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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

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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 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-tocolumnar 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 basal cells abutting the basement membrane. These basal cells undergo lineage allocation as they migrate toward the epithelial surface, becoming early differentiated suprabasal cells and terminally differentiated superficial squamous cells that ultimately desquamate. Experiments performed by Dr Veronique Giroux have identified a murine esophageal progenitor cell population.[34] Using genetic in vivo lineage tracing, she found that the keratin 15 (*Krt15*) promoter marked a long-lived basal cell population capable of allocating all stages of differentiation, and that genetic depletion of *Krt15* lineage-labeled cells resulted in decreased proliferation and epithelial atrophy. Radioresistant *Krt15*+ cells fostered regeneration following radiation-induced esophageal injury, and *Krt15*+ cells in 3-dimensional organoids exhibited enhanced clonogenicity. Dr Rustgi concluded that this *Krt15*+ long-lived progenitor cell population might constitute an esophageal stem cell population.

Expanding on his earlier discussion that metaplasias can develop when mature cells dedifferentiate and proliferate, Jason Mills discussed the contribution of factors like the basic helix–loop–helix transcription factor MIST1 to this process.[35] Increased expression of these factors can scale up a cell's energy use toward maintaining an elaborate secretory apparatus (differentiated status), whereas decreased expression can scale down these processes as the cell undergoes dedifferentiation and reversion to a proliferative state. Dr Mills also discussed evidence that quiescent, differentiated cells are recruited back into the cell cycle during metaplasia via an evolutionarily conserved, invariant sequence of steps. Each step can be blocked by pharmacologic inhibitors or by genetic modifications in mice.

Yoku Hayakawa discussed his observation that Mist1 messenger RNA is expressed, not only in gastric chief cells, but also in quiescent stem cells in the isthmus of gastric corpus glands. [36] Chief cell ablation experiments suggest that it is Mist1+ isthmus stem cells (not Mist1+

chief cells) that are responsible for long-term lineage tracing in the gastric corpus. With the induction of mutant Kras, Mist1+ isthmus stem cells serve as the cell of origin for intestinal metaplasia, and give rise to both intestinal-type and diffuse-type gastric cancers when they lose Apc and E-cadherin, respectively. Dr Hayakawa concluded that Mist1+ stem cells in the isthmus of gastric glands likely are the main source of metaplasia and cancers in the stomach.

Kay Lund described a Sox9-EGFP reporter mouse model that identifies intestinal epithelial cell subtypes by their levels of Sox9-EGFP expression. These include (1) "actively cycling" intestinal epithelial stem cells (IESC; Sox9-EGFP^{Low}), (2) IESC progenitors (Sox9-EGFP^{Sublow}), (3) enteroendocrine cells (Sox9-EGFP^{High}), and (4) differentiated enterocytes, Paneth cells, and goblet cells (Sox9-EGFP^{Negative}). After intestinal injury, a reserve population of Sox9-EGFP^{High} cells is activated to fuel expansion of Sox9-EGFP^{Low} IESC during regeneration.[37] IESC exhibit enrichment of insulin-like growth factor 1 receptor (IGF1R) and insulin receptor isoform-A, and sustained insulin receptor signaling seems to protect against adenomas, perhaps by inhibiting IGF1R signaling.[38,39] MicroRNA (miR375), which has been linked both to cancer and IGF1R regulation, is enriched in IESC and can limit their proliferation.[40] Dr Lund concluded that maintained expression and function of insulin receptors might regulate IESC and prevent adenomas, potentially by inhibiting IGF1R, and that miR375 could be a new target to limit IESC proliferation and tumor growth.

Peter Storz discussed how studies on pancreatic acinar-to-ductal metaplasia (ADM) might be applied to intestinal metaplasia in the esophagus and stomach. In the pancreas, inflammatory macrophages produce factors such as tumor necrosis factor, IL-6, and RANTES that contribute to ADM development.[41,42] This ADM becomes irreversible when it acquires an oncogenic KRas mutation, and neoplastic progression occurs in synergy with inflammation.[43] Nonneoplastic ADM is associated predominantly with inflammatory macrophages, but alternatively activated macrophages, which can drive fibrosis and lesion growth, become more plentiful as neoplasia develops.[44] Interleukins released by cells in precancerous ADM lesions initiate this phenotypic switch in macrophage populations. Thus, using the pancreas as an example, Dr Storz implicated inflammation and inflammatory macrophages as initiators and drivers of the metaplasia–neoplasia sequence.

