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The Role of Osteoblasts in Bone Metastatic Disease

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Abstract

The main function of osteoblasts is new bone production during the process of skeletal growth and bone remodelling. During bone remodelling, osteoblasts interact directly with other osteoblasts and other bone cells, such as osteoclasts, osteocytes, and mesenchymal stem cells, through complex cellular mechanisms. With the contribution of these mechanisms, osteoblasts and osteoclasts are responsible for the preservation of a balance between bone production and bone resorption. Bone metastatic disease is a frequent and unpleasant event in advanced stages of malign tumors. When the tumor cells spread to the bone microenvironment, they use the specific cellular mechanisms, disrupting the homeostasis of the bones. The cross-talk among cancer cells and bone tissue cells is crucial in the maintenance of the metastatic process, including the initial survival and seeding of disseminated tumor cells, activation of inactive micro metastatic lesions, and outspread of osteoblastic or osteolytic metastases. The aim of this review is to describe the role of osteoblasts in bone metastatic disease.

Keywords: *Osteoblasts; Bone metastatic Disease*

Osteoblast Physiology

During embryonic skeletogenesis and bone remodelling, osteoblasts are the bone cells that produce bone tissue. In order to regulate bone formation, osteoblasts produce ECM type I collagen. In addition, they also produce non-collagen proteins such as osteonectin and osteocalcin. For bone ossification, osteoblasts produce growth factors, enzymes and hormones including ALP, MMPs, TGF-β, and IGFs [1]. The combined action of the transcription factors Runx2 and Osx is demanded for the MSCs differentiation to osteoblasts (1). MSCs have the potential to differentiate into cells of mesodermal origin such as chondrocytes, osteoblasts and adipocytes. The connection of osteoprogenitor cells and mesenchymal cells triggers the differentiation of osteoblasts. Gradually, they differentiate into mature functional osteoblasts that express osteoblast genes and finally they are converted to osteocells, embedded into the bone ECM within the bone marrow. The regulation of osteoblastic differentiation is performed through osteogenetic signalling pathways [2]. Runx2 is a transcription factor, vital for bone formation. Its expression is necessary for the differentiation of MSCs into cells of the osteoblastic series. Runx2 binds to the promoter region (OSE-2) of osteoblast genes. Runx2 is expressed very early in skeletal development, in assemblages of MSCs in areas destined for bone tissue. It is also expressed during the postmenopausal period during bone production. Inactivation of the Runx2 gene in Runx2-/- mice results in complete absence of mature osteoblasts, suppressing intramembranous and endochondral ossification. MSCs in these animals may further differentiate into chondrocytes and adipocytes [2]. Osx, β-catenin, ATF4, and DLX5 are additional transcription factors that control osteoblast genesis. They work primarily with Runx2 and guide osteoprogenitor cells in their differentiation to the osteoblastic lineage. Activation of the Wnt / β-catenin signalling pathway stimulates bone production by osteoblasts, inducing the gathering of β-catenin and its transportation to the nucleus, where it connects to LEF / TCF transcription factors by activating genes including Runx2 [3]. Suppression of β-catenin reduces MSCs

differentiation to osteoblasts, indicating that β-catenin is a key molecule in osteoblastic differentiation. NF-κB is transported to the nucleus of osteoblasts, activating specific osteoblastic genes. NF-κB acts via the RANK-RANKL pathway and mainly controls osteoblast differentiation [4]. Three families of growth factors affect osteoblastic activity: TGF-β, IGFs and BMPs. They act mainly through their own interactions, through interactions with hormones or through specialized intracellular mediators that ultimately act on transcription factors. FGFs control specific elements of endochondral bone formation in the early stages of skeletogenesis. They stimulate osteoblast replication, but tend to reduce new bone formation by reducing collagen synthesis. Ihh protein controls the expression, function and phosphorylation of Runx2 and therefore the transcription of osteoblastic genes. BMPs stimulate bone formation in vivo by enhancing the expression of Runx2 in MSCs and prosteoblasts, and Osx in osteoblasts. TGF-β has a significant role in osteoblastic differentiation by promoting bone formation via Runx2 and at the same time by reducing the levels of those transcription factors that promote lipogenesis [5,6]. Once the bone production process is complete, the osteoblasts either turn into osteocytes, remain dormant, trapped inside bone ECM, or undergo cellular apoptosis [7,8]. Osteocytes communicate with other osteocytes as well as with osteoblasts, through extensive cytoplasmic extensions which form tiny channels (canaliculi) within bone ECM. All of the aforementioned cells produce RANKL [9]. Therefore, the interactions between RANKL, osteoclasts, osteoblasts and osteocytes directly influence differentiation of osteoclasts, maintaining osteoclastic bone resorption, and the production of growth factors from bone ECM.

