

A new mouse model of inflammation and gastric cancer

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Chronic inflammation increases the risk of developing several malignancies, including gastric cancer. A better understanding of how inflammation promotes gastric oncogenesis is therefore urgently needed. We have recently developed and characterized a mouse model that will be useful to elucidate the molecular and cellular circuitries bridging inflammation and gastric cancer.

Gastric cancer is the fourth most common and second leading cause of cancer-related deaths worldwide.¹ Most of these deaths are due to adenocarcinomas, which originate from gastric epithelial cells. Chronic gastric inflammation, which is often provoked by *Helicobacter pylori* persistent infection, increases the risk of developing of gastric cancer, at least in part by altering the growth and differentiation of the gastric epithelium. However, only a small fraction of *H. pylori*-infected individuals develops gastric cancer. Evidence indicates that genetic variation in both *H. pylori* and the host alter the likelihood of developing gastric cancer. The genetic factors of *H. pylori*-infected individuals that are associated with an increased propensity of developing gastric cancer include polymorphisms in genes coding for regulators of the immune response. Thus, a better understanding of how the host immune response influences gastric oncogenesis may favor the development of new strategies to reduce the number of gastric cancer-related deaths.

Autoimmune gastritis also provokes a chronic state of gastric inflammation. Recent studies have demonstrated that individuals with severe autoimmune gastritis exhibit an increased risk of developing multiple neoplasms, including

gastric cancer.^{2,3} To understand how to suppress chronic inflammation in the gastric mucosa, we have been developing a murine model of autoimmune gastritis (TxA23 mice).^{4–6} In a recent issue of *Cancer Research*, we have reported that the autoimmune disease affecting TxA23 mice mimics many aspects of the corresponding human condition.⁷ Importantly, we have demonstrated that the inflammatory state associated with autoimmune gastritis in mice provoked many of the pathological and molecular alterations that accompany the development of gastric cancer in humans. For example, the pathogenesis of autoimmune gastritis in TxA23 mice progresses through a series of steps that includes: chronic inflammation, loss of parietal cells (oxyntic atrophy), mucous neck cell hyperplasia, metaplasia, and eventually severe dysplasia including gastric intraepithelial neoplasms (Fig. 1). This sequence of events is very similar to the cascade of pathological changes that occur in the course of gastric oncogenesis in humans, which is often referred to as “Correa pathway”⁸. Moreover, the gastric neoplasms that eventually affect TxA23 mice share many molecular features with their human counterparts, including the overexpression of gastric cancer biomarkers,

the development of spasmodic polypeptide-expressing metaplasia (SPEM), and elevated levels of signal transducer and activator of transcription 3 (STAT3) phosphorylation. Finally, as TxA23 mice age, their pathological condition progressed to include severe dysplasia and gastric intraepithelial neoplasms.

This new mouse model demonstrates that chronic inflammation, even in the absence of *H. pylori* infection, can drive gastric oncogenesis. Our data support recent findings demonstrating that individuals with severe autoimmune gastritis have an increased risk of developing gastric cancer. Moreover, this mouse model will be useful to identify not only novel host factors that influence gastric oncogenesis, but also new therapeutic interventions that may reduce the risk of developing gastric cancer as they suppress chronic inflammation. We are currently crossing TxA23 mice with animals lacking various cytokine-coding genes, in order to investigate the impact of these soluble mediators on the severity of autoimmune gastritis and the progression of gastric cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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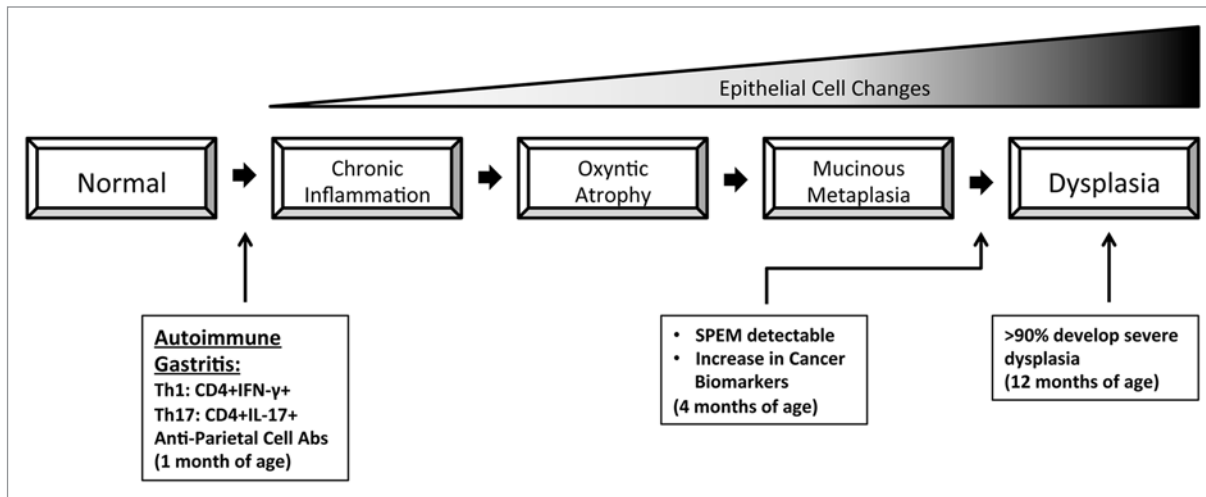


Figure 1. Inflammation-induced gastric carcinogenesis in TxA23 mice mimics several aspects of the corresponding human condition. In TxA23 mice, the source of the chronic inflammatory state that alters the normal gastric epithelium is represented by the self-reactive CD4⁺ T cells that cause autoimmune gastritis. TxA23 mice not only develop oxyntic atrophy and spasmolytic polypeptide-expressing metaplasia (SPEM), but also express several biomarkers that have been associated with human gastric cancer. Ultimately, by 12 months of age, TxA23 mice exhibit severe dysplasia and gastric intraepithelial neoplasms.

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