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Mycobacterium avium subspecies *paratuberculosis* and goblet cells: are Barrett's esophagus and esophageal adenocarcinoma zoonotic infectious diseases?

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There has been a great increase in the incidence of esophageal adenocarcinoma (EAC) in western so-called developed countries in the past several decades[1-3]. This marked increase has led some to speculate that "changing environmental factors and microbial agents"[4] may be contributing factors.

A possible infectious cause of EAC and associated Barrett's esophagus (BE) is *Mycobacterium avium* subspecies *paratuberculosis* (MAP). MAP, a long suspected cause of Crohn's disease, is a probable zoonosis[5], a microorganism that causes disease in humans and is transmitted to humans from animals.

MAP is present in an infected domestic ruminant's manure, milk, and muscle tissue. Humans can become infected with MAP by swallowing MAP organisms in MAP-contaminated potable water, MAP-contaminated milk and other dairy products, and MAP-contaminated meat, or inhaling and then swallowing MAP-contaminated water aerosolized from rivers and lakes.

Presumably MAP-associated Crohn's disease is known to cause oral[6], esophageal[7], and gastric lesions[8]. MAP organisms are present in oral biopsies from patients with Crohn's disease[9].

Goblet cell proliferation that occurs in locations where goblet cells already exist is called goblet cell hyperplasia. Goblet cell hyperplasia of the small and large intestines is a known result of infection with enteropathogenic bacteria and parasites[10]. MAP has the little-known ability to cause acute[11] and chronic[12] goblet cell hyperplasia in the small and large intestines of its natural hosts, domestic ruminants.

MAP has a predilection for human intestinal goblet cells. A single striking study shows MAP organisms actively migrating within the mucus of human fetal small intestines to a position directly above goblet cells, gathering in dense aggregations, and then heavily invading the goblet cells[13]. MAP also appears perfectly capable of invading not just goblet cells, but every cell type in the intestines. A single study documents that MAP can directly infect all cell types of bovine intestinal epithelium, but causes the proliferation or hyperplasia only of infected goblet cells[11].

As MAP organisms actively migrate within human fetal small intestinal mucus to the apical surface of goblet cells and then actively invade the apical granule portion of those goblet cells, MAP organisms may be able to migrate within the mucus layer of the stomach to the apical surface of cardiac surface mucus cells and then

actively invade those cardiac surface mucus cells. If MAP preferentially colonizes the mucus above or the mucus within cardiac surface mucus cells, then the pathologic changes MAP causes will begin in the gastric cardia and work their way up. MAP infected cardiac surface mucus cells that proliferate and 'spill' upward would explain why BE begins at the esophagogastric junction and spreads proximally, referred to as "proximal migration"[14].

MAP infection of the gastric cardia mucus or surface mucus cells, causing their proximal migration, explains what is referred to as the "multilayered epithelium"[15] of BE, with columnar-lined epithelium overlying and slightly compressing the underlying squamous epithelium. Possibly MAP-infected cardiac surface mucus cells sometimes migrate underneath rather than over esophageal squamous epithelium, referred to as "subsquamous"[16] or "buried" BE, which while usually considered a post-ablation artifact is actually common in untreated BE patients[17].

In contrast to goblet cell hyperplasia, the proliferation of intestinal-type goblet cells in the stomach, a location where intestinal goblet cells don't normally exist, is called intestinal metaplasia or goblet cell metaplasia. The possibility that MAP can cause the proliferation of gastric or intestinal type columnar-lined epithelium is suggested by the known ability of *Helicobacter pylori* (HP) to cause intestinal metaplasia. Long term gastric HP infection results first in complete metaplasia, consisting of small intestinal enterocytes and small intestinal-type goblet cells, and then incomplete metaplasia, consisting of colonic-type goblet cells. These colonic-type goblet cells are the immediate precursor lesion of HP-associated gastric cancer[18]. After first causing the proximal proliferation of gastric cardiac mucus cells, MAP may 'do' the same thing as HP, causing their complete, and then incomplete, intestinal metaplasia.

Depending on the country, the diagnosis of BE requires the presence of goblet cells. Goblet cell-containing columnar-lined epithelium or intestinal metaplasia is a requirement for the diagnosis of BE in the United States and continental Europe, but in the United Kingdom and Japan only columnar-lined epithelium is required[19]. Columnar-lined epithelium in Barrett's esophagus has four histologic subtypes, two gastric metaplasias and two intestinal metaplasias. The two types of gastric metaplasia, gastric cardia-type epithelium and gastric fundic-type epithelium, do not contain goblet cells. The two types of intestinal metaplasia, incomplete or small intestinal type, and complete or large intestinal type, do contain goblet cells[20]. Just as chronic HP infection results in the two histologic subtypes of intestinal metaplasia in the stomach, chronic MAP infection of the gastric cardia and esophagus may cause all of the histologic subtypes of gastric and intestinal columnar-lined epithelium in the esophagus, all of which are precursors of EAC.