Colonization and growth of metastatic cancer cells: Role of the bone microenvironment

Bones are a common area of malign tumor metastases, affecting more than 300,000 patients annually in the United States. Prostate and breast cancer are responsible for the 65-80% of bone metastases [10]. When cancer cells escape from the primary cancer sites and spread to distant areas, only a very small percentage survive in the circulation and end up in the secondary organ-targets. The locations of the metastases are not random. In order to grow, cancer cells must reach an environment that is acceptable for colonization and subsequent growth. To do that, cancer cells hijiack normal host functions, express ECM molecules and mobilize bone marrow MSCs, thus creating the so-called “pre-metastatic niche” [11]. Metastatic time of dormancy is a stage of cancer evolution where cancer cells that have disseminated from a primary cancer site to peripheral areas may remain in a state of inactivation for years [12]. In the case of bone metastases, the cancer cells are thought to nest in specific niches, which determine their fate [13,14]. Experimental data show that all of the following niches have an important role in bone metastases and that the cross-talk among these sites determines the activation or inactivation of cancer cells.

- The endosteal niche, consisting mainly of osteoblasts
- The hematopoietic stem cells (HSC) niche
- The perivascular niche and
- The bone marrow adipocyte niche

Endosteal Niche

In experimental studies, prostate and breast cancer cells have been located in bone areas with abundance in osteoblasts. In experimental models of breast cancer, administration of zoledronic acid modifies the endosteal niche resulting in repositioning of cancer cells in new bone sites rich in osteoblasts [15,16]. Osteoblasts release the protein CXCL12, also known as SDF-1. On the other hand, the CXCL12 receptor, which is called fusin or CXCR4, is expressed by the majority of metastatic breast and prostate cancer cells. The interaction between CXCL12 and its receptor is vital for the binding of cancer cells to the endosteal metastatic niche. Once cancer cells install the endosteal niche, osteoblasts keep these cancer cells inactive through CXCR4 / CXCL12 cross-talk, with the same mechanisms used for HSCs inactivation [17]. These osteoblasts are spindle-shaped, positive for N-cadherin. Their binding to cancer cells and the secretion of inhibitory proteins from stromal cells, such as fibronectin, also maintains the state of dormancy of cancer cells. The action of CXCL12 is regulated by NF-κB and the different response of cancer lines to CXCL12 is probably the result of different degrees of NF-κB activation, which with in turn is affected by the expression of androgen receptors in the cell [18].

Hematopoietic stem cell (HSC) niche

Scattered cancer cells tend to migrate into the endosteal bone surface, a niche where non-proliferating HSCs are located. The HSC niche is also abundant in CXCL12, therefore binding to CXCR4 (+) cancer cells in the same manner as the endosteal metastatic niche. When cancer cells colonize the HSC niche, they compete with HSCs for installation in the surface. The following outspread of cancer cells outside the niche, allowing the onset of active metastases, is attained by the mobilization and multiplication of HSCs, a process supported by the perivascular niche [17,19].

Perivascular niche

The perivascular niche has been another site for colonization and accommodation of dormant cancer cells. Within the perivascular niche, cancer cells are located at central points within the bone marrow. Isolated evaluation of the perivascular niche is difficult

because of its proximity to the endosteal niche and the HSC niche. In brain metastases deriving from breast and lung cancer, the cancer cells, after extravasation, remain close to the capillary vessels [20,21]. These metastatic cancer cells spread along the basement membrane around the capillaries and multiply, encapsulating and reshaping the capillary vascular network [21]. Taking all these into account, it turns out that the endosteal niche is important for maintaining the inactivity of the cancer cells, while the HSC niche and the perivascular niche activate the proliferation of cancer cells in active metastases. Thus, it is possible that bone metabolism and activity of osteoblasts regulate the activation of bone metastases from cancer cells that have spread to the bone microenvironment, an observation that has long been made in animal studies [22,23].

