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The role of chronic inflammation in promotion of gastric cancer

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Abstract

Accumulating evidence has suggested that inflammatory responses play an important role in cancer development. About 20% of malignant cancer are associated with chronic infection, also suggesting the role of infection-associated inflammation in tumorigenesis. However, molecular mechanisms of inflammation in cancer development and malignant progression have not fully understood yet. We have constructed gastric cancer model mice that develop gastric cancer caused by transgenic expression of Wnt1, COX-2, and mPGES-1. Expression of these genes results in simultaneous activation of Wnt signaling and COX-2/PGE_2 pathway in gastric mucosa. It has been reported that inflammatory cytokine TNF-α promotes development of skin cancer, liver cancer and ovarian cancer. We thus crossed gastric cancer model mice (*Gan* mice) with TNF-α gene (*Tnf*) knockout mice to examine the role of TNF-α in gastric tumorigenesis. Notably, *Tnf*-/- *Gan* mice showed significant suppression of gastric tumorigenesis, while tumor phenotype was rescued by bone marrow transplantation from wild-type mice. Accordingly, TNF-α derived from stromal cells is an important tumor-promoting factor in the inflammatory microenvironment. By microarray analyses, we found that several genes induced by TNF-α pathway in tumor epithelial cells are important for maintenance of tumorigenicity of gastric cancer cells. It is therefore possible that inhibition of these gene products will be an effective therapeutic strategy against inflammation-associated gastric cancer.