Metaplasia in the gut

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Overview of gastrointestinal metaplasias

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Metaplasia is a reversible change in which one adult cell type is replaced by another. It is always associated with some normal stimulation of tissue growth, tissue regeneration or excessive hormonal stimulation. Heterotopia, on the other hand, takes place during embryogenesis and is usually supposed not to be associated with tissue damage. Pancreatic acinar cell clusters in pediatric gastric mucosa form another example of aberrant cell differentiation. Metaplasia is usually divided into epithelial and connective tissue (e.g., osseous metaplasia of fibroblastic stroma or scar tissue). Metaplasia within a cancer is still another issue.

Epithelial metaplasia is thought to arise from reprogramming stem and reserve epithelial cells. These precursor cells differentiate along a new pathway. Metaplasia may represent an adaptive substitution of sensitive cells by other cell types better able to withstand the adverse environment. This is less clear in connective tissue metaplasia. Metaplasias are patches of ectopic tissue and only rarely and in the later stages involve the entire affected structure, e.g., the entire gastric mucosa.

Metaplasia is caused by malfunction of tissue-specific and differentiation genes stimulated by cytokines, growth factors and extracellular matrix components. These external factors trigger the cascade of transcription factors that lead toward the fully differentiated cell.

The most common epithelial metaplasia is columnar to squamous. Well known is the example of squamous metaplasia in vitamin A deficiency or metaplasia of bronchial epithelium irritated by cigarette smoke. Metaplasia from squamous to columnar or may also occur. This is the case in Barrett’s esophagus.

Epithelial metaplasia is a two-edged sword. Metaplastic cells survive better but some of the functions of the normal epithelium are lost. In addition, a persistent metaplastic process may predispose to cancer transformation. This is the main area of interest even though it is still unclear whether cancer is associated with metaplasia in a causative manner or whether it is simply a bystander providing a warning about the risk of cancer, which however, develops independently.

The substantial contribution to our understanding of aberrant differentiation of gastrointestinal cells was given by Nick Wright and his hypothesis of ulcer-associated cell lineages (1).

In the gastrointestinal system metaplasia is relatively common. Best recognized is intestinal metaplasia of the gastric mucosa. Gastric metaplasia is also common, however. The latter occurs not only in esophagus but also in the duodenum, intestine, gallbladder and even in the pancreas. Well established is columnar metaplasia of esophageal squamous epithelium. Its association with increased risk of esophageal cancer is widely recognized. Recent developments have suggested, however, that only the intestinal type of metaplastic epithelium (classic Barrett’s esophagus) predisposes to cancer. Another field of studies is metaplasia in the short segment at the esophago-cardiac junction, its association with Helicobacter pylori infection and/or reflux disease and intestinal metaplasia in the cardiac and fundic areas.

Studies on gastric mucosa metaplasia could be divided into those concerned with pathogenesis and detailed structural/functional features and those concerned with clinical significance.

We know now that gastric mucosa may show not only complete and incomplete intestinal metaplasia but also others such as ciliary and pancreatic metaplasia. We also know that pylonization of oxyntic mucosa in atrophic gastritis is common. We know that in addition to fully differentiated intestinal cells some cells show dual gastric and intestinal or amorphic features. Subtyping of intestinal metaplasia has led to the conclusion that the “gastric and intestinal mixed” subtype predominates in the antral mucosa while the “solely intestinal” subtype predominates in the oxyntic mucosa.

Studies on the clinical significance of metaplasia within gastric mucosa have been heavily affected by the decade of helicobacterology (2-5). This includes not only the association of metaplasia with H. pylori infection but also reversibility after H. pylori eradication as well as the influence of acid suppression therapy on the proximal extension of inflammation and renewed recognition of gastric mucosa transitional zones. All this was additionally found in experimental conditions by the development of metaplasia and cancer in H. pylori infected gerbils.

Now, in the post-Helicobacter era, there can be a return to Correa’s classic paradigm of gastritis-atrophic gastritis-atrophy-metaplasia-dysplasia-carcinoma sequence (at least for gastric adenocarcinoma). Other environmental and host factors in gastric carcinogenesis can also again be appreciated.

References