Bone Marrow Adipocyte niche

Adipocytes within the bone marrow play a crucial role in the metastatic niche. Their number increases during aging, making the adipocyte niche crucial in the elderly patients who suffer from breast cancer. In an experimental study, breast cancer cells were found to interact directly with bone marrow adipocytes, after their migration into the bone marrow adipose tissue. This interaction was mediated by adipose tissue-derived leptin and IL-1β [24].

Activation of metastatic cells

When cancer cells ultimately depart from the primary tumors and scatter into distant areas, only few of them (below 0.1%) survive during circulation, escape immune surveillance, and end up in the secondary targets [25]. Once installed in the bones, the cancer cells affect the bone cells in two main ways. Usually, cancer cells stimulate osteoclast genesis, increasing the differentiation and activity of osteoclasts, while at the same time inhibiting osteoblasts [8]. When this occurs, osteoclastic bone resorption overdraws osteoblastic bone formation, leading in bone destruction and the creation of osteolytic lesions. Activated osteoclasts trigger the increased proteolytic activity of MMP-9 and cathepsin K, which inactivate the SDF-1 receptor and osteopontin, facilitating the detachment of metastatic cancer cells from the endosteal niche [26,27]. Occasionally, instead of suppressing osteoblastic activity, cancer cells secrete molecules that activate the osteoblast cell line, increasing osteoblast differentiation and bone production. IL-6, PTHrP, EGF, TGFα and CSF are soluble molecules that favour osteolysis. On the other hand, ET-1, BMPs, IGFα, BDGF favour bone formation. Prostaglandins, TNFα, TGFβ, IL-1 and PDGF may enhance either bone production or bone resorption [28]. When bone production by osteoblasts exceeds bone resorption by osteoclasts, increased bone formation leads to "bulges" of the mineralized bone, where the cancer cells multiply causing osteoblastic metastases. As osteoblastic bone lesions are characterized by increased bone resorption and formation of weakened bone with disrupted architecture, osteoblastic metastases are associated with increased fracture risk [29]. Although osteolytic metastases are more common, the distinction between osteolytic and osteoblastic metastases is incomplete and in many cases, bone metastases have both osteoblastic and osteolytic lesions [30]. Osteoblasts may have a direct role on growth of bone metastases. In experimental models of breast cancer bone metastasis, PTH administration resulted in an increase in numbers of actively proliferating bone metastases without modifying the dissemination of cancer cells in bone [31]. On the contrast, daily administration of PTH inhibited cancer progression whilst increasing bone production, in animal models of multiple myeloma [32].

Role of osteoblasts in osteolytic metastases

Osteolytic metastases are the most common type of bone metastases. They occur in solid cancers (lung, prostate, breast, thyroid, kidney) and in haematological malignancies. The osteolytic element is predominant but foci of osteoblastic activity coexist as evidenced by elevated serum ALP levels. Metastatic cells within the bone marrow do not act directly on the bone but they may modify osteoclastic and osteoblastic function. In comparison with osteoclasts, the role of osteoblasts in osteolytic metastases is rather limited. Upon the influence of breast cancer cells, osteoblasts secrete chemokines and growth factors acting on both breast cancer cells and osteoclasts, stimulating the vicious circle of bone metastatic disease and osteolytic lesions [33]. In osteolytic bone metastases, cancer cells release molecules that enhance osteoclastic activity by activating the RANKL / RANK pathway. In addition, cancer cells produce activin A, DKK-1 and sclerostin that suppress osteoblastic activity and differentiation [30]. DKK-1 produced by myeloma cells has been found to inhibit the differentiation of osteoblasts, induces the early differentiation of MSCs and therefore reduces their viability. As the disease progresses, these events upset the balance between osteoblasts and osteoclasts, reducing bone formation and enhancing bone resorption [34]. Moreover, tumor cells induce osteoblasts apoptosis. This causes disequilibrium between bone destruction and bone production in favour of increased bone degradation. Increased bone destruction triggers a vicious circle among cancer cells and osteoblasts, where growth factors (TGF-β, IGF), that had been deposited in the bones by osteoblasts, are secreted from resorption cavities, triggering cancer cell multiplication. Accordingly, tumor cells, further secrete growth factors promoting bone metabolism. Through the dense, interconnected vascular system, bone metaphysis provides plentiful growth factors, such as TGF-β, whose production from bone directly induces the release of PTHrP by cancer cells, stimulating RANKL production [35-37]. Osteoblasts express CXCL12 and RANKL that promote dissemination of breast

