Bone marrow-derived cells: roles in solid tumor

Minireview

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The role of cancer stem cells has been demonstrated for some cancers. Recently, research indicated that solid tumors may originate from bone marrow stem cells. Bone marrow-derived cells have recently been shown to contribute to stromal formation, especially angiogenesis and lymphvasculogenesis. Moreover, the interaction and the cell fusion between cancer cells and bone mesenchymal stem cells could enhance the aggregative ability of cancer cells. Bone marrow derived cells home to tumor-specific pre-metastatic sites to provide a permissive niche for incoming tumor cells. Since bone marrow-derived cells play an important role in carcinogenesis, angiogenesis and metastasis, bone marrow-derived cells are not only the tool for cancer therapy, but also the targets for cancer therapy.

Key words: bone marrow, stem cells, tumor, angiogenesis, metastasis, carcinogenesis

Transplantation of bone marrow cells has been successfully used in hematopoietic diseases. Recently, transplantation of genetically modified bone marrow progenitors was used as a vehicle for the transport of gene therapy in many diseases, including tumors [1]. Moreover transplantation of bone marrow cells has been hopeful by used for tissue regeneration and tissue repair [2,3].Unfortunately, patients undergoing bone marrow transplantation have an increased risk of new solid cancers, especially malignant melanoma and cancers of the buccal cavity, liver, brain or other parts of the central nervous system, thyroid, bone, and connective tissue [4-8]. However, the origin of the cancer by bone marrow transplantation remains elusive. Research on bone marrow derived cell in carcinogenesis has entered a new era of controversy, excitement, and great expectations.

Bone marrow-derived cells and carcinogenesis

The role of cancer stem cells has been demonstrated for some cancers, such as the cancer of hematopoietic system, breast and brain [9-11]. Recently, the clear similarities between stem cell and cancer stem cell genetic programs were used as a basis for the proposal that some cancer stem cells could derive from adult stem cells [11]. Adult mesenchymal stem cells (MSC) may be targets for malignant transformation and undergo spontaneous transformation following long-term *in vitro* culture, supporting the hypothesis of cancer stem cell origin [12-14].

Chronic gastric inflammation, which develops as a consequence of *H. pylori*, leads over time to repetitive injury and repair resulting in hyperproliferation, an increased rate of mitotic error, and progression to adenocarcinoma. Wang *et al* reported that chronic infection of C57BL/6 mice with *H. pylori*, induced repopulation of the stomach epithelial cells with bone marrow–derived cells. Subsequently, these cells progressed through metaplasia and dysplasia to intraepithelial cancer [15]. Bone mesenchymal stem cells (BMSC) but not hematopoietic stem cells (HSC) are the target for malignant transformation.

Hepatic oval cells, the liver stem cells involved in some forms of liver regeneration, express many markers, such as C-kit, CD_{34} and Thy-1, also found on HSC [16-18]. Moreover, bone marrow stem cells could differentiate into oval cells and hepatocytes [19-21]. Hepatoma cells could produce erythropoietin, colony-stimulating factor and myeloid differentiation antigens (CD14, CD68 and HLA-DR) [22,23].Thus the hypothesis is that HCC(hepatoma cells) may originate from bone marrow stem

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cells [24]. In kidney allograft recipients, bone marrow derived-stem cells originating from a grafted kidney may migrate to the skin, differentiate, or fuse as keratinocytes that could, rarely, undergo cancer transformation [25]. Similarly, post-transplant Kaposi sarcoma could originate from bone marrow derived-stem cells originating from a grafted kidney [26]. Thus the hypothesis is that many solid tumors may originate from bone marrow stem cells [27].

Chronic infection by *H. pylori* could induce transformation of bone marrow–derived cells transformed to intraepithelial cancer, while bone marrow cells could not progress to HCC in transgenic mouse induced by treatment with diethylnitrosamine and phenobarbital [13, 28]. Moreover, HSC could fuse with a multipotent intestinal progenitor or stem cell. Local injury is important for BMDC fusion and that this fusion mechanism participates in epithelial regeneration [29]. Thus, the hypothesis is that chronic inflammation plays probably an essential role in the malignant transformation of bone marrow cells [24]. The stromal derived factor (SDF)-1 is a chemokines produced during chronic inflammation. SDF-1-CXCR4 (the receptor for SDF-1alpha) axis may be a master regulator of trafficking in both normal and cancer stem cells [30]. Stromal cell derived factor (SDF)-1 and stem cell factor-1 (two factors identified in mobilization and migration of marrow progenitor cells) were up-regulated in *H. pylori* infected mice compared with uninfected age-matched controls [15]. SDF-1-CXCR4 axis may play a pivotal role in the recruitment of bone marrow cells to origin and transform ation to cancer cells.

