to other members of the TNF superfamily.

5.1.5. TRAIL

Tumour necrosis factor related apoptosis-inducing ligand (TRAIL) [121] is a type 2 transmembrane ligand that causes the death of tumour cells through the extrinsic apoptosis pathway and activation of caspase-8 [122]. TRAIL could be an ideal antitumor candidate for specific tumour types, as in most cases it causes the selective death of malignant cells [123,124]. However, TRAIL has a short pharmacokinetic half-life when administrated intravenously and this limits its usefulness when given systemically [124]. Genetically modified MSCs expressing TRAIL could offer targeted and prolonged delivery of the ligand [125,122]. Viral vectors have already been used to develop transduced MSCs that were studied against lung, renal, pancreatic, cervical, breast and colon cancer, malignant pleural mesothelioma, neuroblastoma, rhabdomyosarcoma, squamous cell carcinoma, metastatic malignant fibrous histiocytoma and multiple myeloma [126]. Recently, in vivo and in vitro studies indicated that MSCs expressing TRAIL caused apoptosis more effectively than recombinant human TRAIL (rh-TRAIL), and overcame TRAIL resistance of some cancer types [126]. Moreover, recent data support that the pancreatic cancer sensitivity to MSC-delivered TRAIL could be restored by combined administration of MSCs expressing TRAIL and a paclitaxel (PTX)-based chemotherapy [127].

5.1.6. Antibodies (Abs)

Antibodies that are produced in vitro and then administrated into the systemic circulation have a short-half life and cannot approach the tumour site. To overcome this difficulty, Compte et al. developed genetically engineered hMSCs to secrete a bispecific diabody, resulting in a powerful systemic antitumoral effect even though the diabodies were produced distantly [125]. In a recent animal study, human umbilical cord-derived MSCs were genetically modified to produce a bispecific Ab (Tandab CD3/CD19) against B cell lymphoma and inhibited cancer cell proliferation [128].

5.1.7. Enzyme/prodrug systems

Ghaedi et al. used lentivirus-transduced hMSCs to deliver α1-antitrypsin (AAT) to solid tumours and caused cytotoxicity against umbilical cord vein endothelial cells [129]. The gene-directed enzyme-producing therapy uses MSCs for targeted chemotherapy through a prodrug conversion approach [130]. Uchibori et al. combined MSCs that produced herpes simplex virus-thymidine kinase retroviral vectors with the prodrug ganciclovir leading to glioma cell death both in vitro and in vivo [131].

Similarly, extensively studied enzyme/prodrug systems included cytosine deaminase (CD) combined with 5-fluorocytosine (5-FC) and carboxylesterase with the prodrug CPT-11 (irinotecan) for the treatment of colon cancer, osteosarcoma [132] or glioblastoma and brain stem glioma, respectively [133]. Mesenchymal stem cells engineered to produce the CD enzyme, which converts the substrate 5-FC to the highly toxic 5-fluorouracil, have been used in melanoma and colon cancer. The tumour size was reduced; however, they also caused toxicity to healthy tissues [134,135].

5.1.8. Other factors

Pigment epithelium-derived factor (PEDF) and NK4 are agents that have been studied against lung carcinoma and gastric cancer, respectively. Transfection of MSCs to secrete these agents was effective in

cancer cell apoptosis and suppression of metastases [136–139].

5.2. Use of transduced MSCs to induce bone sarcoma cell apoptosis

The ability of MSCs to migrate to the primary tumour site raised the possibility of using them like drug or gene carriers. Transduced MSCs producing novel anti-cancer proteins molecules or drug systems such TRAIL, osteoprotegerin, cytosine deaminase/5-fluorocytosine (CD/5-FC) and IL-2 selectively to the tumour site, have also been studied extensively in bone sarcoma models (Table 3).

