cmgh
CELLULAR AND MOLECULAR GASTROENTEROLOGY AND HEPATOLOGY

REVIEW

Murine Models of Gastric Corpus Preneoplasia

Christine P. Petersen,[1,3,4] Jason C. Mills,[5] and James R. Goldenring[1,2,3,4]

[1]Nashville VA Medical Center, Nashville, Tennessee; [2]Section of Surgical Sciences, [3]Department of Cell and Developmental Biology, [4]Epithelial Biology Center, Vanderbilt University, Nashville, Tennessee; [5]Division of Gastroenterology, Department of Medicine, Pathology and Immunology, Department of Developmental Biology, Washington University School of Medicine, St. Louis, Missouri

SUMMARY

While mouse models have been relatively poor at recapitulating true adenocarcinoma in the gastric corpus, a number of models have been successful in modeling pre-neoplastic metaplasias. These models demonstrate key insights into the origins of metaplasia and their modulation by intrinsic mucosal and immune cell-derived factors.

Intestinal-type gastric adenocarcinoma evolves in a field of pre-existing metaplasia. Over the past 20 years, a number of murine models have been developed to address aspects of the physiology and pathophysiology of metaplasia induction. Although none of these models has achieved true recapitulation of the induction of adenocarcinoma, they have led to important insights into the factors that influence the induction and progression of metaplasia. Here, we review the pathologic definitions relevant to alterations in gastric corpus lineages and classification of metaplasia by specific lineage markers. In addition, we review present murine models of the induction and progression of spasmolytic polypeptide (TFF2)–expressing metaplasia, the predominant metaplastic lineage observed in murine models. These models provide a basis for the development of a broader understanding of the physiological and pathophysiological roles of metaplasia in the stomach. *(Cell Mol Gastroenterol Hepatol 2017;3:11–26; http://dx.doi.org/10.1016/j.jcmgh.2016.11.001)*

Keywords: SPEM; Intestinal Metaplasia; Gastric Cancer; TFF2; Chief Cell; Hyperplasia.

Gastric adenocarcinoma is a leading cause of worldwide cancer-related deaths. Poor clinical outcomes result from the lack of early clinical indicators and late presentation. Insights into the progression of preneoplastic processes that promote gastric cancer therefore are needed to facilitate early intervention in gastric carcinogenesis. The sequence of metaplasia to neoplasia is at the root of the most common type of gastric cancer worldwide, intestinal-type adenocarcinoma, which occurs in the setting of chronic infection with the bacterium *Helicobacter pylori*. Murine models currently used are helpful in understanding the molecular mechanisms that drive the development of metaplasia in the stomach and its progression toward neoplasia. Unfortunately, no mouse models have reproduced the human later-stage progression to a true intestinal-type cancer with tumor masses that lead to local or distal metastasis. In short, the greatest utility of mouse models lies in the analysis of mechanisms that are responsible for the induction and progression of precancerous lesions, in particular, metaplasia. The following discussion examines models of metaplasia and gastric neoplasia in the corpus of mice and the insights they can provide into the origin and progression of human disease. To aid in interpretation of the various specific models, we first offer a primer on the terms used for the relevant mouse lesions in the stomach.

Definition of Hyperplastic, Metaplastic, and Preneoplastic Lineages in Mouse Stomach Models

The nomenclature used to describe the gastric pathology in the mouse stomach has never been standardized. Inconsistent terminology hinders progress toward developing and interpreting models that can help elucidate the molecular and cellular progression of metaplastic pathology. Establishing terminology that is specific for particular pathologic features is necessary to accurately classify cellular changes at key stages. Later, we attempt to define the most commonly observed lesions in a way that we hope will guide interpretation of future experiments. First, however, we must define some key pathology terms we use to describe the lesions: hyperplasia, metaplasia, and dysplasia. Hyperplasia refers to a pathologic lesion characterized by expansion of a normal cell lineage that resides in the tissue where it normally is found. Metaplasia refers to the presence of an otherwise normal cell lineage (or lineages) in a tissue where such a lineage is not normally found. Dysplasia is the presence of cells with abnormal cellular features and implies that the cells, which could resemble either normal or metaplastic lineages, have acquired mutations or

Abbreviations used in this paper: ATPase, adenosine triphosphatase; BMP, bone morphogenic protein; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; Hip1r, Huntington interacting protein 1 related; IFN, interferon; MUC, mucin; SDF1, stromal-derived factor 1; SPEM, spasmolytic polypeptide–expressing metaplasia; TFF, trefoil factor; Tg, transgene; TGF, transforming growth factor; Th, T-helper.

Most current article

2352-345X
http://dx.doi.org/10.1016/j.jcmgh.2016.11.001

epigenetic alterations that provide increased risk for malignant (eg, invasive) progression.

