The roles of mesenchymal stem cells in gastric lesion and regeneration : applications in gastric diseases

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Abstract

In recent years, many studies have focused on the roles of mesenchymal stem cells (MSCs) due to their contribution to tissue regeneration and tumorigenesis. However, the full profile of the roles of MSCs in gastric diseases has not been established. In this review, we aim to provide an overview on the roles of MSCs on cell lesion and regeneration in gastric diseases, including gastric ulcer, premalignant conditions and cancer. We will also discuss the mechanisms underlying the behaviors of MSCs in these diseases. (Acta gastroenterol. belg., **2013**, 76, **10-14**).

Key words : mesenchymal stem cell, gastric ulcer, premalignant condition, intestinal metaplasia, gastric cancer.

Introduction

Mesenchymal stem cells (MSCs) are a member of the multipotent adult somatic stem cell family. They are a subset of cells that are able to give rise to bone, cartilage, marrow fat cells, and able to support formation of blood cells (1). Compared with hematopoietic stem cells, MSCs constitute only a small fraction of the bone marrow ; they constitute 0.01%-1% of bone marrow cells and decrease with aging. MSCs can be identified by several criteria, including plastic adherence in established culture, extensive capacity of self-renewal, multi-differentiation and immune modulation, and expression of nonhematopoietic cell surface markers (2,3). These markers include cluster of differentiation (CD) 105, CD73 and CD90, which should be identified in more than 95% of the MSC population by flow cytometry measurement. Additionally, these cells must lack the expression (less than 2% positive) of CD45, CD34, CD14 or CD11b, CD79a or CD19 and human leukocyte antigen (HLA) class II (2). MSCs can migrate in recipient, arrive at special tissue, induce tissue regeneration, and improve organ function (4). The potential of MSCs to promote tissue repair has been investigated in several diseases, including ischemic heart disease, diabetes, Parkinson's disease and gastrointestinal ulcer (5).

Since MSCs are highly proliferative and differentiative in gastric tissue, they are a potential replacement for injured or abnormal cells in gastric diseases. However, the application of MSCs in practical therapies is dependent on the understanding of the mechanism of their behaviors in gastric tissue under pathological conditions. Therefore, this article will serve to review the roles of MSCs in gastric lesions, particularly in gastric ulcer, premalignant conditions and gastric cancer. We will also discuss the roles of MSCs in promotion or suppression of gastric cancer and provide explanations to this discrepancy. We hope this review will provide an overview of stem cell-based therapy in gastric diseases and identify the most promising future strategies.

Therapeutic potentials of MSCs in gastric ulcer

Recent studies have focused on the potential roles of MSCs in gastric injury therapies. MSCs have been found to promote the healing of artificially induced gastric ulcer (6), autoimmune non-healing gastric ulcer and radiation gastric ulcer (7-9). Bone marrow derived cells, or BMDCs, is a general name representing bone marrow stem cells that have potentials to recruit to sites of tissue injury and inflammation, and therefore could be a source of stem cells with potential ability to repair severely damaged tissues. However, they might also represent a potential source of malignancy due to their unexpected degree of plasticity (10). BMDCs of leukemia patients with radiation gastric ulcer can migrate to the human gastrointestinal tract and regenerate damaged epithelia after ulcer formation (11). Significant decrease in ulcer area, stimulation of angiogenesis, improvement of microcirculation, and effective regeneration of ulcers were observed. The same effect was also observed in a later study (6). These studies indicated that BMDCs can circulate in blood, recruit to injury tissue and promote the healing process of gastric ulcers by differentiating into vascular endothelial cells, epithelium and interstitial cells (12-18). BMDCs could be a potential clinical application for repairing severely damaged epithelia in ulcer.

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Although MSCs are highly proliferative and differentiative in gastric tissue and the therapeutic effect of MSCs seems promising, the application of MSCs in practical therapies is dependent on the understanding of the mechanism of their behaviors in gastric tissue under pathological conditions. Early studies from Elia's lab (19) suggested that a novel cell lineage induced by gastrointestinal ulceration, which come from gastrointestinal stem cells, can secrete epidermal growth factor (EGF) to stimulate cell regeneration and ulcer healing. A similar mechanism was also indicated in a later study (11), in which donor bone marrow cells were found to repopulate the epithelia of the recipient gastrointestinal tract during epithelial regeneration after ulcer formation. In another study (20), bone marrow-derived mesenchymal stromal cells (BMSCs, refer to MSCs that originate from bone marrow, recruit to other tissues, and differentiate into osteoblasts, adipocytes, chondroblasts and fibroblasts), were found to express angiogenic factors - vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), and become potential sources of gastric myofibroblasts and fibroblasts in ulcer healing. Okumura and colleagues (21) further suggested that MSCs that express cytokeratin 19 (K19) are most likely responsible for the process since K19-expressing MSC subclones possess all gastric differentiating abilities of MSCs and can give rise to gastric epithelial cells when injected into adult mouse stomachs. In addition, the hedgehog signaling pathway was also suggested to be important in gastric regeneration following gastric ulcer formation (22). In summary, MSCs have the potential to migrate to damaged mucosal surfaces and differentiate into epithelium cells in gastric stroma. They can also secrete matrix proteins and cytokines to promote angiogenesis and cell proliferation in gastrointestinal ulcer healing.

