Journal of Infectious Diseases & Immune Therapies

Commentary Article

A SCITECHNOL JOURNAL

The Paradigms of Causation for Crohn's Disease

Monif GRG*

Abstract

For almost two decades, the paradigms of autoimmunity and *Mycobacterium avium* subspecies *paratuberculosis* (MAP) infection have unsuccessfully attempted to establish one or the other as the etiology of Crohn's disease. The data that defines and excludes both these paradigms are resynthesized by a third paradigm in which Crohn's disease is projected as an immune-mediated disease whose antigen triggers reside with the antigenic array of MAP.

Keywords

Mycobacterium avium subspecies *paratuberculosis*; Crohn's disease; Hruska postulate; Autoimmunity

Commentary Report

Identification of the events that combine to produce disease introduces potential points for therapeutic intervention and prevention. For nearly two decades, a controversy has raged over the pathogenesis of Crohn's disease. Two divergent theories of causation have been advanced: autoimmune and infectious due to *Mycobacterium avium* subspecies *paratuberculosis* (MAP). The foundation for the autoimmunity paradigm resides in the demonstrated ability of immunosuppressants to achieve time-limited mucosal healing and to abort symptomology. However, when the autoimmune paradigm is required to address the questions embedded within the natural history of Crohn's disease, (i.e.

- Why the sudden appearance of a new disease entity?
- Why the epidemic growth of the disease on a global level?
- Why its rarity within economically disadvantaged countries?
- Why breast feeding prevents the subsequent development of Crohn's),

the Autoimmune theory is devoid of plausible answers to these facts and leaves unaddressed its failure to achieve life-long remissions. What therapeutic trials with steroids and biologics have established is that, in some way, the pathogenesis of Crohn's disease involves down regulation of the host's immune system. Like the autoimmune paradigm, the foundation of the infectious disease postulate's strongest evidence for causation is derived from evidence of association and outcome of clinical trials. A large, but not conclusive, body of circumstantial evidence has linked MAP with Crohn's disease.

***Corresponding author:** Gilles RG Monif, Infectious Diseases Incorporated, Bellevue, NE, United States, Tel: 1-402-618-0963; E-mail: gmonif@AOL.com

Received: December 02, 2017 **Accepted:** December 16, 2017 **Published:** December 28, 2017

The disease in cattle (Johne's disease) caused by MAP and Crohn's disease share a common target organ, the gastrointestinal tract. Epidemiologically, MAP infected animals may shed the mycobacterium into their biological fluids: specifically milk [1-3]. MAP is not killed by pasteurization [4-6]. Viable MAP has been both demonstrated and cultured from milk, infant formula, powdered milk, and other milk-based products [7-9]. MAP readily crosses species lines. MAP receptors line the entire small bowel [10]. Milk and related milk-based food items constitute the zoonotic vehicle by which a bovine pathogen accesses human hosts. Individuals whose genetic composition allows enhanced mycobacterium replication have a higher prevalence of Crohn's disease than that projected for the general population. MAP DNA is more likely to be identified in diseased tissue and blood from individuals afflicted with Crohn's disease than healthy individuals [11-15]. In immunocompromised individuals or individuals with markedly enhanced genetic susceptibility, MAP can cause infection. In these situations MAP can be identified by special stains and cultured using standard technology. This is not true for Crohn's disease. The strongest argument for an infectious etiology is derived from isolated case studies and small clinical trials with a limited selection of anti-microbials that have produced a number of prolonged remissions, bordering upon "cures" [16-19]. In doing so, the observation leaves unanswered the question as to why do these selective drugs achieve apparent efficacy when other compounds effective against *M. tuberculosis* were ineffective?

The infectious disease paradigm falls short of becoming an accepted medical pseudo-truth [20]. If MAP replication were the cause of Crohn's disease, use of biologics and steroids would enhance the organism's pathogenicity. Reactivation of *Mycobacterium tuberculosis* is a recognized complication of therapy with biologics. Instead of mucosal healing, exacerbating of signs and symptoms would occur. When infection is due to ingestion of milk containing a virulent mycobacterium, i.e.. *Mycobacterium bovis*, gastrointestinal disease frequently ensues. In these situations, *Mycobacterium bovis* is readily demonstrated with special stain and cultured. This is not the case with Crohn's disease. Despite the presence of MAP DNA in Crohn's diseased tissue, both special stains for acid-fast bacilli and conventional culture isolation technology for mycobacteria are unable to identify or isolate MAP [21]. The occasional ability to demonstrate MAP DNA in healthy small bowel samples and from white blood cells of unaffected individuals further weakens the foundation of the infectious disease paradigm [11,14]. What can be argued is that given the widespread prevalence of MAP in the U.S. food supply, the probability of one having had contact with viable MAP is a function of diet and time; yet the correlation between human MAP infection and Crohn's disease was not supportive of causation. The occasional demonstration of MAP DNA in a given control subject identifies an individual with current, active subclinical infection.

