Mesenchymal stem cells in cancer: a new link to neutrophils

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Mesenchymal stem cells (MSCs) are one of the key components of tumor microenvironment and play critical roles in cancer progression. MSCs within tumor microenvironment acquire novel functions that are not observed in normal MSCs. Emerging evidence suggest that tumor-resident MSCs could skew immune cells to a tumor-promoting phenotype, leading to the escape from immune surveillance. As neutrophils are predominant innate immune cells, we recently explored the interaction between tumor-resident MSCs and neutrophils. Our results revealed that tumor-resident MSCs regulated the biological properties and functional activation of neutrophils in gastric cancer through the release of IL-6 and the activation of STAT3 in neutrophils. Intriguingly, neutrophils activated by tumor-resident MSCs could strongly induce the differentiation of normal MSCs into CAFs, forming a feedback loop to synergistically prompt cancer progression. Our findings that tumor-resident MSCs regulation of neutrophil biology and function provides additional information for understanding the role of MSCs in reshaping tumor microenvironment and may represent a novel target for gastric cancer therapy.

Keywords: Mesenchymal stem cells (MSCs); Neutrophils; Cancer microenvironment; Metastasis; Angiogenesis


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Mesenchymal stem cells (MSCs) are pluripotent stem cells with self-renewal and multi-lineage differentiation abilities. Under injury and inflammation conditions, MSCs are mobilized from bone marrow to the site of damage and exert wound repair and tissue regeneration functions. MSCs have tumor tropism and are critically involved in the formation of tumor microenvironment. The roles of MSCs in cancer have attracted a lot of attention in the past decade. The influences of MSCs on cancer are manifold. First, MSCs produce a variety of bioactive molecules to directly prompt tumor proliferation, invasion and metastasis [1-4]. In addition, MSCs may regulate the maintenance of cancer stem cells (CSCs) and mediate therapy resistance to anticancer drugs [5-8]. Second, MSCs within tumor microenvironment may exert indirect effects on cancer by enhancing tumor angiogenesis [9-11]. Third, MSCs may differentiate into other types of tumor stromal cells in response to the microenvironmental signals. For instance, MSCs have been suggested as the precursors of cancer-associated fibroblasts (CAFs) [12], which have prompting roles in tumor progression [13-15]. Fourth, tumor-resident MSCs may exert immunomodulatory properties through...
the interactions with various immune cells, therefore providing an immuneprivileged environment for cancer cells [16-19]. MSCs have been shown to drive the development of hematopoietic malignancies and determine the efficacy of therapy in these diseases [17, 20, 21]. In addition, MSCs also have prompting roles in a variety of solid tumors, such as breast, colon, lung, prostate, and gastric cancer. Furthermore, MSCs have been suggested as the cell-of-origin for cancer. Houghton et al. demonstrate that MSCs may fuse with mucosal cells in the presence of Helicobacter pylori infection to initiate gastric cancer [22]. In summary, these studies have demonstrated the critical roles of MSCs in human cancer pathogenesis, cancer progression and cancer therapy.

Neutrophils play important functional roles during carcinogenesis and tumor progression. The increased presence of neutrophils in tumor tissues, designated as tumor-associated neutrophils (TANs), has been shown to be associated with advanced disease and poorer outcome in patients with various types of cancer [23, 24]. The role of tumor-derived factors in mediating the infiltration of neutrophils into tumors has been widely studied. For instance, hepatocellular carcinoma (HCC) cells release CXCL5 to modulate the chemotaxis of neutrophils, which in turn enhances the migration and invasion of HCC cells [25]. Head and neck squamous cell carcinoma (HNSCC) cells-derived MIF induces the recruitment and activation of neutrophils, which in turn produce pro-inflammatory factors to enhance the migration of tumor cells in a feedback manner [26]. HCC cells release hyaluronan fragments to activate neutrophils via TLR4 and PI3K/Akt signaling. The activated neutrophils have prolonged survival, express higher levels of pro-inflammatory factors, and stimulate the migration of cancer cells [27]. In addition, Kuang et al. suggest that IL-17 is a strong chemoattractant for neutrophils in HCC. IL-17-activated neutrophils have increased production and activity of MMP-9, resulting in enhanced angiogenesis at invading tumor edge [28]. Queen et al. demonstrate that GM-CSF from breast cancer cells stimulate neutrophils to produce oncostatin M (OSM), which in turn induces VEGF expression in breast cancer cells and enhances the invasive capacity of breast cancer cells [29]. Neutrophils may interact with circulating tumor cells through Mac-1–ICAM-1 interaction and act as a bridge to facilitate interactions between cancer cells and the liver parenchyma, finally prompting liver metastasis [30]. In addition to their pro-metastatic functions, neutrophils could induce tumor angiogenesis through the release of pro-angiogenic factors [31]. Neutrophils have been demonstrated as the main source of MMP-9 and VEGF in tumors and depletion of these cells significantly reduces angiogenesis and inhibits tumor growth [28, 32]. Moreover, Houghton et al. suggest that neutrophil elastase induces the degradation of IRS-1 and increases the interaction between PI3K and PDGFR, thereby promoting tumor cell proliferation [33]. Neutrophils also have immunomodulatory roles in cancer. Mishalani et al. demonstrate that neutrophils recruit Treg cells into tumors through the release of CCL17 to inhibit antitumor immune activity [34]. Fridlender et al. have recently proposed a model of N1–N2 polarization for neutrophils [35]. They demonstrate that TGF-β drives the tumor-infiltrating neutrophils to acquire an N2-polarized phenotype in mice. Blockade of TGF-β by a specific inhibitor induces the change of neutrophils to the antitumoral N1 phenotype in vitro and in vivo. TANs are different from G-MDSCs in genetic profile, suggesting that TANs are a distinct population of neutrophils [36]. Jablonska and coworkers demonstrate that endogenous IFN-β is essential for maintaining neutrophils at antitumoral N1 phenotype and IFN-β deficiency converts the neutrophils to a pro-tumoral N2 type [32]. They injected melanoma and fibrosarcoma cells into wildtype and IFN-β-deficient mice and found that the tumors grew faster and had richer microvessels in IFN-β-deficient mice than that in wildtype mice. They demonstrate that the tumors in IFN-β-deficient mice are infiltrated with more neutrophils and express increased level of MMP-9 and VEGF. Taken together, these findings indicate that neutrophils are critically involved in cancer progression though multiple layers of mechanisms. It is therefore of great interest to exploit the mechanism for the regulation of neutrophil biology and function in cancer.

