Bone marrow derived stem cells in the development of gastric cancer

JeanMarie Houghton MD, PhD

*Helicobacter pylori* is a gram negative microaerophilic organism which infects about one half of the world’s population. It is one of the most common chronic bacterial infections in man, is found throughout the world, and is associated with diseases ranging from chronic gastritis and ulcers to gastric cancer. *Helicobacter pylori* (Hp) is responsible for up to 80% of gastric adenocarcinoma and 90-95% of mucosal associated lymphoid tissue (MALT) lymphoma, making the association between Hp and gastric cancer even stronger than the association between cigarette smoking and lung cancer.

Research in the past few years has clearly identified the host immune response as crucial in determining disease outcome. However, the mechanism by which inflammation in helicobacter infection (or in inflammation associated cancers in general) leads to disease has not been well elucidated. In order to address this issue, we used a mouse model of Helicobacter induced gastric cancer to address the role for bone marrow derived cells (BMDC) in the etiology of gastric cancer (1). We reasoned that in areas of chronic inflammation and persistent tissue damage, BMDC would repair damage, and because they represent the ultimate uncommitted stem cell- would be poised to undergo malignant transformation in the inflamed environment.

Within the past several years, we have gained an increasing appreciation for the degree of plasticity of BMDC. These cells differentiate at the single cell level into endoderm, neuroectoderm and visceral mesoderm in vitro (2), and after single cell injection into mice, these cells have been recovered in virtually every tissue of the body as terminally differentiated cells appropriate to the organ in which they were found (3). While rare under normal conditions, engraftment into peripheral tissues is increased during inflammation and injury with massive tissue damage associated with engraftment into the stem cell niche of peripheral tissues such as the skin and the stomach.
Based on these findings, we raised the logical question of the role of these cells in chronic inflammation based cancer. Using the Helicobacter felis (Hf) mouse model of gastric cancer we first demonstrated mice progress through the ordered histological alterations associated with progression to gastric cancer; chronic gastritis, atrophy, loss of specialized cells, metaplasia dysplasia and finally gastric cancer (4).

We transplanted lethally irradiated mice with sex-mismatched bone marrow containing the trackable marker beta-galactosidase (beta-gal) or green fluorescent protein (GFP). Mice were infected with Hf and evaluated at various time points up to 18 months after infection, and after eradication of bacteria.

While mucosal changes began early, beginning at 8 weeks- it wasn’t until damage was substantial at 20-30 weeks of infection, that BMDC were identified within the mucosa as gastric mucosal cells. Cell identification was by x-gal enzyme activity beta gal IHC, GFP detection, and X/Y FISH analysis combined with cytokeratin (epithelial marker) and CD45 surface antigen detection (WBC). Cells were recovered within metaplastic and dysplastic tissue and within areas of carcinoma. Of special interest; no specialized cells were recovered, and no normal appearing glands were bone marrow derived. Within areas of inflammation, BMDC incorporated into vascular structures as endothelial cells and myofibroblasts, and within stromal tissue as fibroblasts, and adipocytes however, they were a minority of BMDC in these areas.

Based on a previous study, we found that even after long term infection, eradication therapy restores much of the normal architecture. Metaplasia and dysplasia regress, and parietal and chief cells mass is restored. In areas where carcinoma remains or progresses- lesions are embedded in relatively normal appearing mucosa (4). Interestingly- when these experiments were repeated in the transplant model- and the fate of the BMDC tracked after eradication therapy- we saw a gradual loss of BMDC from the mucosa, and a seeming revival of tissue derived stem cell activity such that normal glands and specialized cells were host derived, while severely dysplastic tissue and carcinoma remained BM derived. These findings suggests that BMDC usurp peripheral stem cell function – but may not replace them. With the reversal of inflammation and infection, these peripheral stem cells appear to regain function, and the BMDC are lost- via a mechanism that is not yet clear. Those BMDC that remain may do so because of lingering inflammation or because they have acquired genetic alterations and have transformed.

While these experiments are from mice, there is intriguing information that inflammation may induce bone marrow derived cancers in humans as well. Bone marrow has been shown to contribute to tumor stroma and neovascular formation in a variety of human tumors, and contribute directly to skin, renal and vascular tumors. These findings open exciting avenues for both prevention and treatment of solid tumors, and will reshape the way we approach care of the patient with cancer.

References


**Curriculum Vitae**

Principal Investigator/Program Director (Last, First, Middle): Houghton, JeanMarie

**BIOGRAPHICAL SKETCH**

Provide the following information for the key personnel and other significant contributors in the order listed on Form Page 2. Follow this format for each person. **DO NOT EXCEED FOUR PAGES.**

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<th>NAME</th>
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<td>JeanMarie Houghton, M.D.</td>
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C. RESEARCH PROJECTS ONGOING OR COMPLETED:

Active:
AGA/ R. Robert and Sally D. Funderberg Research Scholar Award (P.I. J. Houghton)
1/1/05-12/31/07

In Gastric Cancer
Stem Cells and Gastric Cancer—The Role of Fusion.
1 RO1 CA113564-01A1 (PI – J Houghton) 12/01/05-11/30/1010

Inhibition of Fas apoptosis in gastric cancer.
Stem cells and gastric cancer.

**Completed:**
K22 CA90518-05 (P.I. – J. Houghton) 9/26/01-8/31/05
Direct role of Fas/NF-κB in H. pylori induced gastric carcinoma.
The goal of this project is determine the *in vivo* association of Fas up-regulation, the specific role of Fas induced NF-κB activation in promoting proliferation in gastric mucosal cells and to employ animal models for confirmation.

GIDH Glaxo Smith Kline Institute for Digestive Health National Cancer (P.I.– J. Houghton) 3/1/02-6/30/03
Gastric Mucosal Immune Response in the Pathogenesis of Helicobacter Infection.

American Cancer Society Institution Research Grant (P.I. - J. Houghton) 2002
Prevention and reversibility of premalignant gastric lesions in Helicobacter infection.

K11 102960 (P.I.-J. Houghton) 1995-2000
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