Could *Mycobacterium avium* subspecies *paratuberculosis* cause Crohn’s disease, ulcerative colitis… and colorectal cancer?

Ellen S. Pierce

**Abstract:** Infectious agents are known causes of human cancers. *Schistosoma japonicum* and *Schistosoma mansoni* cause a percentage of colorectal cancers in countries where the respective *Schistosoma* species are prevalent. Colorectal cancer is a complication of ulcerative colitis and colonic Crohn’s disease, the two main forms of idiopathic inflammatory bowel disease (IIBD). *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the cause of a chronic intestinal disease in domestic and wild ruminants, is one suspected cause of IIBD. MAP may therefore be involved in the pathogenesis of IIBD-associated colorectal cancer as well as colorectal cancer in individuals without IIBD (sporadic colorectal cancer) in countries where MAP infection of domestic livestock is prevalent and MAP’s presence in soil and water is extensive. MAP organisms have been identified in the intestines of patients with sporadic colorectal cancer and IIBD when high magnification, oil immersion light microscopy (×1000 total magnification rather than the usual ×400 total magnification) is used. Research has demonstrated MAP’s ability to invade intestinal goblet cells and cause acute and chronic goblet cell hyperplasia. Goblet cell hyperplasia is the little-recognized initial pathologic lesion of sporadic colorectal cancer, referred to as transitional mucosa, aberrant crypt foci, goblet cell hyperplastic polyps or transitional polyps. It is the even lesser-recognized initial pathologic feature of IIBD, referred to as hypermucinous mucosa, hyperplastic-like mucosal change, serrated epithelial changes, flat serrated changes, goblet cell rich mucosa or epithelial hyperplasia. Goblet cell hyperplasia is the precursor lesion of adenomas and dysplasia in the classical colorectal cancer pathway, of sessile serrated adenomas and serrated dysplasia in the serrated colorectal cancer pathway, and of flat and elevated dysplasia and dysplasia-associated lesions or masses in IIBD-associated intestinal cancers. MAP’s invasion of intestinal goblet cells may result in the initial pathologic lesion of IIBD and sporadic colorectal cancer. MAP’s persistence in infected intestines may result in the eventual development of both IIBD-associated and sporadic colorectal cancer.

**Keywords:** Goblet, Carcinomas, Adenomas, Infection, Cancerization, Serrated, Transitional mucosa, Aberrant foci, Inflammatory bowel disease

**Introduction**

Infectious agents are known causes of human cancers [1–3]. *Mycobacterium avium* subspecies *paratuberculosis* (MAP), the cause of a chronic intestinal disease in domestic and wild ruminants called Johne’s disease [4], is a long suspected cause of Crohn’s disease [5, 6] and a recently proposed cause of ulcerative colitis [7], the other main form of idiopathic inflammatory bowel disease (IIBD). If MAP causes IIBD, it may be one cause of the colorectal cancers that are a complication of IIBD [8, 9]. MAP may also be one cause of colorectal cancer in patients without IIBD (sporadic colorectal cancer) in countries where MAP infection of domestic livestock is endemic [10] and MAP’s contamination of soil [11] and water [12] is extensive.

The possibility that MAP is involved in the pathogenesis of colorectal cancer, in a patient with or without IIBD [13], is based on the following observations.

**Other microorganisms are known causes of colorectal cancer**

*Schistosoma mansoni* and *Schistosoma japonicum* cause a percentage of colorectal cancers in countries where the respective *Schistosoma* species are endemic [14–16].
A particular lesion, goblet cell hyperplasia, is the little-recognized initial pathologic lesion of sporadic colorectal cancer, ulcerative colitis and Crohn’s disease

In 1969, Filipe and colleagues first described the histopathologic components of transitional mucosa [17–19], which will subsequently be referred to as “goblet cell hyperplasia” or the “goblet cell hyperplasia lesion” (see Additional file 1):

1. The actual goblet cell hyperplasia, simply an increase in the number of goblet cells lining the colonic crypts.
2. The hyperplastic goblet cells are hypertrophic, longer and plumber than normal.
3. The crypts lined by hyperplastic goblet cells are either longer and wider or shorter and wider than normal.

