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Rapid gastric tumor development in gp130$^{757F/F}$ knock-in mice

Gastric cancer is the second most prevalent cause of global cancer death, accounting for almost 12% of cancer mortality worldwide. Repeated damage and inflammation of the gastric mucosa appear to be the precursor for DNA damage or replicative error that sets the scene for its malignant transformation. In chronic *Helicobacter pylori* (*H. pylori)* infection in both humans and animals, IL-8 and IL-6 seem to play a pivotal role in this inflammation-initiated gastric disease, focussing attention on these two cytokines.

Mouse models with mutations in tumor suppressor, tumor surveillance and DNA repair genes have been utilized in many studies and have led to a better understanding of gastric cancer development. The hyperproliferative gastric lesions in these mouse models, however, are slow to develop, taking between 12 and 24 months; and they are not specifically informative regarding defects in regulation of the target genes. **Judd *et al***[1] studied a 'knock-in' mouse model of gastric cancer (gp130$^{757F/F}$ mouse), which lacked the SHP2-binding-site on the IL-6 family receptor gp130. In these mice, IL-6 activation of SHP2/ ras/ERK/AP-1 is downregulated, while STAT3-mediated signaling is upregulated. Constitutive activation of STAT3 had been shown to be oncogenic in various tissues. In this study, the investigators fully characterized the temporal development of the stomach tumors, and identified several likely important gene targets for IL-6 such as trefoil peptides 1 and 2 (TFF1 and TFF2), and RegI.

Hyperplastic antral tumors with inflammation and ulceration were evident as early as 4 weeks, and reached maximum size by the age of 20 weeks of age. Gastritis, atrophy, intestinal metaplasia, dysplasia, and submucosal invasion were present at 30 weeks. Tumor development in gp130$^{757F/F}$ mice was similar to that of TFF1 knockout mouse, except that full penetration occurred at 30 weeks, not in 2 years. Loss of TFF1 gene expression occurred as early as 6 weeks in gp130$^{757F/F}$ mice. Contrary to previous belief, this study also demonstrated that tumorigenesis took place even when gastrin levels were low. The authors implied that this marked reduction in gastrin expression was modulated through IL-6 family ligands signaling positively through SHP-2/ Erk/AP-1, or negatively through STAT-3-dependent pathways. RegI protein and EGFr tyrosine kinase expressions were shown to increase in these mutant mice, implicating their oncogenic role. While activation of the mitogen gene RegI was STAT-dependent, the changes in EGFr and its ligands seemed to be STAT-independent.

The authors conclude that there is interplay of different factors mediated by IL-6/STAT3 during gastric tumor development, with some of these factors having a temporal association. They also posit that changes observed in this mouse model may be recapitulated in chronic infection with cagA-positive *H. pylori* resulting in an imbalance in the IL-6/11-signaling.

In this issue of Lab Invest, **Nozaki *et al***[2] demonstrated the noncoordinate upregulation of the barrier-associated small proline-rich proteins 2 (SPRR2) expression on biliary epithelial cells both *in vitro* and in mice with bile duct ligation. Deficient biliary epithelial cell SPRR2 expression associated with impaired barrier function was observed in IL-6$^{-/-}$ knockout mice. These two studies underscore the important role IL-6/STAT3 plays in tumorigenesis and in barrier function of epithelial cells against the environment.

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References

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2 Nozaki I, Lunz III JG, Specht S, *et al*. Barrier-associated small proline-rich proteins 2 are non-coordinately unregulated by IL-6/STAT3 signaling in biliary epithelium after bile duct ligation. Lab Invest 2005;85:109–123.

Inflammatory killing of normal cells can cure established tumors

Different methods to treat established tumor metastases are being studied. One of the methods is to generate immunity by vaccination against metastases, which often requires time-consuming and expensive protocols to isolate either tumor cells or their derivatives. In melanoma, it has been known that many tumor-associated antigens are unaltered proteins of melanogenesis and T cells activated by these antigens can kill both melanoma cells and normal melanocytes.

Daniels *et al*[1], in a recently published study in *Nature Biotechnology*, explored the possibility of curing an established tumor by inducing immune reactivity against its normal tissue of origin. A melanocyte-targeted cytotoxic gene was delivered

intradermally, using plasmid DNA along with heat shock protein 70 (hsp70), into mice to induce direct *in vivo* inflammatory killing of normal melanocytes. The plasmid was constructed with the herpes simplex virus thymidine kinase gene that was transcriptionally controlled by a tyrosinase promoter (Tyr-HSVtk). The mice were then given intraperitoneal ganciclovir (GCV) injection. Cells expressing HSVtk converted GCV to its toxic triphosphate form, which when incorporated into the DNA during synthesis resulted in cell death. The stress protein hsp70 further enhanced the immunostimulatory effect of melanocyte killing.

Injection of Tyr-HSVtk + hsp70 + GCV generated inflammation, tumor necrosis, and induction of interferon-δ at the site of plasmid injection. Inflammatory killing of melanocytes *in situ* generated a rapid activated CD8 + T-cell response directed to melanocyte antigens and was sufficient to eradicate well-established tumors. The investigators also found that the CD8 + T-cell response was short lived. This was because the immune system appeared to generate regulatory T cells to inactivate the CD8 + T-cell response. By doing so, it could avoid triggering the development of an autoimmune disease, which in this case would be vitiligo.

This study demonstrates that deliberate normal tissue destruction can be exploited to generate immunity against malignant disease originating from that tissue, and that the effect of antitumor therapy can be separated from autoimmunity. The excellent record of plasmid DNA use, the simplicity of the delivery, and the availability of GCV will make such treatment regimen easy to implement and widely accessible. 'We believe that this approach represents an important opportunity for the development of biological therapies for cancer and differs in several potentially very important ways from other cancer vaccination approaches', commented Gregory Daniels, principal investigator of this study.

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Reference

1 Daniels GA, Sanchez-Perez L, Diaz RM, *et al*. A simple method to cure established tumors by inflammatory killing of normal cells. Nat Biotechnol 2004;22:1125–1132.