Potential Origins of Metaplasia in the Esophagus and Stomach Session

David Wang reviewed unique anatomic features of the mice and rats used in metaplasia studies, noting that these rodents have a forestomach lined by squamous epithelium and an esophagus that lacks submucosal glands. The rodent esophagus joins stomach at the junction between squamous-lined forestomach and distal glandular stomach, and the squamocolumnar junction has a distinctive "first fundic gland" containing cells that express stem cell markers including LGR5 and DCLK-1.[45,46]

Jianwen Que reviewed mechanisms controlling normal gastroesophageal embryonic development. Around embryonic days 9.5-11.0, live imaging reveals a saddle-like structure that separates esophagus and stomach from trachea and lung.[47] Genetic models suggest that

transcription factors (eg, SOX2, NKX2.1) and signaling molecules (eg, Noggin, Wnt2/2b) are critical for establishing esophagus from foregut,[48] after which esophageal lining changes from columnar into squamous epithelium under control of transcription factors like p63 and SOX2. A *p63* gene deletion prevents this epithelial change, and SOX2 down-regulation causes esophageal progenitor cells to differentiate abnormally into mucin-secreting cells. [48,49] Bmp signaling in the esophagus also is required for normal development of squamous epithelium.[50] In the stomach, multiple signaling pathways (eg, Bmp, Notch, Wnt) and transcription factors (eg, BARX1, NKX2.5, and GATA3) mediate the development of gastric glandular epithelia.

Ramesh Shivdasani discussed how cellular identity is influenced by thousands of distant enhancers that regulate gene transcription, dictated by chromatin structure.[51,52] His laboratory has mapped the enhancer landscape in Barrett's esophagus and in normal esophageal, gastric, and intestinal mucosae, elucidating how Barrett's metaplasia reflects an intestinal enhancer signature and lacks vestiges of an esophageal enhancer signature. In studies on tissue-specific enhancers delineated during mouse organogenesis, the Shivdasani laboratory has found that, although thousands of enhancers specific to adult esophageal and intestinal epithelia are fully demarcated by birth, those regions of chromatin appear equally poised for activation in both mucosal primordia early in development. Dr Shivdasani anticipates that these studies will help to elucidate the chromatin basis of intestinal metaplasia in esophagus and stomach.

David Wang explained how transcommitment, the molecular reprogramming of a progenitor cell, is a possible mechanism whereby cells native to the esophagus could give rise to Barrett's metaplasia. Transcommitment of squamous epithelial progenitor cells into intestinal-type columnar cells likely requires a stepwise process that includes the down-regulation of squamous transcription factors, and sequential upregulation of columnar, intestinal, and mucus-associated transcription factors. Dr Wang also described potential roles for Hedgehog and downstream bone morphogenetic protein (BMP)-4 signaling pathways in regulating these transcription factors.[53,54]

Andrea Todisco explained that BMP signaling, which targets gastric epithelial cells in mice with *Helicobacter* gastritis, has important antiinflammatory actions and effects on gastrointestinal cell growth and differentiation.[55,56] Mice genetically engineered to express noggin (a BMP inhibitor) in the stomach exhibit decreased parietal cell numbers, increased epithelial cell proliferation, and development of spasmolytic polypeptide-expressing metaplasia (SPEM).[55,56] Noggin-expressing mice also show enhanced *Helicobacter*-induced inflammation and epithelial cell proliferation, accelerated dysplasia development, and increased expression of STAT3 and AID (molecules implicated in gastric tumorigenesis).[56] In isolated canine gastric epithelial cells, BMP4, BMP2, and BMP7 inhibit expression of *IL8*, a proinflammatory chemokine.[56] Dr Todisco concluded that BMP signaling reduces inflammation, and decreases metaplasia and dysplasia development in the *Helicobacter*-infected mouse stomach.

James Goldenring noted that both acute and chronic parietal cell depletion in mice leads to SPEM development in the gastric body.[57] Lineage mapping shows that this SPEM emerges

through transdifferentiation of chief cells into metaplastic mucous cells.[58] Although this process might promote wound repair,[59] it can lead to intestinal metaplasia development in the setting of chronic inflammation. When chief cells are induced to express active KRas, SPEM develops throughout the gastric body within 2-3 weeks, and intestinal metaplasia appears by 3–4 months.[60] Administration of a MEK inhibitor (Selumetinib) to mice 3 months after active KRas induction leads to arrest of metaplasia and extrusion of metaplastic glands through recrudescence of normal gastric lineages from a dormant normal progenitor cell population.[60] Dr Goldenring concluded that MEK inhibitors someday might be used to reverse metaplasia and enable repopulation of the gastric mucosa with normal oxyntic mucosal lineages.