While providing a theoretical explanation for the spread, the infectious disease paradigm does not adequately address why the epidemic spread of a new disease, why breast feeding extends relative protection against the future development of Crohn's disease [22-28], and why there is the near absence of Crohn's disease in economically stressed populations [29-32]. In third world and economically stressed populations, breast milk is the principle source

of affordable infant nutrition. In 2015, a third paradigm of causation for Crohn's disease was proposed that united the autoimmunity and infectious disease paradigms [33]. The Hruska Postulate states that pathogenesis of Crohn's disease is the consequence of two distinct interactions between MAP with the host's immune system. First, adequate MAP infectious challenge had to occur in the absence of acquired immunity. Unlike *M. bovis*, MAP is a relatively weak mycobacterium. For Johne's disease to develop, infection needs to be ongoing for months or years. It is argued that inherent immunity is capable of aborting continued mycobacterium replication: but, at a price, loss of immunological tolerance to MAP's antigenic array. The immune system's pro-inflammatory response to MAP's antigenic array becomes fixed within immunological memory. The third paradigm draws heavily from experiments in nature that document the importance of acquired immunity in arresting replication of organisms whose containment is primarily a function of cellular immunity, i.e. rubella, cytomegaloviruses, Herpes simplex viruses, *M. tuberculosis*. In the absence of acquired or ineffective immunity, the pathological consequences documented are markedly exaggerated in comparison to those observed when the same infections occur in the presence of intact immunity [34,35]. Acquired immunity is believed to be effectively functional late in the neonatal period. This fact puts into value the epidemiological studies indicating that breastfeeding confers a significant degree of protection against the future development of Crohn's disease. Indirectly supportive of this concept is the paucity of individuals afflicted with Crohn's disease in economically stressed populations where breast milk is the principle source of infant nutrition. It is argued that, in the absence of acquired immunity, MAP infection may so challenge inherent immunity that the resultant pro-inflammatory response required to abort continued mycobacterium replication becomes fixed within immunological memory. Immunological tolerance that would normally be anticipated to manifest upon re-exposure to MAP does not occur. In the immediate neonatal period, mucosal immunity is compromised by the relative absence of polysaccharide A (PSA) produced by the gastrointestinal microbiota. PSA is thought to promote mucosal tolerance by promoting the differentiation of functional Treg cells. What is theorized is that MAP challenge when Fox3+ Treg population is low results in fixation of the elicited pro-inflammatory response. For the anti-MAP cytokine cascade to be elicited requires re-introduction of the trigger antigens in insulated populations where disease development could be documented, The establishment of potential for future induction of Crohn's disease is created by an infectious disease process. For fixation of the pro-inflammatory response to MAP's antigenic array to translate to disease status, requires an immune-mediated disease process. Population studies have shown that MAP became widespread among milk-producing domestic animals well in advance of the development of Crohn's disease within the population [5]. Frequent and dense antigen challenges by dead or viable MAP are the requisites required to ultimately overcome the regenerative capacity of the small bowel mucosa. The interval between neonatal MAP infection and onset of disease is theorized to be a function of the strength and frequency of these antigen challenges necessary to undermine mucosal integrity. Crohn's disease is an immune-mediated disease entity that become complicated by superimposed microbial invasion by the gastrointestinal microbiota.

Why the new disease? The failure to make MAP status a requisite on an animal's certificate of health has allowed MAP infected animals to be transported across state and national boundaries, introducing MAP infection into previously uninfected herds [36]. Today over 90% of U.S. dairy herds contain MAP infected animals. MAP infected animals have the potential to shed viable and non-viable organisms into their biological fluids: specifically milk. Milk protein being prominent within the diet of industrialized nations, MAP's antigenic array is now widely disseminated within their food sources.

Why the Crohn's disease epidemic? In 2005, 49% of 51 brands of infant formula, manufactured by 10 different producers, in seven different countries were demonstrated to contain MAP DNA [11]. The identification of MAP DNA and/or culture recovery of MAP from infant formula is well-documented [37-40]. The progressive abandonment of breast feeding and adoption of infant formula created the potential for a newborn infant to be infected by a sufficient MAP challenge so as to lose future immunological tolerance when re-exposed to MAP' antigenic array.