Other authors emphasized one additional feature of transitional mucosa, the greatly increased amount of extracellular mucus coating the lesion produced by the hypertrophic and hyperplastic goblet cells [20, 21].

Beginning in 1991, two groups published their gross and histologic tangential (parallel to the mucosal surface) visualization of transitional mucosa, noticing the crypts were wider than normal but not that they were lined predominantly or exclusively by goblet cells, and called their lesion “aberrant crypt foci,” which is merely the goblet cell hyperplasia lesion in cross section [22–25].

In 2003, Torlakovic and colleagues [26] redefined the “hyperplastic” polyp as a serrated polyp and split the former hyperplastic polyp into two categories, the microvesicular type serrated polyp and the goblet cell type serrated polyp. They recognized that their goblet cell type serrated polyp is the precursor of the microvesicular type serrated polyp and noted its similarity to transitional mucosa, but they did not realize that it is the identical lesion as transitional mucosa [26].

Goblet cell hyperplasia is the rarely recognized initial pathologic lesion of Crohn’s disease and therefore of Crohn’s disease-associated intestinal cancers. Van Patter and colleagues’ 1954 treatise on regional enteritis [27] described goblet cell hyperplasia as follows:

The epithelium of the small bowel normally contains a variable number of secreting units – the goblet cells. In the vicinity of the lesions, the number of goblet cells was increased enormously, frequently to the point of complete replacement of other epithelial elements [27].

They speculated that whatever caused Crohn’s disease was the cause of the observed goblet cell hyperplasia:

There is some evidence to suggest that the etiologic agent is to be found in the fecal stream and that it makes its first appearance in the proximal portion of the small bowel...If this agent resides in the fecal stream it may exert its influence on the normal epithelial cells in the region of the future lesion, causing them to be replaced by goblet cells [27].

A sparse literature discusses goblet cell hyperplasia and its prominent extracellular mucus component as major pathologic features of Crohn’s disease [28, 29] and as the precursor lesion of epithelial dysplasia and therefore of Crohn’s disease-associated intestinal cancers, calling the lesion hyperplastic-like mucosal change [30].

Described as “epithelial hyperplasia,” “metaplastic changes,” “goblet cell rich epithelium” or “hypermucinous mucosa,” more subtle but more extensive goblet cell hyperplasia has occasionally [31–35] been recognized as the precursor of dysplasia and colorectal cancer in ulcerative colitis. A single article describes goblet cell hyperplasia in ulcerative colitis as such and documents its uniform presence in ulcerative colitis-affected colons with dysplasia [32].

Known as “transitional mucosa,” goblet cell hyperplasia is the precursor of dysplasia and adenomas [36] in the classical colorectal cancer pathway [37]. Transitional mucosa lines the stalks of pedunculated polyps [38, 39], forms the bases of tubular and villous adenomas [38, 39] and surrounds colorectal carcinomas [18, 19, 40, 41]. Transitional mucosa is a major component of the field cancerization theory in colorectal cancer [42].

Known as the “goblet cell type serrated polyp” [26, 43], goblet cell hyperplasia is the precursor lesion of the microvesicular type serrated polyp [26] and therefore of the sessile serrated adenoma [43] – serrated dysplasia [44] – serrated carcinoma [45] serrated colorectal cancer pathway [46]. The “transitional polyp” [21, 47] has rarely been recognized as the precursor lesion in both classical and serrated colorectal cancer pathways [48].

Of course, dysplasia and colorectal cancer develop from the goblet cell hyperplasia lesion seen in cross section, aberrant crypt foci, by either [49] the classical [22–25, 36, 50–52] or serrated [49] pathways.