The mechanism of cellular fusion of bone marrow stem cell with host cells in organs has been illustrated by using serially transplanted cells and extensive karyotyping of engrafted cells [31, 32]. Other studies, however, suggest that bone marrow stem cell incorporate into organs through transdifferentiation into tissue specific stem cells [33,34]. Further evidence is presented that bone marrow in addition to $CD45^{positive}$ HSCs contains a rare population of heterogeneous $CD45^{negative}$ nonhematopoietic tissue committed stem cells. Thus some cancers may originate from the differentiation block of nonhematopoietic tissue committed stem cells [35]. Whether the mechanism occurs through differentiation block, trans-determination, or cell fusion is a key unresolved issue. Moreover, if cancer could originate from bone marrow stem cell, who (HCC, BMSC or tissue committed stem cells) is the real troublemaker?

Bone marrow-derived cells and angiogenesis

Cancer-stromal interaction is well known to play important roles during cancer progression. The MSC self-renew by proliferation while maintaining their stem-cell phenotype and give rise to differentiated stromal cells. The recruitment of bone marrow-derived vascular endothelial cells and myofibroblasts is required for stromal formation during cancer progression [36]. Approximately 25% of myofibroblasts in pancreatic insulinomas were bone marrow-derived, and these were concentrated toward the edge of the tumor [37].

The traditional view of angiogenesis and lymphvasculogenesis emphasizes proliferation and migration of vessel wall-associated endothelial cells or the pre-existing local lymphatic network. Recently, the role of bone marrow-derived cells in tumor angiogenesis and lymphvasculogenesis was currently the subject of intense research. The debate focus on the innocent supportive or constitutive role of bone marrow-derived cells in tumor angiogenesis and lymphvasculogenesis [38-44]. Bone-marrow-derived cells have recently been shown to contribute to tumor angiogenesis [45-53]. Transplanted bone marrow cells preferentially home to the vessels of in situ generated tumors rather than of normal organs [54].

A human pancreatic cancer cell line, Capan-1, was transplanted into 5 different sites: subcutaneous tissue, peritoneum, liver, spleen and lung. Dramatically, tumors in the subcutaneous tissue and peritoneum induced desmoplastic stroma and contained bone marrow-derived vascular endothelial cells and myofibroblasts, but weak stromal induction without recruitment of bone marrow-derived vascular endothelial cells or myofibroblasts was observed the liver, spleen and lung humors. Thus the cancer microenvironment is important in the recruitment of bone marrow-derived cells [36].

Recruitment of vascular endothelial growth factor (VEGF)-responsive bone- marrow-derived cells is necessary and sufficient for tumor angiogenesis [55]. Although targeting of either vascular endothelial growth factor receptor(VEGFR)1 or VEGFR2 alone partially blocks the growth of tumors, inhibition of both VEGFR1 and VEGFR2 was necessary to completely ablate the tumor growth [56]. Recruited bone marrow-derived circulating cells summoned by VEGF express a distinct different than endothelial progenitor cells. Retention of bone marrow-derived cells in close proximity to angiogenic vessels is mediated by SDF-1, a chemokine induced by VEGF in activated perivascular myofibroblasts [57].

Hypoxia is a central stimulus of VEGF gene expression [58]. The expression of SDF-1 is directly regulated by hypoxia-inducible factor-1 [59]. BMSC may have the capacity to participate in tumor angiogenesis through regulation of their angiogenic properties in the atmosphere of low oxygen that closely approximates the tumor microenvironment. Expression of membrane-type1-matrix metalloproteinase (MMP) was strongly induced by hypoxia. Functional inhibition of membrane-type1-MMP by a blocking antibody strongly suppressed BMSC ability to migrate and generate capillary-like structures [60]. Thus a hypoxic environment such as that encountered in tumor masses regulates BMSC angiogenic properties by pathways of VEGF-VEGFR and SDF-CXCR4 (Fig.1).

Tumor derived plateletderived growth factor receptor (PDGFR) beta (+) progenitor perivascular cells (PPC) that have the ability to differentiate into pericytes and regulate vessel stability and vascular survival in tumors. A subset of PDGFR beta (+) PPC is recruited from bone marrow to

perivascular sites in tumors [61]. In particular, basic fibroblast growth factor, a key mediator of angiogenesis, was found to be the most potent growth factor for inducing BMSC proliferation, migration, and tubulogenesis [62]. Granulocyte colony-stimulating factor (G-CSF) markedly promoted growth of the colon cancer inoculated into the subcutaneous space of mice, whereas G-CSF had no effect on cancer cell proliferation in vitro. G-CSF may have a potential to promote the tumor growth, at least in part, by stimulating angiogenesis in which bone marrow-derived EPC play a role [63]. Loss of Id1 in tumor endothelial cells results in down-regulation of several proangiogenic genes, including alpha6 and beta4 integrins, matrix metalloprotease-2, and fibroblast growth factor receptor-1 [64]. BMSC could be recruited at the sites of active tumor neovascularization through paracrine regulation of their angiogenic properties.