Why the effectiveness of some anti-mycobacterial drugs and not others? Polymerase chain reaction detection of MAP DNA in diseased tissues and white blood cells identifies spheroclastic forms of MAP. To be effective against spheroclasts, microbial therapy needs to be able to adversely affect ribosomal function. The spheroclastic forms of MAP are theorized to be the immunological templates that sustain the pro-inflammatory cytokine response to MAP's antigenic array. MAP antimicrobial drugs attack, not MAP as a pathogenic organism, but MAP in its spheroclastic as the immune template. Why don't infants die of neonatal acquired MAP infection? Any of the three variables can impact on outcome. Compared to *M. tuberculosis* or *M. bois*, MAP is a weak pathogen. In domestic animals, Johne's disease develops months to years after challenge dose. While MAP crosses species barriers readily, it does so at a price, the loss of virulence.

Summary

The integration of the three paradigms for the causation of Crohn's disease has produced a plausible pathogenesis that identifies therapeutic intervention points for the prevention and possible induction of permanent remission from Crohn's disease [40,41].

Crohn's disease has been labeled but never proven to be an autoimmune disease. The concept that, in the absence of acquired immunity, a pro-inflammatory response to a given antigen or antigens can become fixed within immunological memory opens to re-thinking other autoimmune diseases that have the classic tell: suppression of symptomology by biologics and steroids.

References

1. Hruska K, Pavlik I (2014) Crohn's disease and related inflammatory diseases: from a single hypothesis to one superhypothesis. Veterinarni Medicina 59: 583-630.
2. Ahrens P (2000) Detection of Mycobacterium avium subsp. paratuberculosis in milk from clinically affected cows by PCR and culture. Vet Microbiol 77:291-297.
3. Pinedo PJ, Williams JE, Monif GRG, Rae DO, Buergelt CD (2008) Mycobacterium paratuberculosis shedding into milk: association of ELISA seroreactivity with DNA detection in milk. Intern J Appl Res Vet Med 6: 137-144.
4. Ellingson JL, Anderson JL, Koziczkowski JJ, Radcliff RP, Sloan SJ, et al. (2005) Detection of viable Mycobacterium avium subspecies paratuberculosis in retail pasteurized whole milk by two culture methods and PCR. J Food Prot 68: 966-972.
5. Ayele WY, Svastova P, Roubal P, Bartos M, Pavlik I (2005) Mycobacterium avium subspecies paratuberculosis cultured from locally and commercially pasteurized cow's milk in the Czech Republic. Appl Envir Microbiol 71: 1210-1214.

