GM-CSF facilitates the development of inflammation-associated colorectal carcinoma

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Colorectal carcinoma is one of the most common fatal malignancies worldwide. Recent studies have suggested a tight link between the onset of colorectal oncogenesis and inflammation.1 In line with this notion, inflammatory conditions such as inflammatory bowel disease (IBD) and Crohn disease are associated with an increased risk of developing colorectal carcinomas. Although the molecular mechanisms underlying the transition from colitis to colorectal cancer are incompletely understood, it has been proposed that a series of pro-inflammatory cytokines produced by immune and non-immune cells contributes to malignant transformation in the setting of chronic intestinal inflammation.2

Granulocyte macrophage colony-stimulating factor (GM-CSF) is a hematopoietic cytokine that promotes the differentiation of bone marrow precursors, mobilizes and stimulates the maturation of myeloid cells, and enhances immune responses. Accumulating evidence points to GM-CSF as a key regulator in inflammatory disorders, including IBD. Indeed, the levels of GM-CSF were found to be significantly elevated in the inflamed tissues of IBD patients as well as in rodents subjected to experimental colitis.3 In line with this notion, the genetic ablation of GM-CSF increased the susceptibility of mice to dextran sulfate sodium (DSS)-induced colitis, as shown by clinical and histological parameters, allowing for an augmented production of pro-inflammatory cytokines.4 Conversely, the administration of GM-CSF to DSS-instilled mice reduced the severity of colitis, a process that was associated with a hyperproliferation of the intestinal epithelium and mucosal healing.5 However, the precise role of GM-CSF in the progression of colitis to colon cancer has long remained unclear. We addressed this issue in a recent study.5 In particular, using a widely employed mouse model of colitis-associated colon cancer (CAC) based on the intraperitoneal administration of azoxymethane (AOM) followed by the repeated oral administration of DSS, we demonstrated that GM-CSF played a disease-promoting role in CAC. Indeed, blocking the activity of GM-CSF by specific neutralizing antibody virtually abrogated the development of CACs in response to AOM/DSS.6

Colonic epithelial cells (CECs) turned out to constitute the major source of GM-CSF during the malignant transformation of the colonic epithelium. This finding is in line with previous results in murine model of colitis.7 Intriguingly, we also found that the translocation of the commensal flora across the intestinal barrier was important for GM-CSF expression by CEC, as antibiotic treatments as well as the ablation of Toll-like receptor 4 (TLR4) considerably impaired this process.

We propose that GM-CSF promotes colorectal carcinogenesis through an immune system-independent pathway (Fig. 1). Tumor-derived GM-CSF appeared indeed to drive the epithelial secretion of vascular endothelial growth factor (VEGF) via an autocrine and/or paracrine circuitry. VEGF is major mediator of neoangiogenesis in the course of tumor growth and metastatic dissemination. Furthermore, intestinal epithelial cells obtained from colorectal carcinoma patients and rodents with CAC not only manifested the activation of VEGF receptor 2 (VEGFR2), but also proliferated in response VEGF stimulation via a VEGFR2- and signal transducer and activator of transcription 3 (STAT3)-dependent pathway.3,8 In line with this notion, blocking GM-CSF with neutralizing antibodies reduced the proliferation of CECs and angiogenesis within neoplasia, resembling the phenotype of mice treated with anti-VEGF antibodies.

In conclusion, we uncovered the importance of the GM-CSF/VEGF signaling axis in colonic carcinogenesis. We also demonstrated that macrophages residing in the CAC microenvironment constituted another cellular source of GM-CSF and VEGF. Thus, the
GM-CSF/VEGF axis may also be operational in macrophages, perhaps underlying a crosstalk between epithelial and immune cells that may be relevant for colorectal carcinogenesis. In the progression of colitis to colon cancer, GM-CSF may indeed mediate pro-tumor effects that depend on the immune system, as recently demonstrated by a study reporting that tumor-derived GM-CSF potently induces the development of immunosuppressive myeloid-derived suppressor cells (MDSCs).9 We found that Gr-1+ MDSCs accumulated in the CAC microenvironment and that blocking GM-CSF dramatically inhibited this phenomenon. The immune system- (in particular MDSC-) dependent effects of GM-CSF on colorectal carcinogenesis are being actively investigated.