5.2.1. TRAIL

Transduced MSCs expressing TRAIL are promising for several cancer types; however, their efficacy against bone sarcomas remains controversial [126]. As noted previously, TRAIL delivered by ADMSCs had a greater anti-tumorigenic effect on osteosarcoma than rh-TRAIL alone. Despite the high levels of OPG, TRAIL cell delivery could be effective against SAOS-2 cells since MSCs offer a longer half-life and more stable TRAIL delivery and secretion of synergizing factors [140]. Transduced MSCs expressing TRAIL have anticancer activity in sarcoma models causing extensive apoptosis of sarcoma and potent antiangiogenic functions both in vitro and in vivo. This pro-apoptotic effect is thought to be controlled by the activation of caspase-8 [140]. Grisendi et al. also demonstrated the effectiveness of the approach in a metastatic lung model of Ewing's sarcoma, as ADMSCs were capable of migrating into the lung and persisting after last inoculation [140].

Several pre-clinical studies have proved the effectiveness of TRAIL against cancer cells, however, some Ewing sarcoma cell lines were TRAIL-resistant in vitro [141–143]. To overcome this resistance, Guiho et al., developed transduced ADMSCs producing TRAIL that induced cell death even in rh-TRAIL-resistant Ewing sarcoma cell lines. Direct cell-to-cell contact of Ewing sarcoma cells and the transduced ADMSC was necessary to cause cancer cell apoptosis through the clustering of a high level of death receptors. Two different orthotopic in vivo Ewing sarcoma models in mice also confirmed the efficiency of ADMSC expressing TRAIL [144]. In a more recent study, of a para-tibial orthotopic osteosarcoma mouse model using rh-TRAIL resistant K-HOS cells, the delivery of ADMSCs expressing TRAIL into the tumour site did not slow down tumour progression [145]. This was despite promising in vitro data demonstrating that MSC-TRAIL could induce significant K-HOS cell apoptosis in direct co-culture. Possible reasons given for the in vivo findings were the non-optimal target: effector ratio and lack of physical contact between the SCs and cancer cells. Furthermore, two of the MSC inoculated treatment groups demonstrated accelerated tumour progression [145].

5.2.2. Osteoprotegerin (OPG)

Osteoprotegerin is a soluble glycoprotein and a member of the TNF receptor superfamily. It has a crucial role in bone metabolism as a decoy receptor for RANKL in the RANK/RANKL/OPG axis, inhibiting osteoclastogenesis and bone resorption [146]. Osteoprotegerin impedes osteosarcoma progression by inhibiting RANKL whose secretion is enhanced in the bone tumour microenvironment. However, OPG was ineffective outside bone as it could not prevent pulmonary metastasis [147]. Qiao et al. developed MSCs transfected with adenoviruses carrying the OPG gene to prolong OPG's half-life and enhance its delivery directly to a tumour site. When administered to mice with osteosarcoma through the tail vein, the engineered MSCs were capable of migrating to the osteosarcoma site, producing OPG locally, reducing tumour growth and inhibiting bone destruction by osteosarcoma. The tumour volume at day 30 in mice that received MSCs-OPG was reduced by 65.2% compared to those administrated with PBS solution. Additionally, transduced MSCs were detected in treated mice, but with no increase in serum OPG levels was seen even 30 days after systematic administration, demonstrating fewer side effects of systemic administration [148].

5.2.3. CD/5-FC

Cytosine deaminase (CD) is a lethal gene which encodes an enzyme catalyzing the conversion of cytosine into uracil and the non-toxic prodrug 5-fluorocytosine (5-FC) into the cytotoxic agent 5-FU which has anti-tumour activity. The CD/5-FC system is very effective against human cancers by inhibiting DNA synthesis and promoting apoptosis of tumour cells [149].

MSCs expressing the CD/5-FC product (CD/5-FC MSCs) to promote cancer cell apoptosis is a novel but insufficiently studied model. They have been already evaluated in colorectal cancer and lung metastases with promising results [150,151]. Nguyen Thai et al. assessed the efficacy of CD/5-FC MSCs against human osteosarcoma cells in vitro and in vivo. They administrated MSCs bearing the CD gene combined with the nontoxic 5-FC prodrug. Interestingly, transduced MSCs were more capable of migrating towards osteosarcoma cells than native MSCs. The tumour volume increased at days 2–3 following the administration of CD MSCs, however, when the 5-FC prodrug was administered the tumour volume was gradually decreased from the fifth day. CD MSCs that were taken together with the 5-FC prodrug showed significant cytotoxicity against osteosarcoma cells in an animal model [132].