Inhibit on of angiogenesis is a promising strategy for treatment of cancer and several other disorders [65,66]. Transplantation of genetically modified bone marrow progenitors may represent a vehicle for the transport of gene therapy to tumors [67-73].

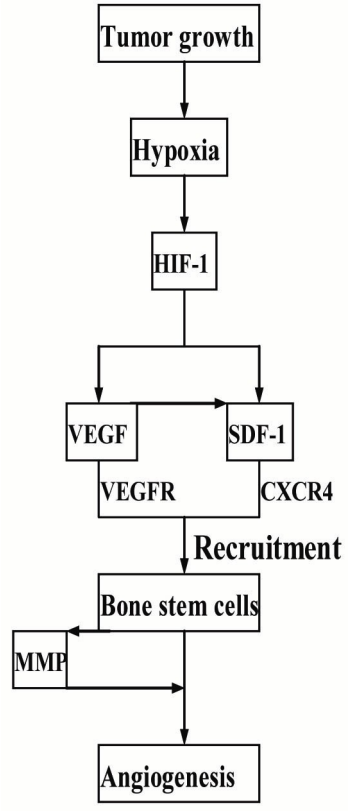

Fig.1 Bone stem cells and tumorous angiogenesis
The expression of SDF-1 and VEGF is directly regulated by HNF-1, which induced by hypoxia. SDF-1 is also induced by VEGF in activated perivascular myofibroblasts. VEGFR(+) and/or CXCR4(+) BMSC may be recruited and have the capacity to participate in angiogenesis under hypoxic microenvironment. Expression of membrane-type1- MMP, which play an important role of migrating and generating capillary-like structures, was strongly induced by hypoxia. Thus a hypoxic environment of tumor masses recruits and regulates BMSC angiogenic properties by pathways of VEGF-VEGFR and SDF-CXCR4.
HNF-1: hypoxia-inducible factor-1, MMP: matrix metalloproteinase, SDF-1: Stromal cell derived factor-1, VEGF: vascular endothelial growth factor, VEGFR: vascular endothelial growth factor receptor.

Bone marrow-derived cells and metastasis

Metastasis is a sequential process including breaking off the cells from the primary tumor, traveling through the bloodstream and stopping at a distant site. Dramatically, bone marrow-derived haematopoietic progenitor cells that express VEGFR1 home to tumor-specific pre-metastatic sites and form cellular clusters before the arrival of tumor cells. VEGFR1+ cells express integrin alpha4beta1, adhesion molecules which joint the cells and ECM, and that tumor-specific growth factors up-regulate fibronectin-a integrin alpha4beta1 ligand-in resident fibroblasts, providing a permissive niche for incoming tumor cells [74]. MMP-9 cell production by multiple myeloma cells is up-regulated in vivo by the interaction of multiple myeloma cells with BMEC [75].The expression of MMP-9 from bone marrow-derived cells could promote lung tumor colonization of injected tumor cells. MMP-9 from the bone marrow contributes to early survival and establishment of tumors in the lung and has no effect on subsequent growth [76].

After co-culture with BMSC, changes were detected in the morphology, proliferative capacity and aggregation pattern of human breast cancer MCF-7 cells, but these parameters were not affected after the co-culture of BMSC with a non-tumorigenic breast epithelial cell line, MCF-10. VEGF and IL-6 cells mimic the effects produced by BMSC or its products on the proliferation and aggregation properties of MCF-7, cells, respectively [77]. When epithelial metastatic breast cancer MCF-7s cell were set in co-culture with BMSC or in feeder layer of 3T3 fibroblasts, MCF-7 cells grow in clusters on 3T3, but disperse on BMSC. Concomitant with the lost of their aggregation status, MCF-7 cells on BMSC expresses low levels of the intercellular adhesion molecules, E-cadherin and epithelial-specific antigen [78]. Thus the interaction between cancer cells and BMSC could enhance the aggregative ability of cancer cells.

Tumor cell becomes metastatic by fusion to normal cells that travel throughout the body freely, such as lymphocytes or macrophages [79, 80]. It has been hypothesized that bone marrow stem cells could fuse with transformed intestinal epithelium to confer phenotypic and genotypic diversity to the tumor [81,82]. HSC but not BMSC, could fuse with a multipotent intestinal progenitor or stem cell [82]. HSC are not involved in tumor initiation in the small intestine, but with undifferentiated or stem cell-like tumor cells [82]. These fusion events may lead to a cell type that possesses greater metastatic characteristics [81, 83].

Conclusion

Studies have shown that some cancers cells and even stromal,connected especially with angiogenesis and lymphvasculogenesis, may originate from bone marrow stem cells. Moreover, bone marrow derived cells could enhance the aggregative and metastatic ability of cancer cells. Since bone marrow-derived cells play an important role in carcinogenesis, angiogenesis and metastasis, bone marrow-derived cells are not only the tool for cancer therapy, but also potential targets for cancer therapy. The long biosafety of bone marrow transplant or bone marrow derived cells for patients with or without cancer seems to need still more study.

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