Cancer-related inflammation is now recognized as a central node in many malignancies and considered as a new hallmark of cancer [37]. MSCs in tumor microenvironment are often exposed to a variety of inflammatory signals and therefore may acquire novel functions that are not present in normal MSCs. Given that neutrophils are critically involved in tumor metastasis and angiogenesis, whether tumor-resident MSCs may regulate neutrophils to exert pro-tumoral roles has not been characterized. We have previously demonstrated that human MSCs from distinct sources can prompt tumor growth in vitro and in vivo through paracrine mechanisms [38, 39]. More recently, we have identified tumor-resident MSCs from gastric cancer tissues (GC-MSCs) and suggest that GC-MSCs display the characteristics of CAFs [40-42]. In our recent publication, we have further revealed a bi-directional interaction between GC-MSCs and neutrophils in cancer [43]. GC-MSCs recruit neutrophils and prolong their survival by protecting them from spontaneous apoptosis. The increasing life-span seems to be an important feature of N2 neutrophils. Andzinski et al. recently reported that depletion of endogenous IFN-β prolonged the survival of tumor-infiltrating neutrophils in mice [44], which is consistent with their previous findings showing that IFN-β deficiency converted neutrophils to an N2 pro-tumoral phenotype. In addition to the roles in cell survival and chemotaxis, GC-
MSCs also induce the activation of neutrophils. GC-MSCs activated neutrophils express higher levels of N2 markers such as IL-8 and CCL2, which is in line with a recent report from Mishalian et al. showing that neutrophils develop protumoral properties in the late stage through the production of these factors \[45\]. We also suggest that GC-MSCs enhanced the production of Mac-1 and OSM in neutrophils, which is in support of the notion that neutrophils prompt cancer metastasis and angiogenesis through Mac-1 and OSM. Neutrophils activated by GC-MSCs further enhances the metastatic potential of gastric cancer cells and the proangiogenic ability of endothelial cells in vitro, showing that GC-MSCs have the potential to convert neutrophils to a pro-tumoral phenotype. Our mechanistic work suggests that GC-MSCs derived IL-6 induces the activation of STAT3 in neutrophils. IL-6R antagonist and STAT3 inhibitor attenuated the prolonged survival and activation of neutrophils by GC-MSCs. IL-6 has been suggested to drive the progression of inflammation-related cancer and found to be highly produced in distinct types of cancer \[46\]. Human bone marrow MSCs (BM-MSCs)-derived IL-6 has been shown to rescue neutrophils from apoptosis through the activation of STAT3, suggesting that STAT3 is a key transcription factor in regulating the survival of neutrophils \[47\]. In this study, we have further demonstrated that tumor-resident MSCs could regulate neutrophils through the production of IL-6. Given that IL-6 are produced by both cancer cells and stromal cells, it is therefore reasonable to propose that IL-6 may serve as a key factor in cancer to induce the N2 polarization of neutrophils. Moreover, we found that neutrophils primed by GC-MSCs could induce the differentiation of normal MSCs to CAFs and the expression of IL-6 in normal MSCs, thus forming a feedback loop for MSCs-neutrophils interaction in cancer. Comito et al. have demonstrated that M2-polarized macrophages and CAFs synergestize to prompt the progression of prostate cancer \[48\]. In analog to macrophages, N2-polarized neutrophils may also synergistically interact with tumor-resident MSCs to prompt cancer progression.

In conclusion, our findings suggest that there is a reciprocal crosstalk between GC-MSCs and neutrophils to cooperatively drive cancer progression. Our findings not only shed lights on the functional role of MSCs in remodeling tumor microenvironment, but also provide potential target for cancer therapy. To further clarify the roles of MSCs-neutrophils interaction in cancer, the following issues need to be addressed in future studies: 1) Whether the regulation of neutrophil function by IL-6 is a common feature in human cancer is apparently an open question to be answered; 2) Whether MSCs can modulate neutrophil biology and function through other mechanisms is another interesting question to be answered; 3) In vivo data from animal models is needed to substantiate the contribution of MSCs-mediated activation of neutrophils to cancer progression; 4) Could target the IL-6–STAT3 signaling pathway in tumor-associated neutrophils to convert their phenotypes from N2 to N1 be an effective approach for cancer therapy?

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**Conflicting interests**

The authors have declared that no competing interests exist.

**References**