Timothy Wang discussed mouse models suggesting a gastric cardia origin for Barrett's metaplasia. L2–IL-1β mice, which overexpress IL-1β in the esophagus, develop a Barrett's-like metaplasia that begins in the gastric cardia and expands into the esophagus.[61] The gastric cardia normally is rich in stem/progenitor cells, including Lgr5+ and CCK2R+ cells, and transgenes marking either of those progenitor cell types can lineage-trace metaplasia in the L2–IL-1β mouse. Human Barrett's esophagus and gastric cardia exhibit strong expression of CCK2R (a gastrin receptor), and progression of Barrett's-like metaplasia in mice is accelerated by hypergastrinemia and inhibited by CCK2R blockade.[62,63] Gamma-secretase inhibitors, which block Notch signaling, increase goblet cells and reduce proliferation in rodent Barrett's metaplasia, suggesting that Notch signaling might drive neoplastic progression.[61,62] Dr Wang concluded that the abundance and activity of undifferentiated stem cells, rather than the presence of goblet cells, likely drives cancer risk in Barrett's esophagus.[64]

Nicholas Wright explained that Barrett's metaplasia exhibits a range of gland phenotypes, each showing functional compartmentalization, bidirectional migration, and derivation from a shared clonal progenitor.[65] Barrett's glands have an evolutionary life history, comprising segments exhibiting a spatial gradient of phenotypes as well as heterogeneous and differential tissue age, with older glands located proximally.[66] Dr Wright suggested that the mechanism of phenotypic evolution in intestinal metaplasia is probably biased drift occurring after a multilineage stem cell change, followed by clonal expansion through gland fission.[67] Because Barrett's glands are clonal, they are units of selection, including selection in neoplastic progression.[67] Although classically neoplasia develops only in goblet cell-containing Barrett's epithelium, Dr Wright noted that esophageal nongoblet columnar epithelium can also undergo clonal expansion and harbor premalignant TP53 mutations.[68]

Frank McKeon suggested that the identification of the Barrett's cell of origin might inform preemptive therapies for eliminating Barrett's esophagus. He and Wa Xian have traced the origin of Barrett's-like metaplasia in mice to gastroesophageal junction cells with a unique developmental lineage.[69] Using novel technologies for cloning gastrointestinal stem cells,[70] they cloned 3 distinct stem cells in the distal esophagus (ones committed to esophageal, gastric, and Barrett's differentiation), and the Barrett's stem cells exhibited genomic alterations typical of Barrett's metaplasia.[71] By extending these cloning techniques to patient-matched tissues, they have adapted Barrett's and patient-matched gastric cardia stem cells to high-throughput drug screening platforms that have revealed molecules with

potentially selective toxicity for Barrett's stem cells. This raises the intriguing possibility that such selectively toxic molecules might be used to eradicate Barrett's metaplasia.

Inflammation and the Development of Metaplasia Session

Rick Peek highlighted the pivotal role of CagA, an *H pylori* oncoprotein, in intestinal metaplasia development in the stomach. CagA+ *H pylori* strains interact specifically with stem cells in gastric glands,[72] and CagA can confer stemness properties to gastric epithelial cells.[73] Dr Peek discussed the usefulness of *H pylori* eradication for inducing regression of intestinal metaplasia and, thereby, reducing gastric cancer risk. Novel therapies showing promise for inducing such regression in animal models were discussed, including MEK inhibitors used by the Goldenring laboratory.[60] Finally, Dr Peek discussed the role of microbial species other than *H pylori* in generating gastric intestinal metaplasia, and he identified potential collaborations between *H pylori* and other constituents of the gastric microbiota as promising areas for future research.[74]

Rhonda Souza discussed her studies on reflux esophagitis pathogenesis. In a rat model, she found that refluxed acid and bile did not kill esophageal squamous cells directly, but rather stimulated them to release inflammatory cytokines.[75] To test her concept that reflux esophagitis develops as a cytokine-mediated injury, she studied acute reflux esophagitis induced by stopping proton pump inhibitors in patients with reflux esophagitis healed by proton pump inhibitors.[76] Reflux esophagitis returned within 2 weeks, and this human acute reflux esophagitis was characterized histologically by T lymphocyte infiltration of esophageal mucosa. In vitro studies showed that acid and bile salts cause esophageal epithelial cells to stabilize hypoxia inducible factor (HIF)-$2a$, a transcription factor that can increase proinflammatory molecule expression.[77] In patients developing reflux esophagitis, she found a positive correlation between increased esophageal HIF-$2a$ levels and increased proinflammatory molecule expression. These studies suggest that gastroesophageal reflux causes esophagitis through cytokine-mediated mechanisms triggered by HIF-$2a$.