Of note, the exogenous administration of GM-CSF did not modify the growth of colorectal cancer cells, but significantly enhanced their invasive potential. This indicates that GM-CSF may play a pivotal role in promoting the metastatic dissemination of colorectal cancer. This hypothesis is supported by the observation that GM-CSF favors osteolytic bone metastases in rodent models of breast carcinoma by stimulating the development of osteoclasts.10 Further studies on the relationship between GM-CSF and the metastatic dissemination of colorectal cancer are warranted.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References
1. Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet 2001; 357:539-45; PMID:11229684; http://dx.doi.org/10.1016/ S0140-6736(00)04046-0
2. Fantini MC, Pallone F. Cytokines: from gut inflammation to colorectal cancer. Curr Drug Targets 2008; 9:375-80; PMID:18473763; http://dx.doi.org/10.2174/138945008784221206
3. Noguchi M, Hiwatashi N, Liu ZX, Toyota T. Increased secretion of granulocyte-macrophage colony-stimulating factor in mucosal lesions of inflammatory bowel disease. Digestion 2001; 63(Suppl 1):32-6; PMID:11173907; http://dx.doi.org/10.1159/000051908
4. Xu Y, Hunt NH, Bao S. The role of granulocyte macrophage-colony-stimulating factor in acute intestinal inflammation. Cell Res 2008; 18:1220-9; PMID:19030026; http://dx.doi.org/10.1038/cr.2008.310
5. Bernasconi E, Favre L, Maillard MH, Bachmann D, Pyrhönd C, Bouzourene H, Croze E, Velichko S, Parkinson J, Michetti P, et al. Granulocyte-macrophage colony-stimulating factor elicits bone marrow-derived cells that promote efficient colonic mucosal healing. Inflamm Bowel Dis 2010; 16:428-41; PMID:19639560; http://dx.doi.org/10.1002/ibd.21072
6. Wang Y, Han G, Wang K, Liu G, Wang R, Xiao H, Li X, Hou C, Shen B, Guo R, et al. Tumor-derived GM-CSF promotes inflammatory colon carcinogenesis via stimulating epithelial release of VEGF. Cancer Res 2014; 74:716-26; PMID:24366884; http://dx.doi.org/10.1158/0008-5472.CAN-13-1459
7. Egea L, McAllister CS, Lakhadari O, Minevi I, Shenouda S, Kagnoff MF. GM-CSF produced by nonhematopoietic cells is required for early epithelial cell proliferation and repair of injured colonic mucosa. J Immunol 2013; 190:1702-13; PMID:23325885; http://dx.doi.org/10.4049/jimmunol.1202368
8. Waldner MJ, Wirtz S, Jefremow A, Warntjen M, Neufert C, Artyea R, Becker C, Weigmann B, Vieth M, Rose-John S, et al. VEGF receptor signaling links inflammation and tumorigenesis in colitis-associated cancer. J Exp Med 2010; 207:2855-68; PMID:21098094; http://dx.doi.org/10.1084/jem.20100438
9. Bayne LJ, Beatty GL, Jhala N, Clark CE, Rhim AD, Stanger BZ, Vanderheide RH. Tumor-derived granulocyte-macrophage colony-stimulating factor regulates myeloid inflammation and T cell immunity in pancreatic cancer. Cancer Cell 2012; 21:822-35; PMID:22698406; http://dx.doi.org/10.1016/j.ccr.2012.09.025
10. Park BK, Zhang H, Zeng Q, Dai J, Keller ET, Giordano T, Gu K, Shah V, Pei L, Zarbo RJ, et al. NF-kappaB in breast cancer cells promotes osteolytic bone metastasis by inducing osteoclastogenesis via GM-CSF. Nat Med 2007; 13:62-9; PMID:17159966; http://dx.doi.org/10.1038/nm1319