Known by its alternative names, including the recently rediscovered “flat serrated change” [53] or “serrated epithelial changes” [54–56], goblet cell hyperplasia is the precursor of flat and elevated dysplasia [57] and dysplasia-associated lesions or masses [58] in IIBD-associated intestinal cancers as well as of classical adenomas in IIBD patients [59–62]. Like sporadic colorectal cancer patients, IIBD patients develop colorectal cancer by the classical or serrated pathways [63, 64]. Like in IIBD patients, the flat dysplasia (“flat adenoma”) – flat carcinoma pathway occurs in sporadic colorectal cancer patients [52, 65–67].
Pathogenic microorganisms are the only natural cause of intestinal goblet cell hyperplasia

While small intestinal goblet cell hyperplasia results from azoxymethane administration [68] and massive small intestinal resection [69], pathogenic bacteria and parasites are the only natural causes of intestinal goblet cell hyperplasia [70, 71], including the protozoan parasite Giardia lamblia/intestinalis [72], the helminthes Trichinella spiralis [73] and Nippostrongylus brasiliensis [74, 75], the bacteria Yersinia enterocolitica [76] and various Shigella species [77].

Goblet cell hyperplasia results from infection with the human pathogenic helminths Schistosoma mansoni and Schistosoma japonicum [78, 79], where it has been specifically referred to as “transitional mucosa” [14] and is the precursor lesion of dysplasia and colorectal carcinoma in infected patients [14–16].

Since colonic type goblet cell hyperplasia caused by the human pathogenic bacterium Helicobacter pylori occurs in the stomach, where colonic type goblet cells are not normally present, it is called incomplete intestinal (colonic) metaplasia and is the immediate precursor lesion of gastric cancer [80, 81].

Goblet cell hyperplasia is the rarely recognized histopathologic feature of the resolving phase of the murine pathogenic bacterium Citrobacter rodentium (Fig. 1b) [82, 83], which is an animal model of IIBD [84], epithelial-mesenchymal transition and tumorigenesis [85, 86]. Citrobacter rodentium’s effects on and interactions with goblet cells have been documented to cause the more well-known pathologic features of transmissible murine colonic hyperplasia, including the elongation of crypts, “depletion” of the mucus granule compartment and variable shapes of the goblet cells (Fig. 1a) [87, 88].

MAP causes goblet cell hyperplasia

A single article demonstrates MAP flooding into and hovering in clouds above human intestinal goblet cells [89]. MAP attaches to and invades bovine intestinal goblet cells [90, 91] and causes acute [91] and chronic [92] goblet cell hyperplasia.

The persistence of a microorganism within infected tissues is one way that microorganism causes cancer, with proposed carcinogenic mechanisms including cycles of chronic inflammation and repair, chronic hyperplasia (‘proliferation’) which destabilizes DNA and suppression of apoptosis [2, 3].

MAP has been accidentally discovered in the intestines of patients with sporadic colorectal cancer

A follow-up to an article demonstrating that MAP organisms are small and require oil immersion (×100 oil immersion objective or ×1000 total magnification) to be identified by light microscopy [93] identified Mycobacterium avium organisms (of which MAP is a subspecies) in two of three control patients with sporadic colorectal cancer [94].

Conclusion: The possibility that MAP causes colorectal cancer is a testable hypothesis

MAP organisms may be concentrated [95] in the following locations:

1. in the extracellular mucus that is a prominent component of the goblet cell hyperplasia lesion and mucinous and serrated carcinomas, and comprises the “mucus cap” [96, 97] or “coat” [98] of sessile serrated adenomas, contravening current recommendations [43, 98] to carefully wash off this prominent histopathologic feature.
2. within the hypertrophic apical granule compartment of the hyperplastic goblet cells lining the goblet cell hyperplasia lesion.
3. in the lamina propria and submucosa of the goblet cell hyperplasia lesion and adenomas.
4. within the tumor stroma of colorectal cancers.

MAP can also be identified in humans by culture, polymerase chain reaction and antibody evaluations of tissue, blood and stool [99–107].

Additional file

Additional file 1: Descriptions and illustrations of the goblet cell hyperplasia lesion. The supplementary file discusses the descriptions and illustrations of the goblet cell hyperplasia lesion found in some of the references in the main text. (DOC 200 kb)

Abbreviations
IIBD: Idiopathic inflammatory bowel disease; H&E: Hematoxylin and eosin; MAP: Mycobacterium avium subspecies paratuberculosis; PAS: Periodic Acid-Schiff

Acknowledgements
My research would not be possible without the assistance of librarians past (Sandy Keno, Gail Leong and Kathryn Kane) and present (Dr. Beth Hill) at the Providence Sacred Heart Medical Center and Children’s Hospital’s Health Sciences Library in Spokane, Washington, now part of the Providence Library system, as well as the other libraries that participate in the FreeShare Library group within the Docline National Network of Libraries of Medicine. Dr. Bruce Vallance very kindly provided photographs for Fig. 1. Thank you to Judi Heidel of Perfectly Clear Copyediting Services for editing this paper. Dedicated to the memory of Cyrus E. Rubin, MD, mentor and friend.