cancer cells and evolution of bone metastases [38]. Initiation of bone resorption is mediated by pre-osteoblasts producing RANKL, which enhances osteoclast genesis [39]. In vitro experiments have shown that human breast cancer cells induce the activation of the COX-2/PGE2 system and stimulate the increase of RANKL in osteoblasts ultimately leading to osteolysis. Osteoblasts are stimulated by both soluble agents and intercellular interactions. Removal of stimulation using antibodies to β1 integrin's suggests their possible involvement in this process [40]. At the initial stages, when the size of tumors is small, an increase in osteoclastic activity and elimination of osteoblasts at the tumor / bone interface, are observed. The compensation for this local increase in bone resorption growth factors by absorbed bone triggers osteoblast genesis on the adjacent bone surface, causing a local increase in RANKL production that stimulates osteoclasts [41]. The simultaneous culture of osteoblasts and osteoclasts enhances the stimulatory effect of PGE2 due to increased RANKL and decreased OPG in osteoblasts. Additionally, osteoclast genesis is stimulated by the COX-2 / PGE2 system through the increase of IL-6 secreted by osteoclasts and osteoblasts [42]. This is the point when bone metastases develop while at the advanced stages of metastatic disease, the role of osteoclasts dominates. After the establishment of osteolytic metastases in bone, the release of TGF-β from resorption cavities attenuates osteoblast genesis, thereby suppressing bone formation, and further contributing to metastatic bone disease [43].

Quantitative histomorphometric analysis of bone biopsies showed that in addition to a decrease in number of osteoclasts, there was a decrease in the number of osteoblasts, the surface and the absolute volume of the osteoid, and an increase in bone cavities lacking osteocytes in the area around the metastatic lesion [44]. In addition, another study indicated that elimination or disruption of osteoblastic activity is observed near the metastatic site [45]. Osteoblasts have been found to surround breast cancer micro metastases. The cross-talk between breast cancer cells and osteoblasts is affected by junctions by N-cadherins and E-cadherins leading to increased mTOR activity in tumour cells and ultimately to the awakening of inactive cancer cells and transition into active metastases [38]. As previously mentioned, Runx2 is an important factor for the differentiation and function of osteoblasts during skeletal formation. Evidence for the role of Runx2 in osteotropy was obtained indirectly when the expression of target genes (MMP-3, bone sialoprotein) was detected in bone metastases [46,47]. According to these studies, Runx2 is indeed involved in the expression of these genes, giving cancer cells osteomimetic characteristics. The resulting osteolytic metastases were characterized by inhibition of osteoblast differentiation and enhanced osteoclastogenesis. These effects were eliminated when corresponding cancer cell lines expressing a shorter, non-functional Runx2 were used.

Role of osteoblasts in osteoblastic metastases

They are the most frequent type of bone metastasis in prostate cancer and are less common in breast cancer (15-20%), colon, pancreas and cervix. They are characterized by a disturbance of the normal balance of bone tissue, with a predominance of the osteoblastic bone formation. However, the produced bone does not have a normal architecture resulting in an increased rate of fractures combined with severe pain. In osteoblastic bone metastases, there is also a vicious circle among cancer cells and bone cells, as happens in osteolytic disease. However, in addition, cancer cells in the bones produce osteoblast stimulants such as BMPs, EGFs and PDGFs. Prostate cancer cells produce various growth factors (TGF-β, FGF-9, BMP-4, PDGF, VEGF, FGF), which promote the multiplication and differentiation of osteoblasts, inducing the growth of prostate cancer cells [26,27]. Runx2 has been found to be expressed in prostate cancer cells from bone metastases [48]. Prostate cancer cells also produce FGF inducing osteoblast apoptosis [49]. These activated osteoblasts release signalling molecules such as MCP-1, IL-6, and MIP-2, which further enhance the colonization and proliferation of tumor cells within the bone microenvironment. Prostatic osteoblastic metastases are caused by the strong interaction among prostate cancer cells and osteoblasts. Natural contact of osteoblasts with cancer cells promotes the proliferation of prostate cancer cells in vitro [50]. In another study, the co-culture of osteoblasts and prostate cancer cells caused a decrease in prostate cancer cell growth [51]. Another study showed that molecules secreted by osteoblasts inactivated prostate cancer cells in vitro and in vivo [52]. Experimental data have underlined that osteoblasts have growth inhibitory properties, a feature that can be used both to promote the delay of bone metastases and to prevent the progression of bone metastases [53]. Circulating met prostate cells are associated with the endosteal bone surface where they connect with osteoblasts via bonding with the annexin-2 receptor [54]. These micro-metastasic lesions form in areas of new bone tissue production, where differentiated and active osteoblasts are sited. Moreover, the interaction among osteoblasts and breast cancer cells has been shown that molecules secreted during osteoblasts differentiation process enhance cancer cell growth. VEGF is involved in osteoblastic metastases. Based on findings that VEGF stimulates osteoblastic activity and induces bone remodeling, Kitakawa et al suggested that prostate cells initially support the proliferation of cancer cells in the bone through VEGF secretion [55]. In a second stage, continued VEGF secretion triggers the activation of pro-osteoblasts to mature, active osteoblasts through its binding to neuropilin-1 [56]. However, it has not been shown that VEGF alone can induce the