Roles of MSCs on premalignant conditions and gastric carcinogenesis

Previous evidence suggests that MSCs have a function of being recruited to areas of injury or inflammation to repair the injured tissue. However, what long-term consequence of this recruitment has on chronic inflammation is unknown.

During the period of esophageal regeneration, intestinal metaplasia derived from foreign BMDCs was found in some of the esophageal epithelial cells (23). *H. pylori* play a key role in the development of both atrophic gastritis and intestinal metaplasia (24). MSCs are suggested to promote gastric premalignant changes in the presence of *H. felis* or *H. Pylori* (25). MSCs could be progenitor cells for metaplasia in the stomach. Inflammation induced by *H. felis* caused BMDCs to migrate to the stomach and differentiate into stomach epithelial cells. During the period of differentiation, cells with abnormal morphology appeared, and severe epithelial dysplasia were observed (10). Paneth cells in pyloric glands, which may be related to gastric and intestinal mixed-type intestinal metaplasia of the human stomach, preserve their normal direction of migration but exhibit abnormal cell differentiation in intestinal metaplasia lesions (26).

Infection with *H. Pylori* is also a key factor in gastric carcinogenesis. The progression of gastric cancer follows an *H. Pylori* inflammation→ atrophy→ metaplasia→ dysplasia→ carcinoma route. It could be that MSCs, after infection by *H. Pylori*, initiate metaplasia in stomach and lead to subsequent malignant changes. It is therefore hypothesized that these cells might also play a role in the development of cancer and named them 'cancer stem cells' (10,26-28). The environment of gastric mesenchyme under normal physiology conditions and during gastric cancer may also be a key factor affecting the MSCs' behaviour. MSCs can be attracted to the tumor tissues by tumor cells or tumor stromal microenvironment components (29). Carcinoma were observed during the period of helicobacter infection (10), suggesting that BMDCs play a key role in gastric cancer development, and mice infected with *H. felis* develop gastric cancer with the same course as human gastric cancer infected with *H. pylori*. Similarly, MSCs were shown to promote the in vivo growth of breast cancer cells and colon cancer cells (30-31) by contributing to the tumor microenvironment (32). Specifically, MSCs were shown to secrete cytokines and chemokines to affect the growth and metastasis of tumor cells (33). MSC-like cells were isolated from gastric cancer tissue (hGC-MSCs) and their neighboring noncancerous tissues (hGCN-MSCs) (34-35). Although there were some differences in biochemical properties between hGC-MSCs and hGCN-MSCs, these cells shared most of the biochemical characteristics of normal MSCs. Fibroblasts are the primary cell type, which comprise tumor stroma and microenvironment (36). Neoplasia-associated myofibroblasts have been identified in the rectal adenoma and gastric cancer models (37), and partly derived from BMDCs (38).

Above-reviewed studies seem support the idea that BMDCs or MSCs play an important role in tumorigenesis. However, the roles of MSCs in gastric cancer are very controversial, and evidence from other studies does not support the theory. At present, over 1000 patients have not formed tumors after treatment with MSCs for different reasons (36). The presence of MSCs, either mixed with cancer cells in vitro (39-40) or injected into cancer tissues in vivo (39,41-42), was shown to inhibit cancer cell growth in colon carinoma (41), Kaposi's sarcoma (39), and subcutaneous melanomas (40). No tumors were found 1 or 3 months after initial subcutaneous injection of MSCs or MSC-like cells into nude mice (20,34-35). Further evidence is needed to show that BMDCs indeed differentiate into cancerous cells rather than merely fusing with epithelial cells in Houghton's mouse model (10,43). In Worthley's study, male donors' bone marrow was transplanted to female recipients for treatment of leukemia. However, secondary cancers, including skin cancers, gastric cancers and rectal adenoma, were identified in 18 out of 4374 patients. Although

many of the fibroblasts found in female receipts were BMDCs from male donors (identified by Y-chromosomes), some fibroblasts did not contain Y-chromosomes. It is likely that the male donors' BMDCs, in addition to female recipients' local tissue compartments, harbor cells capable of developing into cancer-associated fibroblasts (44-45). Furthermore, Lin-CD44hiScal-cKit+ CD34- cells, a type of isolated bone marrow stem cells, not only shared characteristics of MSCs, but also reduced the progression of gastric dysplastic changes in *H. felis* infected mice. Reducing the level of Th17-associated cytokine in responding mice may account for the prevention of gastric dysplasia (46).

Possible mechanisms of MSCs effects on tumor

In recent years, the studies of MSCs in gastric cancer's carcinogenesis and therapy have been a hot spot. However, the roles of MSCs in gastric cancer are very controversial. Above studies have revealed different opinions of MSCs on gastric cancer. In this section, we will identify the possible reasons for this discrepancy.