Funding
None

Availability of data and materials
Not applicable

Authors’ contributions
Not applicable

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The author declares that no competing interests exist.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 29 June 2017 Accepted: 12 December 2017
Published online: 04 January 2018

References
1. Kuper H, Adami HO, Trichopoulos D. Infections as a major preventable cause of human cancer. J Intern Med. 2000;248:171–83.
2. Lax AJ, Thomas W. How bacteria could cause cancer: one step at a time. Trends Microbiol. 2002;10:293–9.
3. Vennervald BJ, Polman K. Helminths and malignancy. Parasite Immunol. 2009;31:886–96.
4. Clarke CJ. The pathology and pathogenesis of paratuberculosis in ruminants and other species. J Comp Pathol. 1997;116:217–61.
5. Kuenstner JT, Naser S, Chamberlin W, Borody T, Graham DY, McNees A, Hermon-Taylor J, Hermon-Taylor A, Dow CT, Thayer W, et al. The consensus from the Mycobacterium Avium Ssp. paratuberculosis (MAP) conference 2017. Front Public Health. 2017;5:208.
6. Davis WC, Kuenstner JT, Singh SV. Resolution of Crohn’s (Johnie’s) disease with antibiotics: what are the next steps? Expert Rev Gastroenterol Hepatol. 2017;11:393–396.
7. Pierce ES. Ulcerative colitis and Crohn’s disease: is Mycobacterium Avium subspecies paratuberculosis the common villain? Gut Pathog. 2010;2:21.
8. Kim ER, Chang DK. Colorectal cancer in inflammatory bowel disease: the risk, pathogenesis, prevention and diagnosis. World J Gastroenterol. 2014;20:9872–81.
9. Choi PM, Zelig MP. Similarity of colorectal cancer in Crohn’s disease and ulcerative colitis: implications for carcinogenesis and prevention. Gut. 1994;35:950–4.
10. Lombard JE, Gardner IA, Jafarzadeh SR, Fossler CP, Harris B, Capsel RT, Wagner BA, Johnson WO. Hind-Hevel level of Mycobacterium Avium subsp. paratuberculosis infection in United States dairy herds in 2007. Prev Vet Med. 2013;108:234–8.
11. Rhodes G, Henrys P, Thomson BC, Pickup RW. Mycobacterium Avium subspecies paratuberculosis is widely distributed in British soils and waters: implications for animal and human health. Environ Microbiol. 2013;15:2761–74.
12. King DN, Donohue MJ, Vesper SJ, Villegas EN, Ware MW, Vogel ME, Furlong EF, Kolpin DW, Glassmeyer ST, Pfaller S. Microbial pathogens in source and treated waters from drinking water treatment plants in the United States and implications for human health. Sci Total Environ. 2016;562:987–95.
13. Rhodes JM. Unifying hypothesis for inflammatory bowel disease and associated colon cancer: sticking the pieces together with sugar. Lancet. 1996;347:40–4.
14. Ming-Chai C, Chi-Yuan C, Pei-Yu C, Jien-Chun H. Evolution of colorectal cancer in schistosomiasis: transitional mucosal changes adjacent to large intestinal carcinoma in colectomy specimens. Cancer. 1980;46:1661–75.
15. Madbouly KM, Senagore AJ, Mukerjee A, Hussien AM, Shehata MA, Navine P, Delaney CP, Fazio WW. Colorectal cancer in a population with endemic Schistosoma Mansoni: is this an at-risk population? Int J Coler Dis. 2007;22:175–81.
16. Wang M, QB W, He WB, Wang QZ. Clinicopathological characteristics and prognosis of schistosomal colorectal cancer. Color Dis. 2016;18:1005–9.
17. Filipe MJ. Value of histochemical reactions for mucosubstances in the diagnosis of certain pathological conditions of the colon and rectum. Gut. 1969;10:577–86.
18. Filipe MI, Branfoot AC. Abnormal patterns of mucus secretion in apparently normal mucosa of large intestine with carcinoma. Cancer. 1974;34:282–90.
19. Geaves P, Filipe MI, Branfoot AC. Transitional mucosa and survival in human colorectal cancer. Cancer. 1980;46:764–70.
20. Sundblad AS, Paz RA. Mucinous carcinomas of the colon and rectum and their relation to polyps. Cancer. 1982;50:2504–9.
21. Heilmann KL, Schmidbauer G, Schyma G. The transitional polyp of the colorectal mucosa. Pathol Res Pract. 1987;182:690–3.
22. Pretlow TP, Barrow BJ, Ashton WS, O’Riordan MA, Pretlow TG, Jurcisek JA, Stellato TA. Aberrant crypts: putative preneoplastic foci in human colonic mucosa. Cancer Res. 1991;51:1564–7.
23. Pretlow TP, O’Riordan MA, Pretlow TG, Stellato TA. Aberrant crypts in human colonic mucosa: putative preneoplastic lesions. J Cell Biochem Suppl. 1992;16G:55–62.
24. Roncucci L, Stamp D, Medline A, Cullen JB, Bruce WR. Identification and quantification of aberrant crypt foci and microadenomas in the human colon. Hum Pathol. 1991;22:287–94.
25. Roncucci L, Medline A, Bruce WR. Classification of aberrant crypt foci and microadenomas in human colon. Cancer Epidemiol Biomarkers Prev. 1991;1:57–60.
26. Torlakovic E, Skovlund E, Snover DC, Torlakovic G, Nesland JM. Morphologic reappraisal of serrated colorectal polyps. Am J Surg Pathol. 2003;27:65–81.
27. Van Patter WN, Bargen JA, Dockerty MB, Feldman WH, Mayo CW, Waugh JM. Regional enteritis. Gastroenterology. 1954;26:437–450.
28. Dvorak AM, Connell AB, Dickerin GR. Crohn’s disease: a scanning electron microscopic study. Hum Pathol. 1979;10:165–77.
Kuramoto S, Oohara T. Minute cancers arising de novo in the human large intestine. Cancer. 1983;51:213–8.

