A Summary of the 2016 James W. Freston Conference of the American Gastroenterological Association: Intestinal Metaplasia in the Esophagus and Stomach: Origins, Differences, Similarities and Significance

Q2 Stuart J. Spechler,[1] Juanita L. Merchant,[2] Timothy C. Wang,[3] Parakrama Chandrasoma,[4] James G. Fox,[5] Robert M. Genta,[6] James R. Goldenring,[7] Yoku Hayakawa,[8] Ernst J. Kuipers,[9] Pauline K. Lund,[10] Frank McKeon,[11] Jason Mills,[12] Robert D. Odze,[13] Richard M. Peek, Jr.,[14] Thai Pham,[15] Jianwen Que,[16] Anil K. Rustgi,[17] Nicholas J. Shaheen,[18] Ramesh A. Shivdasani,[19] Rhonda Souza,[1] Peter Storz,[20] Andrea Todisco,[21] David H. Wang,[22] and Nicholas A. Wright[23]

[1]Center for Esophageal Diseases, Baylor University Medical Center and Center for Esophageal Research, Baylor Scott and White Research Institute, Dallas, Texas; [2]Department of Internal Medicine, Division of Gastroenterology, University of Michigan Health System, Ann Arbor, Michigan; [3]Division of Digestive and Liver Diseases, Department of Medicine, Irving Cancer Research Center, Columbia University Medical Center, New York, New York; [4]Keck School of Medicine, University of Southern California, Los Angeles, California; [5]Division of Comparative Medicine, Massachusetts Institute of Technology, Cambridge, Massachusetts; [6]Miraca Life Sciences Research Institute, Irving, Texas; [7]Nashville VA Medical Center and the Section of Surgical Sciences and Epithelial Biology Center, Vanderbilt University Medical Center, Nashville, Tennessee; [8]Department of Gastroenterology, Graduate School of Medicine, University of Tokyo, Japan; [9]Erasmus University Medical Center, Rotterdam, the Netherlands; [10]Division of Biomedical Research Workforce, Office of Extramural Research, National Institutes of Health, Bethesda, Maryland; [11]Department of Biology Biochemistry, University of Houston, Texas; [12]Division of Gastroenterology, Departments of Medicine, Pathology & Immunology, and Developmental Biology, Washington University School of Medicine, St. Louis, Missouri; [13]Department of Pathology, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts; [14]Vanderbilt University Medical Center, Nashville, Tennessee; [15]Esophageal Diseases Center, Department of Surgery, University of Texas Southwestern Medical Center and Surgical Service, Dallas VA Medical Center, Dallas, Texas; [16]Department of Surgery, Division of Digestive and Liver Diseases, Center for Human Development, Department of Medicine, Columbia University Medical Center, New York, New York; [17]Division of Gastroenterology, Departments of Medicine and Genetics, University of Pennsylvania Perelman School of Medicine; Philadelphia, Pennsylvania; [18]Center for Esophageal Diseases and Swallowing, Division of Gastroenterology & Hepatology, University of North Carolina, Chapel Hill, North Carolina; [19]Dana-Farber Cancer Institute and Harvard Medical School, Boston, Massachusetts; [20]Department of Cancer Biology, Mayo Clinic, Jacksonville, Florida; [21]Department of Internal Medicine, Division of Gastroenterology, University of Michigan Health System, Ann Arbor, Michigan; [22]Esophageal Diseases Center, Department of Internal Medicine and the Simmons Comprehensive Cancer Center, University of Texas Southwestern Medical Center and Medical Service, Dallas VA Medical Center, Dallas, Texas; [23]Centre for Tumor Biology, Barts Cancer Institute, Queen Mary University of London, United Kingdom

Metaplasia, wherein 1 type of adult tissue replaces another, is a consequence of chronic inflammation.[1] Presumably, metaplasias develop and persist because they are more adept than the native tissue at resisting injury from the underlying inflammatory condition. In the stomach, intestinal metaplasia develops in the setting of chronic *Helicobacter pylori* gastritis, whereas intestinal metaplasia in the esophagus results from chronic esophagitis caused by gastroesophageal reflux disease (GERD). Limited dialogue between investigators studying intestinal metaplasia in the stomach and those studying it in the esophagus has been a barrier to progress in understanding these conditions. The 2016 James W. Freston Conference of the American Gastroenterological Association was unique in bringing these groups together. Senior investigators delivered lectures on basic and clinical features of intestinal metaplasia in the esophagus and stomach, and young faculty and trainees gave oral and poster presentations.

Introductory Session

Robert Genta reviewed the histologic features of intestinal metaplasia, and Jason Mills provided a historical overview, noting that Rudolph Virchow coined the term "metaplasia" at the VIIIth International Medical Congress in Copenhagen in 1884. In 1900, the pathologist George Adami presciently contended that there are "mother" (stem) cells that regenerate normal tissue and, "under abnormal conditions, the fully differentiated functioning cells of certain

Abbreviations used in this paper: **ADM, acinar-to-ductal metaplasia; BMP, bone morphogenetic protein; GERD, gastroesophageal reflux disease; HIF, hypoxia inducible factor; IESC, intestinal epithelial stem cell; IGF1R, insulin-like growth factor 1 receptor; MDSC, myeloid-derived suppressor cell; SPEM, spasmolytic polypeptide-expressing metaplasia.**

0016-5085/$36.00
http://dx.doi.org/10.1053/j.gastro.2017.05.050

tissues are capable of proliferation and giving rise to cells of like nature, but this is only after a preliminary reversion to a simpler, more embryonic type." Adami proposed that this process of dedifferentiation leading to increased proliferation might result in "glandular cancer."[2] During the 1930s, developmental biologists largely abandoned Adami's concepts, instead embracing Conrad Waddington's notion that stem cell differentiation was unidirectional. However, recent evidence vindicates Adami, showing that differentiated cells can indeed contribute to metaplasia.