5.2.4. IL-12

The beneficial activity of IL-12 has been shown in several cancer models; however, initial enthusiasm faded due to severe toxicity with systemic administration. To overcome this, local gene delivery strategies have been used. Aerosol therapy including a polycationic IL-12-gene carrier was effective in reducing both the number of lung metastases and the nodule size in mice with established osteosarcoma lung metastases [152]. In addition, IL-12 increased Fas expression in osteosarcoma and Ewing's sarcoma cells through the enhancement of Fas promoter activity, causing cancer cell apoptosis [153,154]. The local gene delivery of IL-12 using adenoviral vectors may be effective for Ewing's sarcoma but not in patients with distant tumour metastases [155]. The anti-tumoural effect of IL-12 to osteosarcoma and Ewing's sarcoma and the ability of MSCs to migrate to the tumour site can be combined to deliver IL-12 locally to tumours. Murine MSCs infected with an adenoviral vector carrying the IL-12 gene injected into mice bearing Ewing's sarcoma were localized and produced IL-12 selectively in the tumour. Moreover, MSCs were also found in the lungs, spleen, and liver without harming these organs. p35 and p40 subunits of IL-12 were expressed in the tumour site, inhibiting tumour growth [156].

6. MSCs as delivery vehicles of anti-tumor nanoparticles to trigger bone sarcoma cell death

The tropism of MSCs to cancer tissue suggests their use as vehicles for local delivery of antineoplastic agents. Mesenchymal stem cells can pass through endothelium and following blood flow migrate to the tumour site increasing targeting efficiency and reducing normal tissue toxicity [157]. Moreover, human MSCs can use an active efflux pump system to gain resistance to anticancer drugs they transfer [158,159]. However, according to a study published by Belmar-Lopez et al., the MSC lineage to be used in a cell therapy should be carefully chosen as its safety and efficacy could vary between tumour types [160]. Moreover, antineoplastic agents that are used in MSC delivery systems would possibly destroy MSCs and lead to failure of this technique. To overcome this obstacle, Duchi et al. developed MSCs loaded with core-shell PMMA nanoparticles (FNPs) and meso-tetrakis (4-sulfonataphenyl) porphyrin (TPPS) which is a photosensitizer. When these MSCs were co-cultured with human osteosarcoma cell line U2OS-RFP-TUBA1B in vitro and upon light irradiation, they induced controlled osteosarcoma cell death through the generation of reactive oxygen species [161].

7. Clinical evidence of MSC use for bone defect regeneration after osteosarcoma resection

The biological filling of a bone defect [BD] after the surgical resection of a tumour is often difficult. Physiological healing mechanisms cannot cope with defects greater than 2 cm [178]. The dominant role of MSCs in bone regeneration and fracture healing [162,163] combined with their antitumor properties raised the possibility of a role in filling the BD after bone sarcoma therapy [164].

Contemporary engineering and regenerative medicine techniques [165] using molecular [166–168] and mechanical “guidance” [169–171] can differentiate ADMSCs into various tissue types. Previous animal studies (157,155) demonstrated the regenerative ability of SCs that were applied either intravenously or topically, loaded on a different type of scaffolds [172,173,100]. Although MSCs have been used in humans to promote bone formation, concerning bone sarcoma, there are obvious limitations in their use [101,174,175]. Following the first application of MSCs by Herzog in 1951, many steps forward have been accomplished to find better, more effective and less harmful techniques [176] but still, we are far from fully understanding the complex intracellular mechanisms, or safe use in clinical practice and from broad application of MSCs at BDs following osteosarcoma treatment [177]. To the best of our knowledge, three reported techniques use MSCs to fill musculoskeletal BDs after bone tumour extraction.