Johnson DH, Khanna S, Smyrk TC, Batts KP, Weinberg DI, McCabe RP. Mo1705 Flat Serrated Epithelial Changes: Does It Predict the Development of Colonic Mucosal Dysplasia in Inflammatory Bowel Disease? Gastroenterology. 2013;145:11.

Parran A, Kho JW, Badamas J, Giardiello FM, Montgomery EA, Lazarev M. 42 Serrated Epithelial Changes Are Associated With Colorectal Dysplasia in Inflammatory Bowel Disease. Gastroenterology. 2013;145:11.

Parian A, Kho J, Limkertkai BN, Eluri S, Rubin DT, Brant SR, Ha CY, Bayless TM, Giardiello F, Hart, J et al: Association between serrated epithelial changes and colorectal dysplasia in inflammatory bowel disease, Gastrointest Endosc. 2016;84:87–95 e81.

Matsuki K, Chen ZE, Rao MS, Yang GY. Dysplastic lesions in inflammatory bowel disease: molecular pathogenesis to morphology. Arch Pathol Lab Med. 2013;137:336–50.

Blackstone MQ, Riddell RH, Rogers BH, Levin B. Dysplasia-associated lesion or mass (DALM) detected by colonoscopy in long-standing ulcerative colitis: an indication for colectomy. Gastroenterology. 1981;80:366–74.

Torres C, Antoniolli D, Ozde RD. Polypoid dysplasia and adenomas in inflammatory bowel disease: a clinical, pathologic, and follow-up study of 89 polyps from 59 patients. Am J Surg Pathol. 1998;22:275–84.

Engels-Jeid J, Farfay AE, Ozde RD. Polypectomy may be adequate treatment for adenoma-like dysplastic lesions in chronic ulcerative colitis. Gastroenterology. 1999;117:1288–94. discussion 1488–1291.