formation of osteoblastic metastasis, but apparently cooperates with other factors such as BMP, Wnt and ET-1.

In 1995, Nelson et al correlated ET-1 with osteoblastic metastases of prostate cancer by finding elevated serum levels in patients [57]. It is hypothesized that cancer cells of bone metastasis secrete ET-1, which stimulates the proliferation of osteoblasts and consequently new bone formation. In turn, stimulated osteoblasts in turn enrich the bone microenvironment with growth factors (IL-1β, IL-1α, EGF, TNFα, TGF-β), which further enhance the production of ET-1 by tumor cells, thus closing a vicious circle, resulting in the formation of osteoblastic metastasis [58]. Moreover, tumor cells produce ET-1, downregulating DKK-1 factor biosynthesis and stimulating osteoblastogenesis [43]. Prostate cancer cell function is affected by factors secreted by osteoblasts, such as osteopontin, osteonectin, osteocalcin, and bone sialoprotein [26,27]. Osteonectin has a chemotactic effect on various types of cancer. In a study with tissue extracts, it was concluded that bone enhances movement of prostate cancer cells [59]. Similar findings exist for the directed migration of breast cancer cells. Osteopontin is another protein that is overexpressed in bone ECM and plays a role in the chemotaxis of cancer cells. Its role in the directed migration of cancer cells is mainly regulated by integrin αvβ3 and includes cancers such as melanoma and breast cancer, while there is a possible role of the integrin β1 chain in combination with α chains [60]. This migration depends on at least two growth factors and their receptors (HGF / c-met axis, EGF and their ligands) as well as multiple signaling pathways [61]. In bone metastatic lesions, osteopontin mRNA has been detected in cancer cells which are in contact with the bone, possibly mediating interactions at tumor-host interface. Berger et al. using antisense oligonucleotides, reduced the expression of both osteopontin and bone sialoprotein in human breast cancer cells, thereby inhibiting the formation of osteolytic metastases [62]. Studies in the same cellular type have shown a great increase in metastatic capacity in the presence of high osteopontin levels [63]. Also, intravenous infusion of B16 melanoma cells in osteopontin deficient mice led to reduced bone metastatic lesions compared to normal mice [64]. In addition, binding of osteopontin to αvβ3 integrin induces osteoblast activation in osteolytic metastases [65]. There have been reports of a possible role for osteopontin as a factor in inducing osteoblast apoptosis [66]. The central role of osteopontin in the metastatic process has led to the search for possible therapeutic applications targeting either osteopontin itself or its receptors (CD44 and integrins). The fact that osteopontin produced by cancer cells differs from endogenous osteopontin makes this molecule attractive as a therapeutic target. Bone sialoprotein is another of the non-collagenous proteins of bone marrow that plays a significant role in the chemotaxis of cancer cells to bone tissue. Over time, both host as well as cancer cell-derived bone sialoprotein have been involved in the metastatic process. Tumor cells probably attach to the bone ECM by a mechanism similar to that of osteoclasts through integrins interaction [67]. A study in breast cancer cells has shown that this is achieved by binding to integrin αvβ3 and depends on an arginine-glycine-asparagine tripeptide (RGD). However, the involvement of regions independent of the RGD tripeptide is also possible [68,69]. Similar data exist for melanoma cells [70]. Ectopic expression of bone sialoprotein is probably due to the activation of intracellular pathways and the action of the transcription factors Runx2 and MSX2. There is evidence that bone sialoprotein may be involved in the angiogenetic process of the metastatic lesions [71]. The aforementioned increased osteoblastic activity leads to an increase in calcium and phosphorus deposition, causing hypocalcaemia, resulting in increased PTH secretion (secondary hyperparathyroidism), which activates the production of RANKL in MSCs and osteoblasts, enhancing osteoclastogenesis and bone absorption. As a result, growth factors are produced from the bone ECM, promoting cancer cells growth. Regarding prostate cancer, and given that osteoblasts express the androgen receptor (AR) and the expression of these receptors increases as osteoblasts mature into osteocytes, there is a possibility that androgens may also be implicated in the pathogenesis of bone metastases [72,73]. Elevated BMP levels of prostate cancer cells or, consequently, the presence of BMP in the bone microenvironment are important factors for the colonization and survival of cancer cells in bone tissue. In an earlier study, BMP-7 was detected in the majority of bone metastasis samples, but not in normal bone samples [74]. BMP-2 could contribute to the formation of osteolytic bone metastasis and induce osteoblast apoptosis, as suggested by a similar study [75]. In addition, osteoblasts and osteocytes also release LIF and activation of LIF receptors in breast cancer cells appears to keep them in a state of inactivity. Loss of LIF receptors results in reduced expression of genes involved in cell inactivity. Experimental knockdown of LIF receptors increases the migration and penetration of cancer cells and the differentiation of osteoclasts. Overexpression of PTHrP also reduces LIF receptors signalling [76].