Clinical and Histologic Issues Session

Stuart Spechler reviewed how concepts about intestinal metaplasia have evolved. Early investigators thought intestinal epithelium in the stomach was congenital, and not until the 1930s did it become widely regarded as a metaplasia caused by gastritis.[3] In the 1970s, Japanese pathologists categorized intestinal metaplasia associated with gastric cancer as "complete" or "incomplete" based on how closely it resembled normal small intestine.[4] In the 1980s, Jass and Filipe[5] used mucin immunohistochemistry to categorize 2 types of intestinal metaplasia in the stomach. Type I was histologically "complete," comprising absorptive cells and goblet cells expressing sialomucins. Type II was "incomplete," comprising goblet cells and gastric foveolar-like cells, and subcategorized as IIB if it expressed colonic-type sulfomucins, and as IIA if it did not. Esophageal researchers instead used terms like "specialized columnar epithelium" and "specialized intestinal metaplasia" to categorize the incomplete intestinal metaplasia of Barrett's esophagus. By the 1980s, it had become accepted that chronic reflux esophagitis resulted in intestinal metaplasia that predisposed to esophageal adenocarcinoma.[6] In the 1990s, Pelayo Correa proposed that chronic *H pylori* gastritis caused the intestinal metaplasia that predisposed to gastric adenocarcinoma.[7]

Ernst Kuipers reviewed data on cancer risk for intestinal metaplasia. Recent, population-based studies describe esophageal adenocarcinoma incidence rates for Barrett's esophagus in the range of 1.2 to 1.6 per 1,000 patient-years.[8–10] Dr Kuipers debunked the popular notion that intestinal metaplasia in the stomach has a lower cancer risk than in Barrett's esophagus, noting a study of 97,837 Dutch patients with preneoplastic gastric lesions that found a gastric cancer incidence of 4 per 1000 patient-years,[11] with similar incidence rates found in cohorts from the United States and Sweden.[12,13] As in the esophagus, cancer risk in the stomach is proportional to the extent of intestinal metaplasia. Therefore, physicians should consider endoscopic surveillance for patients with extensive gastric intestinal metaplasia (involving both the antrum and the fundus).[14,15] Surveillance can lead to early detection of gastric cancer and improved survival, but data showing that endoscopists miss 1 out of 9 early cancers suggest that recognition of these early lesions needs improvement.[16]

Robert Odze explained that Barrett's metaplasia has (1) a surface/crypt epithelial compartment with columnar cells exhibiting variable degrees of gastric and intestinal differentiation, and (2) an underlying glandular compartment composed of mucus glands, oxyntic glands, or both. Although goblet cells have been considered the sine qua non for Barrett's intestinal metaplasia, Dr Odze noted that esophageal nongoblet columnar epithelium also expresses transcription factors of intestinal differentiation.[17] Furthermore, goblet cells can be missed by biopsy sampling error,[18] and nongoblet esophageal cells can be mistaken for goblet cells, resulting in false-negative and false-positive Barrett's diagnoses, respectively.[19] Nongoblet esophageal columnar epithelium can exhibit DNA content abnormalities,[20] and a recent report found an inverse association between goblet cell density in Barrett's metaplasia and risk of esophageal adenocarcinoma.[21] Dr Odze noted that it is inaccurate to call esophageal nongoblet columnar epithelium "cardiac epithelium," because it is the underlying mucus gland compartment that identifies mucosa as cardiac type (not the surface/crypt epithelium). He concluded that goblet cells are not a consistent, sensitive, or specific biomarker for Barrett's esophagus or its cancer risk.

Nicholas Shaheen explained why it is difficult to estimate the cancer risk for cardiac mucosa without goblet cells. Despite the high prevalence of this mucosal type in the general population,[22,23] studies on its cancer risk have focused largely on patients with GERD symptoms who have cardiac mucosa extending above the gastric folds into the esophagus. It is unclear if their cancer risk differs from asymptomatic individuals with cardiac epithelium at a normally positioned Z-line. Furthermore, some studies have found a cancer risk similar to that for Barrett's patients, whereas others have shown a much lower cancer risk.[24–27] The reasons for these discrepancies are unclear, but may include inadequate biopsy sampling (misclassifying patients as intestinal metaplasia-negative),[28,29] small study sample sizes, and short durations of follow-up. Dr Shaheen concluded that, presently, no blanket recommendation for surveillance of patients with cardiac mucosa is advisable.

Parakrama Chandrasoma presented his controversial contention that cardiac mucosa without goblet cells is never normal and always metaplastic, irrespective of whether it is found above or below the endoscopically identified gastroesophageal junction. He cited a study showing that cardiac mucosa exhibits the same morphologic and molecular features irrespective of its location,[30] and discussed reasons to believe that cardiac mucosa represents a squamous-to-columnar metaplasia of the esophagus caused by GERD.[31] Endoscopists demarcate the gastroesophageal junction at the top of gastric folds, but Dr Chandrasoma argued that this is an unreliable landmark in GERD patients in whom the distal esophagus has dilated and developed rugal-like folds easily mistaken for gastric folds.[32,33] Dr Chandrasoma proposed that the finding of cardiac mucosa might be used as an objective, histologic marker for the presence of GERD.

Stem Cells and their Lineage in Normal Development Session

Anil Rustgi explained that the esophagus has a prototypical stratified squamous epithelium with proliferative