Oxyntic Atrophy

Atrophy, to a pathologist, means loss of cells. Parietal cells, whose primary job is to secrete acid, also are known as oxyntic cells. Thus, oxyntic atrophy is the pathologic process characterized by loss of parietal cells. In human beings and mouse models, loss of parietal cells usually correlates with the onset of metaplastic lesions, such that oxyntic atrophy has been termed the sine qua non for metaplasia.[1,2] In human beings and mice, chronic *Helicobacter* infection can lead to loss of parietal cells in the corpus of the stomach.[3–6] Oxyntic atrophy is diagnosed easily on H&E staining because the absence of highly eosinophilic parietal cells is obvious. During oxyntic atrophy, mature chief cells (digestive enzyme–secreting or zymogenic), which are mixed H&E positive, also are absent. Work in mouse models and human beings suggests that the loss of mature chief cells may not simply be because they all die similar to parietal cells, but rather that chief cells, in response to loss of parietal cells, change their differentiation state. Specifically, they reprogram into metaplastic mucous cells.[7–11] Such a reprogramming of cell fate also is known as transdifferentiation. For a more definitive analysis beyond H&E, cell-type and lineage-specific markers can be used with immunofluorescent or immunohistochemical techniques: for example, antibodies against the proton pump, H+/K+–adenosine triphosphatase (ATPase) (α or β subunit) will label only mature parietal cells, whereas antibodies against the basic Helix-Loop-Helix transcription factor, MIST1 (A15), will label only chief cells.[2,7,12]

Foveolar Hyperplasia

Foveolar cells are the simple columnar mucous cells lining the surface of the stomach and extending downward toward the gastric gland (Figure 1). They face the harshest conditions, being closest to the lumen of the stomach, and turn over the fastest.[13,14] Gastric units are shaped roughly like a funnel, with the glandular portion (the part with the parietal and chief cells) below the neck of the funnel, and the foveolar cells in the wide mouth.[15] Thus, the foveolar region also resembles the opening to a pit. Hence, foveolar cells also are known as pit cells in the literature. Hyperplasia, as mentioned, is an expansion of normal cells. Hence, foveolar hyperplasia represents an expansion of these surface or pit mucous cells. Foveolar hyperplasia (Figure 1) usually is associated with an increase in proliferation in the normal progenitor cells in the isthmus of the gastric unit.[10] A common cause of foveolar hyperplasia in mice and human beings is an increase of gastrin.[16] Increased signaling through the epidermal growth factor (EGF) receptor (eg, by increased abundance of its ligand transforming growth factor α) also causes foveolar hyperplasia; human Ménétrier disease is caused by such overactive signaling.[17,18] Interestingly, oxyntic atrophy and foveolar hyperplasia often are linked. Long-term loss of parietal cells causes decreased stomach acid (hypochlorhydria), which causes gastrin-secreting cells in the antrum of the stomach (G cells) to secrete gastrin in an attempt to stimulate parietal cell function. The increased gastrin has several effects, including inducing foveolar hyperplasia.[10] Gastrin-secreting tumors of the gastrointestinal tract (as occurs in Zollinger–Ellison syndrome), also can result in foveolar hyperplasia.[19] Thus, in general, foveolar hyperplasia correlates with hypochlorhydria and hypergastrinemia.

Mucous Neck Cell Hyperplasia/ Mucinous Metaplasia

Mucous neck cell hyperplasia connotes expansion of normal mucous neck cells (Figure 1). A related term often used by pathologists, especially veterinary pathologists, is *mucous metaplasia*, which often may be the same lesion as mucous neck cell hyperplasia. A reason for the possible confusion is that mucous metaplasia typically is diagnosed by conventional histochemical staining (H&E, periodic acid–Schiff, and Alcian blue). It describes a lesion characterized by abnormally increased numbers of mucous-expressing neck cells in the glands of the stomach (ie, not in the foveolar/pit region). In our experience, mucinous metaplasias usually are caused by expansion specifically of normal mucous neck cells. Thus, mucous metaplasia is often a misnomer because no new (metaplastic) cell lineages are found in the stomach. Mucous neck cells may have a metaplastic look when they expand markedly because in the normal stomach they usually are difficult to see, given that their cytoplasms do not stain with H&E, and those non-staining cytoplasms are localized predominantly in the lumen of the gland because parietal cells occupy the vast majority of the basement membrane.[20] When mucous neck cells expand significantly, they do so at the expense of parietal cells, giving a morphology that appears as if a new population of cells has appeared. On immunohistochemical or immunofluorescent staining, however, the cells in these lesions label exclusively with mucous neck cell lineage markers (including *Griffonia simplicifolia lectin (GS-II)*, Trefoil factor 2 (TFF2), mucin 6 (MUC6), and gastrokine 3 (GKN3)).[21,22] Thus, this lesion is best described as mucous neck cell hyperplasia.

Mucous neck cell hyperplasia has been reported in a number of settings with alterations of ion channels (eg, loss of KVLQT1) or endocrine cell influences.[22] In our experience, mucous neck cell hyperplasia also arises spontaneously in otherwise healthy mice. The lesion usually is focal and characterized by a neutrophil-predominate inflammatory infiltrate. The expansion of mucous neck cells usually is not associated with markedly increased proliferation within the mucous neck cell population, but rather appears to reflect either an increased production of mucous neck cells from multipotent progenitors or a slowing of differentiation of mucous neck cells into chief cells.[7,23] It is important to note that combinations of mucous neck cell hyperplasia can exist in association with other truly metaplastic lesions. For example, spasmolytic polypeptide (TFF2)-expressing metaplasia (SPEM), which will be discussed later, often is characterized by abundant mucous-containing cells (Figure 1). SPEM may look like mucous neck cell hyperplasia on