7.1. Direct local application of MSCs

Hernigou et al. as mentioned earlier, evaluated the local application of autologous BMMSCs to enhance the healing of the host-to-allograft bone junction following bone tumour resection in 92 patients with chondrosarcoma, osteosarcoma, Ewing's sarcoma or other tumours. MSCs were harvested from the patients' ilium using aspiration, collected in a 30 ml syringe and applied at the host bone-allograft junction. They aimed to retrospectively evaluate the risk of local tumour recurrence after surgical tumour resection at a mean of 15.4 years. Using three control groups, they concluded that the use of MSCs is probably safe, demonstrating no increase in the risk of local recurrence for all cancer types [100]. There were some safety concerns about human ADSC included in fat grafts, however, that were found to increase migration and metastases in a breast tumour and osteosarcoma models [74,101].

7.2. In vitro differentiation on scaffolds and re-implantation

Morishita et al. used tissue-engineered osteogenic ceramics to fill BDs after bone tumour curettage. They isolated BMMSCs that were osteogenic differentiated to osteoblasts after culture on porous hydroxyapatite ceramics [178], shaped based on specific patient needs and implanted in three patients suffering from a bone tumour. Impressively, the ceramic consolidated with the bone with no relapse nor loosening at the 3-month follow up in all patients. The limb was fully loaded at two and three weeks postoperatively, and no adverse events were reported in the long-term follow-up.

7.3. Formation of 3D like bone grafts

In a recent study, Dufrane et al. presented a novel technique to treat a bone nonunion in extreme clinical and pathophysiological conditions using a human autologous scaffold-free osteogenic 3-dimensional (3D) graft derived from ADSCs [179]. Autologous ADSCs were in vitro differentiated in osteogenic medium, and after 15 to 18 days Demineralized Bone Marrow (DBM) was added to form a 3D scaffold-like graft. Scaffolds were produced and applied to three patients with bone tumours and three patients with non-unions. The 3D grafts were placed at the junction between the native host bone and the bone allograft or the growing prosthesis in cases of tumours. The final osteogenic product

was stable and did not induce acute or long-term donor site morbidity up to 4 years after transplantation. This research team reported the use of the same graft in other 11 patients, with bone non-unions [180]. In total, six patients with bone sarcoma were treated (three osteosarcomas, two Ewing sarcomas and one with chondrosarcoma). Except for the DBM, no other donor tissue was used, thus overcoming all the host-to-donor and donor-to-host complications, increasing the safety of the technique and the chances of graft survival significantly. The 3D-scaffold was used as a bridge between the native host bone and the metallic grafts or bone allografts that were used for mechanical stabilization. Abnormal tissue formation was reported in one patient who had osteosarcoma recurrence, likely related to insufficient surgical margins after primary tumour resection. Another patient underwent surgical removal of the graft due to infection. Neither the age of the patients nor the previous chemotherapy affected the bone healing process. The patients had a satisfactory quality of life at three years. A disadvantage of the technique is the time interval between the fat tissue sample extraction and the application of the 3D-like graft that can be as long as four months (107 ± 28 days); however, this is a safe period that minimizes the chance of a subclinical tumour late recurrence.

8. Conclusions and future direction

Novel cellular therapies including Mesenchymal stromal cells, Dendritic cells, Natural Killer cells, Tumour Infiltrating Lymphocytes, Chimeric Antigen Receptor T cells, and $\gamma\delta$ T cells constitute a potential alternative path in bone sarcoma treatment. Using these cell types, we can achieve greater accumulation of antineoplastic agents in the tumour site while reducing adverse effects [181,182]. Mesenchymal stromal cells therapies have the potential to alter our therapeutic strategies, and improve outcomes for patients.