Quinn AM, Farfay AE, Naini BV, Cerdas S, Coulous J, Li Y, Khor T, Ozde RD. Polygodic is adequate treatment for adenoma-like dysplastic lesions (DALMs) in Crohn’s disease. Inflamm Bowel Dis. 2013;19:1186–93.

Neumann H, Veth M, Langner C, Neurath MF, Mucins and colorectal cancer. Front Mol Carcinol. 2017;6:149–56.

Gebes K, De Hertogh G, Bischos P, Gebes K. Flat adenomas, significance, detection, treatment. Ann Gastroenterol. 2010;23:266–9.

Naravadi V, Gupta N, Early D, Jonnalagadda S, Wani SB, Saddam S, Sharma P, Edmundowicz SA, Bansal A, Rostogi A. Preservation of advanced histological features and synchronous neoplasia in patients with flat adenomas. Gastrointest Endosc. 2016;83:795–9.

Shen J, Gibson JA, Chute S, Khurma H, Farfay AE, Levine J, Burakoff R, Cerdas S, Qazi T, Hamilton M, et al. Clinical, pathologic, and outcome study of hyperplastic and sessile serrated polyps in inflammatory bowel disease. Hum Pathol. 2015;46:1548–56.

Geboes K, De Hertogh G, Bispohs R, Geboes K. Flat adenomas, significance, detection, treatment. Ann Gastroenterol. 2010;23:266–9.

Naravadi V, Gupta N, Early D, Jonnalagadda S, Wani SB, Saddam S, Sharma P, Edmundowicz SA, Bansal A, Rostogi A. Preservation of advanced histological features and synchronous neoplasia in patients with flat adenomas. Gastrointest Endosc. 2016;83:795–9.

Cheng L, Lai MD. Aberrant crypt foci as microscopic precursors of colorectal cancer. World J Gastroenterol. 2003;9:264–9.

Rosenberg DW, Yang S, Pleau DC, Greenspan EJ, Stevens RG, Rajan TV, Arora S, Ginnetti RA, Neumann H, Riddell RH, Mucins and colorectal cancer. World J Gastroenterol. 2011;17:3838–41.

Shinoka T, Kagi W, Ohashi T, Kondo H, Kondo H, Kato M, Tajiri N, Takahashi M, Murakami S, Itoh T, et al: Colorectal dysplasia and inflammation and inflammation and inflammation. Cancer Res. 2007;67:3551–7.

Shinoka T, Kagi W, Ohashi T, Kondo H, Kondo H, Kato M, Tajiri N, Takahashi M, Murakami S, Itoh T, et al: Colorectal dysplasia and inflammation and inflammation and inflammation. Cancer Res. 2007;67:3551–7.

Soga K, Yamauchi J, Kawai Y, Yamada M, Uchikawa T, Tegoshi T, Mutsfui S, Yoshikawa T, Arisono N. Alteration of the expression profiles of mucous membra and goblet cells in the expulsion of adult Trichinella spiralis. Parasitology. 2008;135:655–70.

Kuroda K, Yamauchi J, Kawai Y, Yamada M, Uchikawa T, Tegoshi T, Mutsfui S, Yoshikawa T, Arisono N. Alteration of the expression profiles of mucous membra and goblet cells in the expulsion of adult Trichinella spiralis. Parasitology. 2008;135:655–70.

Kato H, Kato A, Yamasaki T, Tanabe M, Takeuchi T, Ikawa T, Kawanomoto K, Furusawa T, Ohtani M, Fuji H, Kayasu S. Intrahepatic bile ducts in the liver of a patient with JTH2 cytokines and adipose tissue-associated c-kit+/+c1a+/+ lymphoid cells. Nature. 2010;463:540–4.
cells and mucus: morphometrics, histochemistry, and biochemistry. Gut. Microbiol. 1991;32:1131–8.

77. Yang JY, Lee SN, Chang SY, Ko HJ, Ryu S, Kweon MN. A mouse model of shigellosis by intraperitoneal infection. J Infect Dis. 2014;209:203–15.