Juanita Merchant discussed her studies showing that acute *Helicobacter felis* in mice causes gastric parietal cells to release sonic hedgehog that recruits myeloid cells into the stomach.[78] Chronic *Helicobacter* gastritis induces parietal cells to atrophy and release damage-associated factors that polarize the myeloid cells in the stomach toward an immunosuppressive phenotype. The resulting myeloid-derived suppressor cells (MDSCs) create an environment favoring metaplasia. Myeloid cell polarization into MDSCs requires hedgehog-regulated transcription factor GLI1, which induces gastric MDSCs to express *Schlafen 4*, a myeloid differentiation factor.[79] Dr Merchant showed that a nucleic acid signature for MDSCs in plasma correlates with gastric metaplasia presence in both mice and humans. Collectively, her studies suggest that MDSCs are present in the gastric microenvironment before neoplastic transformation, and that they might serve as a biomarker for gastric cancer risk.

Models of Metaplasia in the Esophagus and Stomach Session

Robert Odze discussed his study on intestinal metaplasia development in rats with reflux esophagitis induced by esophagojejunostomy.[80] Esophageal ulceration developed at the esophagojejunal anastomosis at postoperative week 2 and, over subsequent weeks, esophageal columnar epithelium with intestinal-type immunohistochemical features seemed to arise from budding jejunal crypts migrating into the ulcerated distal esophagus. Dr Odze concluded that these findings support a wound healing model for Barrett's metaplasia pathogenesis in which gastric columnar cells migrate proximally to repair the reflux-damaged distal esophagus.

Thai Pham noted that an ideal animal model for Barrett's esophagus would be inexpensive and technically simple, using gastroesophageal reflux to induce metaplasia in genetically modifiable animals with a human-like esophagus. Most Barrett's models have involved the surgical induction of reflux through esophagoenterostomy in rats. Although this model is inexpensive and technically simple, rats are not easily manipulated genetically, and the rat esophagus differs substantially from human. Dr Pham discussed his model of Barrett's esophagus in mice,[81] noting that the surgery is technically challenging, but the ability to genetically manipulate mice is a major advantage. He concluded that rodent models of Barrett's esophagus are useful, albeit not ideal, investigational tools.

James Fox explained how early attempts to develop animal models of chronic *H pylori* gastritis were unsuccessful until investigators used *H felis* (a close relative of *H pylori*) to infect germfree Swiss Webster mice.[82] In C57BL and INS/ GAS mice, *H felis* (and later mouse- adapted *H pylori*) recapitulated human *H pylori* lesions including parietal and chief cell depletion and SPEM development.[83–86] Although SPEM lacks goblet cells, the predominant SPEM phenotype that develops in mice infected with *H felis* or *H pylori*[87] and in gerbils infected with *H pylori*[88] has intestinal features. Non- *Helicobacter* gut bacteria can profoundly influence the degree and severity of *Helicobacter* gastritis, especially when the *Helicobacter* infection causes parietal cell loss with achlorhydria that enables other organisms to colonize the stomach.[89,90] Dr Fox noted that both the gender of C57BL mice and their commercial source influence the degree of gastritis and metaplasia developing with *H pylori* infection,[91] and that the origin of the metaplastic lineages remains unclear.

Conclusions

The 2016 Freston Conference was unique in bringing experts on intestinal metaplasia in the esophagus together with experts on intestinal metaplasia in the stomach. The conference provided opportunities for new collaborations among established investigators, and a stimulating environment for young investigators and trainees to interact with senior scientists. The conference highlighted numerous similarities between gastric and esophageal intestinal metaplasia, suggesting that the mechanisms underlying metaplasia in these adjacent organs are not as dissimilar as has been assumed. For future studies, it might be more productive to focus on those similarities rather than differences.

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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

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