Mesenchymal stromal cells have promise as they can be used as vectors of antineoplastic agents and for bone defect regeneration after bone sarcoma resection. However, MSCs may not be safe as a sole therapy for bone sarcomas because most existing data suggest that they could accelerate pulmonary metastases after resection of the primary tumour, promote proliferation of cancer cells at the tumour site and increase chemoresistance in doxorubicin and cisplatin when interacting with cancer cells. However, the use of transduced MSCs to express specific anti-cancer proteins selectively to the tumour site is a promising therapeutic approach. MSCs expressing TRAIL, OPG, IL-12 or the CD/5-FC prodrug selectively to tumour site have been studied in vitro and in vivo animal models with promising results. Moreover, MSCs could be suitable for delivering drugs in osteosarcoma site using photodynamic techniques.

Bone marrow and adipose tissue were the primary cell source in most studies using MSCs. However, MSCs isolated from neonatal tissues appear to have advantages over adult sources; they are usually discarded without use, can be isolated easily and atraumatically with modern techniques and are associated with fewer adverse effects in clinical trials. Moreover, MSCs isolated from neonatal tissues have a lower risk of mutations and present superior proliferative, regenerative and immunosuppressive potentials over those from adult sources [183]. When it comes to comparison between different neonatal sources, it seems that foetal MSCs, especially those isolated from the chorionic membrane and umbilical cord, show a significantly higher expansion capacity than maternal MSCs [184]. However, the use of foetal MSCs is challenging as their isolation is possible during the early stages of life and can harm fetal development.

Recently, there has been a comparison between MSCs derived from induced pluripotent stem cells and ADMSCs regarding their use for tissue engineering with both presenting vessel [185] and bone formation capabilities [186,187], topically tumour progression control [188] and ease of use for tissue engineering [189,190]. In vivo data for the use of ADMSCs expressing membrane TRAIL is promising for Ewing's sarcoma. For osteosarcoma, further in vivo study is required. Determining the

optimal target: effector ratio and degree of physical contact between the MSCs and cancer cells are areas for future investigation. Also, in vitro findings may not be found in vivo due to the more heterogeneous cell populations. A key need is the ability to study microenvironments using tools which allow for disease modelling and personalized therapeutic evaluations. Emerging biofabrication [191] and organ-on-a-chip approaches seem to offer significant promise in this regard, although a critical challenge is the rate and cost of such models [192]. The development of high-throughput techniques to create and assess validated micro-tissue models for specific sarcomas would allow for cellular approaches to be assessed in vitro across heterogeneous populations and on personalized tissue models.

As no defined protocols exist for treating large bone defects after tumour resection, the above studies offer some promising results of different techniques [193]. Technology provides us with the means to “navigate” the MSCs and transform them into other cell types with different capabilities promoting healing and playing an antitumor role. Thus, using tissue engineering technology, we can build a portfolio of smart biomaterials and have a more personalized therapy applied, potentially with antitumor and osteogenic capabilities. Nowadays, we can manipulate the implanted grafts pre- or intra-operatively. Two and three-dimensional co-cultures systems have been widely studied in order to understand the relationship between cancer and surrounding cells, follow cancer progression and study different drugs. 3D co-cultures are gaining importance as they can closely mimic the cancer environment using porous and ECM-like structures that allow a more biological cell response when compared with the 2D cultures. This will be reflected not only on fundamental culture properties, such as proliferation or cell morphology but also in protein and gene expression profiles. These enhanced and more realistic cell properties are appealing for drug screening assays. Concerning bone sarcomas, these strategies can mimic sarcoma biological microenvironment, giving more realistic information about the diseases. Gao et al., thoroughly reviewed this topic.

Although cellular strategies offer promise, cell behaviour is complex and in vitro and animal models are not always predictive of human in vivo response. Thus, better models which allow mechanistic studies using human cells are required. MSC may have value in creating improved patient derived xenograft (PDX) models of osteosarcoma. The addition of MSC to a tumor specimen may enhance implantation into an immunodeficient mouse in a manner superior to that seen with Matrigel alone. We may not be far from the broad application of mesenchymal stromal cells as first-line therapy for bone sarcoma, as there have been made steps to more personalized cell therapy.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Declarations of interest

None.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jbo.2019.100231.

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