Researchers are divided on the relationship between gastroesophageal reflux disease (GERD), BE and EAC. Some researchers believe that all cases of BE are preceded by GERD or reflux esophagitis. They explain the lack of preceding GERD in some patients with BE or EAC by arguing that not all cases of GERD are symptomatic. If GERD is a necessary precursor of BE, then MAP must be able to invade squamous epithelium, causing the acute inflammation of reflux esophagitis. There are no studies of MAP infection of the upper gastrointestinal tract in animals, despite the common perception that MAP infection in animals occurs exclusively by the fecal-oral route. Esophageal Crohn's disease is characterized by ulcers and chronic inflammation as well as strictures[7]. It is possible that MAP infection of esophageal squamous epithelium may result in the acute inflammation of GERD.

Pathologists have, however, noted that the damaged squamous epithelium, including ulcers and erosion, of reflux esophagitis/GERD in humans is replaced by regenerating squamous epithelium, not by Barrett's columnar mucus epithelium[21]. The majority of patients with EAC and BE do not have a clinical history of GERD[21]. If BE is not a direct pathologic sequela of GERD, what aspect of MAP might explain the close association between MAP and GERD?

The usually close association between GERD and BE may be explained by MAP's requirement for exogenous iron and MAP's possible preference for acidic environments. MAP can't make its own iron and therefore requires exogenous iron. The acid of GERD may 'help' MAP by making iron more soluble and therefore absorbable[22], which may enhance the growth and/or persistence of MAP in the esophagus. Acidity enhances but is not required for the growth of MAP in soil[23]. Acidity enhances but is not required for the growth of nontuberculous mycobacteria such as MAP in natural bodies of water[24]. Similarly, the acidic environment of GERD may enhance MAP's ability to colonize gastric cardia surface mucus or surface mucus cells but is probably not required.

The majority of EAC cases that arise in BE don't actually arise in goblet cell-containing epithelium. Instead, cardiac mucus epithelium surrounds the majority of minute esophageal adenocarcinomas[25]. A recent study showed that the greater the number of goblet cells in BE, the less the risk of EAC[26]. The presence of goblet cells may indicate a more 'successful' immune response to continuing MAP infection, as goblet cell hyperplasia is a protective mechanism of the intestines against other enteric pathogens[10]. In murine intestinal *Citrobacter rodentium* (CR) infection, for example, goblet cell hyperplasia occurs not during the initial phases of the infection, but only during the resolving phase when the CR organism has been successfully eliminated[27]. Goblet cell hyperplasia is a mechanism by which the intestines successfully expel the rodent helminth *Nippostrongylis*

brasiliensis[28]. The studies showing MAP causing acute and chronic goblet cell hyperplasia place MAP organisms in the underlying lamina propria[11, 12], suggesting MAP-induced goblet cell hyperplasia does not successfully expel the organism, but may indicate a more aggressive immune response to MAP that helps contain the organism.

Why MAP may have a predilection for gastric cardiac mucus surface cells rather than fundic or pyloric surface mucus cells is unknown, but may involve MAP's possible preference for the sulphomucins and sialomucins produced by cardiac glands.

HP infection is inversely correlated with Barrett's esophagus[29], suggesting HP colonization of gastric mucus precludes MAP colonization. HP colonization of gastric mucus may crowd out MAP from doing so.

MAP's perhaps preferential colonization of the acidic cardiac mucus and/or cardiac mucous surface cells may also explain the inverse relationship between idiopathic inflammatory bowel disease and BE[30]. Having colonized MAP's perhaps preferred location, MAP organisms may not descend further into the intestinal tract.

The common assumption that cancers in general are a result of unspecified chronic inflammation is not supported by the pathology. GERD for example is chronically inflamed squamous epithelium, yet GERD is not associated with an increased risk of esophageal squamous cell carcinoma. Instead, species of fungi[31] and human papillomavirus types 16 and 18[32] are associated with esophageal squamous cell carcinoma.

The possibility that MAP may be involved in the pathogenesis of BE and associated EAC does not rule out the effect of co-factors on the development of EAC. As high salt diets and smoking 'help' HP cause gastric cancer[33], co-factors including obesity and high sucrose diets may 'help' MAP cause EAC. Obesity is associated with an increased risk of infection[34]. Adipocytes are storage cells for *Mycobacterium tuberculosis* organisms[35]; similarly, adipocytes may be storage cells for MAP organisms, possibly explaining the relationship between obesity and EAC[36]. MAP is more invasive in hyperosmolar, high lactose, environments[37], and may be more invasive in high sucrose western diet environments, possibly explaining the relationship between high sugar diets and an increased risk of BE[38, 39] and EAC[40].

As an enteric pathogen, MAP organisms or antibodies to MAP organisms may be present in EAC and BE patients' esophagi, serum and feces. The regression or resolution of BE, and an improved survival rate of EAC patients treated with anti-MAP therapies in addition to standard surgical and chemotherapy, including dietary alterations such as the specific carbohydrate diet, anti-MAP antibiotics such as RedHill Biopharma's RHB-104 triple antibiotic combination and anti-infective ultraviolet blood irradiation would lend additional support to this hypothesis.

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