78. Manillier KS, Michels C, Smith EM, Fick LC, Leea M, Dewals B, Hornshell W, Bormbacher F. IL-4/IL-13 independent goblet cell hyperplasia in experimental helminth infections. BMC Immunol. 2008;9:11.

79. Couto JL, Ferreira Hda S, da Rocha DB, Duarte ME, Assuncao ML, Coutinho Ede M. Structural changes in the jejunal mucosa of mice infected with Schistosoma mansoni, fed low or high protein diets. Rev Soc Bras Med Trop. 2002;35:601–7.

80. Corea P, Houghton J. Carcinogenesis of helicobacter pylori. Gastroenterology. 2007;133:659–72.

81. Semino-Mora C, Doi SQ, Marty A, Simko V, Carlstedt I, Dubois A. Intracellular and interstitial expression of helicobacter pylori virulence genes in gastric precancerous intestinal metaplasia and adenocarcinoma. J Infect Dis. 2003; 187:1165–7.

82. Barthold SW, Coleman GL, Jacoby RO, Livestone EM, Jonas AM. Transmissible murine colonic hyperplasia. Vet Pathol. 1978;15:225–36.

83. Bergstrom KS, Morampudi V, Chan JM, Bhinder G, Lau J, Yang H, Ma C, Huang T, Ryz N, Sham HP, et al. Goblet cell derived RELM-beta recruits CD4 + T cells during infectious colitis to promote protective intestinal epithelial cell proliferation. PLoS Pathog. 2015;11:e1005108.

84. Higgins LM, Frankel G, Douc G, Dougan G, MacDonald TT. Citrobacter rodentium infection in mice elicits a mucosal TH1 cytokine response and lesions similar to those in murine inflammatory bowel disease. Infect Immun. 1999;67:3021–8.

85. Chandrakesan P, Roy B, Jakkula LU, Ahmed I, Ramamoorthy P, Tawfik O, Higgins LM, Frankel G, Douce G, Dougan G, MacDonald TT. Citrobacter rodentium infection in surgically isolated bovine ileal segments. Clin Vac Immunol. 2013;20:156

86. Chandrakesan P, Roy B, Jakkula LU, Ahmed I, Ramamoorthy P, Tawfik O, Higgins LM, Frankel G, Douce G, Dougan G, MacDonald TT. Citrobacter rodentium infection in surgically isolated bovine ileal segments. Clin Vac Immunol. 2013;20:156

87. Chandrakesan P, Roy B, Jakkula LU, Ahmed I, Ramamoorthy P, Tawfik O, Higgins LM, Frankel G, Douce G, Dougan G, MacDonald TT. Citrobacter rodentium infection in surgically isolated bovine ileal segments. Clin Vac Immunol. 2013;20:156

88. Chan JM, Bhinder G, Sham HP, Ryz N, Huang T, Bergstrom KS, Vallance BA. CD4 + T cells drive goblet cell depletion during Citrobacter rodentium infection. Infect Immun. 2013;81:4649–58.

89. Goyal L, Livneh-Kol A, Gonen E, Yagel S, Rosenshine I, Shigel NY. Mycobacterium Avium paratuberculosis invades human small-intestinal goblet cells and elicits inflammation. J Infect Dis. 2009;199:350–6.

90. Schleif PM, Buerger CD, Davis JK, Williams E, Monif GR, Davidson MK. Attachment of Mycobacterium Avium subspecies paratuberculosis to bovine intestinal organs cultures: method development and strain differences. Vet Microbiol. 2005;108:271–9.

91. Khare S, Nunes JS, Figueredo JF, Lawhon SD, Rossetti CA, Gull T, Rice-Ficht AC, Adams LG. Early phase morphological lesions and transcriptional responses of bovine ileum infected with Mycobacterium Avium subspecies paratuberculosis. Vet Pathol. 2009;46:717–28.

92. Charavaryamath C, Gonzalez-Cano P, Fries P, Gomis S, Doig K, Scruten E, Potter A, Nappeer S, Sriebel PJ, Host responses to persistent Mycobacterium Avium subspecies paratuberculosis infection in surgically isolated bovine ileal segments. Clin Vac Immunol. 2013;20:156–65.