Vascular formation

MSCs have been reported to secrete various growth factors, including VEGF, HGF, transforming growth factor-α1 (TGF-α1) and platelet-derived growth factor (PDGF)[47-48). These cytokines could facilitate angiogenesis, and promote tumor migration and proliferation. However, other experiments showed the growth-suppressing effect of MSCs. MSCs induced capillary endothelial cell apoptosis in vitro and reduced tumor growth and vascular density in established melanomas model (40).

Fibrovascular network

Fibroblasts are critical components of tumor microenvironment. MSCs in vivo and in vitro were shown to promote tumorigenesis by enhancing tumor-associated fibroblasts (TAFs) in multiple tumor models after exposure to tumor microenvironment (49-52). It is possible that MSCs form a tumor's fibrovascular network, and differentiate into TAF, endothelial-like or vessel-attached cells (53).

Intrinstic antineoplastic properties

MSCs possess intrinsic antineoplastic properties in vitro and in vivo. The ability to inhibit target cell Akt activity may account for this tumor-suppressive effects of MSCs in vivo (39). Up-regulation the expression of p21 and induction protease caspase 3-associated apoptosis could be the mechanism of inhibitory effects (42).

Immunomodulatory effects

MSCs possess the characteristics of low immunogenicity and immunomodulatory effects. They can directly suppress the function of T and B lymphocytes, dendritic cells and natural killer cells (54-57). Higher incidence of melanoma formation induced by the immunosuppressive action of MSCs was already reported (58). However, MSCs have complex immunomodulatory effects, and can counteract inflammation by suppressing host immune responses and preventing fibrosis. Mesenchymal progenitor cells can attract more monocytes and granulocytes infiltration when mixed with tumor cells, and inhibit the growth of colon carcionma in rat models (41). A Series of agents, including interferon-β, cytosine deaminase, tumor necrosis factor-related apoptosis-inducing ligand, and oncolytic viruses also can be released by MSCs to yield potent antitumor effects (51-52,59).

Inflammatory microenvironment

Chronic inflammation is associated with increased risk of malignancy. Prolonged exposure to excessive proinflammatory activity has been regarded as one of the risk factors of tumorigenesis. Inflammatory cells, cytokines, growth factors, chemokines, blood vessels and connective tissue were involved in neoplastic process (60). Normal inflammation is self-limiting, because the following release of anti-inflammatory cytokines can eliminate the proinflammatory cytokines. However, persistence of inflammatory reactions and unclearance of the initiating factors seems to be relevant to chronic inflammation (61). In chronic inflammation, inflammatory cells, including leukocytes, monocytes and other phagocytes, can generate physical and chemical agents to induce DNA damage and cell mutation (62). In addition, inflammatory cytokines and chemokines contribute directly to malignant progression and malignant cells also can produce inflammatory cytokines. This could be an important factor in the formation of stem cell-derived neoplasia in Houghton's murine model, in which the procedure of stem cell transplantation accompanied by chronic helicobacter infection.

The homogenicity in MSCs

Due to lack of notable cell surface markers, it is difficult to isolate MSCs at present. In most cases, the isolation of MSCs still depend on some nonspecific characteristics, such as the adhesion to plastic culture dishes, expression of nonhematopoietic cell surface markers, and capability to differentiate into other cell types. The infused MSCs in most studies are heterogeneous, which may be the major factor bring about the conflicting reports about the effects of MSCs in tumors.

Wang *et al*. (46) acquired more homogeneous MSCs by fluorescence-activated cell sorting analysis. He and his colleagues elucidated that MSCs could reduce the progression of low-grade gastric dysplasia in chronic Helicobacter felis-infected mice. It is a potent proof to indicate that homogeneous stroma plays an important part in preventing tumor formation.

Conclusions

MSCs can effectively contribute to gastric tissue repair. During tissue repair, MSCs induce the infiltration of monocytes and granulocytes, secrete cytokine and growth factors to form fibrovascular networks, and complete epithelial and interstitial repairs. MSC-mediated tissue repair shares many important properties with normal inflammation and tumour stroma formation, including infiltrating inflammatory cells, secreting cytokine and growth factors, and forming fibrovascular networks. MSCs are stromal cells, which share similar phenotype with epithelial cells, endothelial cells and muscle cells (63), while the cell surface markers are variable (64). During tissue injury, various stromal cells secrete different cytokines, growth factors and chemokines. Risks of malignancy may be increased if the inflammatory microenvironment persists, no matter whether it is caused by MSCs or by chronic inflammation. Therefore, understanding the relationship between MSCs and chronic inflammation or inflammatory microenvironment is critical.

Prospects for future research

In future, studying the earlier stages of gastric carcinogenesis, such as chronic gastritis or intestinal metaplasia may be useful for further understanding the role of MSCs in human gastric cancer. Furthermore, MSCs have the tropism for tumors. If inflammatory microenvironments can be manipulated to overcome the putative tumor-promoting effects of MSCs, antitumor cytokines could be expressed from engineered MSCs to develop novel therapeutic strategies.

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