Conclusions

Scientific data have shown that osteoblasts are important contributors in the pathogenesis of metastatic bone disease, but their exact contribution to homing, dormancy, and survival of the tumor cells has not yet been clarified. In comparison with osteoclasts, the role of osteoblasts in bone metastasis and the formation of metastatic niche is rather low and under-investigated. A better understanding of the interaction of osteoblasts with cancer cells within the bone tissue will be needed for the identification of novel management methods for patients with bone metastatic disease.

Abbreviations list

ALP: Alcaline Phosphatase
ATF-4: Activating transcription factor 4
BMPs: Bone Morphogenetic Proteins
COX-2: Cyclooxygenase 2
CXCR4: C-X-C Motif Chemokine Receptor 4
CXCL12: C-X-C Motif Chemokine Ligand 12
DKK-1: dickkopf-1 factor
DLX-5: distal-less homeobox 5
ECM: Extracellular matrix
EGF: Epidermal growth factor
ET-1: Endothelin-1
FGF: Fibroblast growth factors
HGF/c-met: Hepatocyte growth factor /c-mesenchymal-epithelial transition receptor
HSCs: Hematopoietic stem cells
IGF-β: insulin-like growth factors - β
Ihh: Indian hedgehog
IL-1a: Interleukin-1a
IL-1β: Interleukin-1β
1IL-6: Interleukin-6
LEF/TCF: T-cell factor/lymphoid enhancer factor
LIF: Leukemia inhibitory factor
MCP-1: Monocyte chemoattractant protein-1
MIP-2: macrophage inflammatory protein-2
MMPs: Matrix metalloproteinases
MMP-3: Matrix Metalloproteinase – 3
MMP-13: Matrix Metalloproteinase – 13
MSX2: Msh Homeobox 2
MSCs: Mesenchymal stem cells
NF-κB: Nuclear factor-κB
OPG: Osteoprotegerin
OSE2: osteoblast specific cis-element 2
Osx: Osterix
PDGF: Platelet-derived growth factor
PGE2: Prostaglandin E2
PTH: Parathyroid hormone
PTHrP: Parathyroid hormone-related protein
RANK: receptor activator of NF-kappaB
RANKL: RANK ligand
Runx2: Runt-related transcription factor 2
SDF-1: stromal cell-derived factor 1
TGF-β: transforming growth factor – β
TNFa: Tumor necrosis factor-a
VEGF: Vascular endothelial growth factor

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