93. Jeyanathan M, Alexander DC, Turenne CY, Girard C, Behr MA. Evaluation of in situ methods used to detect Mycobacterium Avium subspecies paratuberculosis in samples from patients with Crohn's disease. J Clin Microbiol. 2006;44:2942–50.

94. Jeyanathan M, Boutsos-Tadros O, Radhi J, Semnet M, Bittor A, Behr MA. Visualization of Mycobacterium Avium in Crohn's tissue by oil-immersion microscopy. Microbes Infect. 2007;9:1567–73.

95. Pierce ES. Where are all the Mycobacterium Avium subspecies paratuberculosis in patients with Crohn's disease? PLoS Pathog. 2009;5:e1000234.

96. Lee EJ, Kim MJ, Chun SM, Jang SJ, Kim DS, Lee DW, Youk EG. Sessile serrated adenoma/polyps with a depressed surface: a rare form of sessile serrated adenoma/polyp. Diagn Pathol. 2015;10:75.

97. Pereyra L, Gomez EI, Gonzalez R, Fischer C, Eran GF, Torres AG, Corea L, Mella JM, Panigati GN, Luna P, et al. Finding sessile serrated adenomas: is it possible to identify them during conventional colonoscopy? Dig Dis Sci. 2014;59:3201–6.

98. Sweetser S, Smyrk TC, Sugumar A. Serrated polyps: critical precursors to colorectal cancer. Expert Rev Gastroenterol Hepatol. 2011;5:627–35.

99. Nazer SA, Chobrial G, Romero C, Valentine JF. Culture of Mycobacterium Avium subspecies paratuberculosis from the blood of patients with Crohn's disease. Lancet. 2004;364:1039–44.

100. Timms VJ, Daskalopoulos G, Mitchell HM, Neilian BA. The association of Mycobacterium Avium subspecies paratuberculosis with inflammatory bowel disease. PLoS One. 2016;11:e0148731.

101. Singh AV, Singh SV, Malakria GR, Singh PK, Solal JS. Presence and characterization of Mycobacterium Avium subspecies paratuberculosis from clinical and suspected cases of Crohn's disease and in the healthy human population in India. Int J Infect Dis. 2008;12:190–7.

102. Banche G, Allizzond V, Sostegni R, Lavagna A, Bergallo M, Sidoti F, Daperno M, Rroca R, Cuffini AM. Application of multiple laboratory tests for Mycobacterium Avium Ssp. paratuberculosis detection in Crohn's disease patient specimens. New Microbiol. 2015;38:57–67.

103. Singh SV, Kumar N, Solal JS, Singh AV, Singh PK, Agrawal ND, Gupta S, Chaukey KK, Kumar A, Rawat KD. First mass screening of the human population to estimate the bio-load of Mycobacterium Avium subspecies paratuberculosis in North India. J Biol Sci. 2014;14:237.

104. Singh SV, Kuenstner JT, Davis WC, Agrawal N, Kumar N, Gupta S, Chaukey KK, Kumar A, Misri J, et al. Concurrent resolution of chronic diarrhea likely due to Crohn's disease and infection with Mycobacterium Avium paratuberculosis. Front Med. 2016;3:49.

105. Tuci A, Tonon F, Castellani L, Sartina A, Roda G, Marocchi M, Caponi A, Munari A, Rosati G, Ugozoli G, et al. Fecal detection of Mycobacterium Avium paratuberculosis using the IS900 DNA sequence in Crohn's disease and ulcerative colitis patients and healthy subjects. Dig Dis Sci. 2011;56:257–62.

106. Feller M, Huxler K, Stephan R, Altpeter E, Shang A, Furrer H, Pfyffer GE, Jemmi T, Baumgartner A, Egger M. Mycobacterium Avium subspecies paratuberculosis and Crohn's disease: a systematic review and meta-analysis. Lancet Infect Dis. 2007;7:607–13.

107. Abubakar I, Myhill D, Aliyu SH, Hunter PR. Detection of Mycobacterium Avium subspecies paratuberculosis from patients with Crohn's disease using nucleic acid-based techniques: a systematic review and meta-analysis. Inflamm Bowel Dis. 2008;14:401–10.