6. Grant IR, Ball HJ, Rowe MT (2002) Incidence of Mycobacterium paratuberculosis in bulk raw and commercially pasteurized milk from approved dairy processing establishments in the United Kingdom. Appl Envir Microbiol 68: 2428-2435.
7. Hruska K, Baros M, Kralik P, Pavlik I (2005) Mycobacterium avium subspecies paratuberculosis in powdered infant milk: paratuberculosis in cattle-the public health problem to be solved. Veterinarni Medicina 50: 327-335.
8. Clark DL, Anderson JL, Kozickowski JJ, Ellingson JLE (2006) Detection of Mycobacterium avium subspecies paratuberculosis in cheese curds purchased in Wisconsin and Minnesota. Molecular Cell Probes 20: 197-202.
9. Ikonomoplus J, Pavilk I, Bartos M, Svastova P, Ayele WY, et al. (2005) Detection of Mycobacterium avium subspecies paratuberculosis in retail cheese from Greece and Czech Republic. Appl Environ Microbiol 71: 8935-9036.
10. Schleig PM, Buergelt CD, Davis JK, Williams E, Monif GRG, et al. (2005) Attachment of Mycobacterium avium subspecies paratuberculosis to bovine intestinal organ cultures; method development and strain differences. Vet Microbiol 108: 271-279.
11. Sechi LA, Scanu AM, Molicotti P, Molicotti P, Cannes S et. al (2005) Detection and isolation of Mycobacterium avium subspecies paratuberculosis from intestinal biopsies of patients with and without Crohn's disease in Sardinia. Am J Gastroenteriol 100:1529-1534.
12. Bull TL, McMinn EJ, Sidi-Boumedine K (2003) Detection and verification of Mycobacterium avium subspecies paratuberculosis in fresh ileocolonic mucosal biopsies from individuals with and without Crohn's disease. J Clin Micro 41: 2915-2923.
13. Autschback F, Eisold S, Hinz U (2005) High prevalence of Mycobacterium avium subspecies paratuberculosis IS900 DNA in gut tissue from individuals with Crohn's disease. Gut 54: 944-949.
14. Juste RA, Elguezabal N, Pavon A, Garrido JM, Sevilla I, et al. (2009) Association of Mycobacterium avium subspecies paratuberculosis DNA in blood and cellular and humeral immune response in inflammatory bowel disease patents and controls. J Infect Dis 13: 247-254 27.
15. Naser SA, Collins MT, Crawford JT, Valentine JF (2009) Culture of Mycobacterium avium subspecies paratuberculosis (MAP) from the blood of patients with Crohn's disease: A follow-up blind multi-center investigation. The Open Inflam J 2: 22-24.
16. Borody TJ, Bilkey S, Wettstein AR (2007) Anti-mycobacterial therapy in Crohn's disease heals mucosa with longitudinal scars. Dig Liver Dis 39: 438-444.
17. Shafran I, Burgeunder P (2008) Rifaximin for the treatment of newly diagnosed Crohn's disease: a case series. Am J Gastroenterol 103: 2158-2160.
18. Chamberlin W, Borody TJ, Campbell J (2011) Primary treatment of Crohn's disease: combined antibiotics taking center stage. Expert Rev Clin Immunol 7: 751-750.
19. Biroulet IP, Neut C, Colombel JF (2008) Anti-mycobacterium therapy in Crohn's disease: the end of a long controversy?. Prac Gastr 1: 11-17.
20. Monif GRG (2016) The Mycobacterium avium subspecies paratuberculosis dilemma. Bio Med 8: 2.
21. Van K, Kruiningen HJ (2011) Where are the weapons of mast destruction – Mycobacterium paratuberculosis in Crohn'sdisease. J Crohn's Colitis 5: 6338-6441.
22. Koloski NA, Bret L, Radford-Smith G (2008) Hygiene hypothesis in inflammatory bowel disease: A critical review of the literature. World J Gastrioenterol 14: 165-173.
23. Hornell A, Lagstrom H, Lande B, Thorsdottri I (2013) Breastfeeding, introduction of other foods, effect on health a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nut Res 57.
24. Klement E, Cohen RV, Boxman J, Joseph A, Reif S(2004) Breastfeed¬ing and risk of inflammatory bowel disease: a systemic review with meta-analysis. Am J Clin Nutr 80: 1342-1352.
25. Ip S, Chung M, Raman G, Chew P, Magula N, et al. (2007)Breastfeeding and maternal and infant health outcomes in developed countries, Evid Rep Technol Assess 153: 1-186
26. Hornell A, Lagstrom H, Lande B, Thorsdottri I (2013) Breastfeeding, intro¬duction of other foods effect on health a systematic literature review for the 5th Nordic Nutrition Recommendations. Food Nut Res 57.
27. Horta B, Bahl R, Martinez J, Victora C(2007) Evidence on the long term effects of breast feeding: systemic reviews and meta-analysis: World Health Organization, Geneva, Switzerland.
28. Barclay AR, Russell RK, Wilson ML, Gilmour WH, Satsangi J, et al. (2009) Systemic review: The role of breastfeeding in the development of pediatric inflammatory bowel disease. J Pediat 155: 421-426
29. Hruska K, Pavlik I (2014) Lower incidence of Crohn's disease in the Gypsy population of Hungary, the Maori population of New Zealand, Palestinians in Israel, Indians in Canada New Zealand.
30. Congilosi SM, Rosendale DE, Herman DL (1992) Crohn's disease – A rare disorder in American-Indians. West J Med 157: 682-683.
31. Odes HS, Locker C, Neumann L, Zirkin HJ, Weizman Z, et al. (1994) Epidemiology of Crohn's-disease in Southern Israel. M J Gastroenterol 89: 1859-1862.
32. Niv Y, Abuksis G, Fraser GM (1999) Epidemiology of Crohn's disease in Israel; A survey of Israeli kibbutz settlements. Am J Gastroenterol 94: 2961-2965.
33. Monif GRG (2015) The Hruska postulate of Crohn's disease. Med Hypoth 85: 878-881
34. Monif GRG (1969) Viral Infections of the Human Fetus. New York, Macmillan.
35. Monif GRG, Baker DA (2010) Infectious Diseases in Obstetrics and Gynecology. Partheon Publication, Informa, London, United Kingdom.
36. Monif GRG (2008) Certification of health for dairy cows. Paratuberculosis Newsletter: 13-14
37. Botsaris G, Swift BMC, Slana I, Liapi M, Christodoulou M, et al. (2016) Detection of viable Mycobacterium avium subspecies paratuberculosis in powdered infant formula by phage-PCR and confirmed by culture. Intern Food Microbiol 216: 91-94
38. Hassan KL, Ali AA (2012) Detection of Mycobacterium avium in milk powder using species specific PCR. Intern J Adv Sci Eng Tech 2: 115-119.
39. Hruska K, Slana I, Kralik P, Pavlik I (2011) Mycobacterium avium subsp. paratuberculosis in powdered infant milk: F57 competitive real time PCR. Vet Med 56: 226-230.
40. Monif GRG (2016) Translation of hypotheses to therapy in Crohn's disease. J Inflam Bowel Dis Disorder 2.
41. Monif GRG (2017) The enhanced role of diet in Crohn's disease. Adv Res Gastroenterol Hepatol 3.

Author Affiliations

Top

Infectious Diseases Incorporated, Bellevue, NE, United States; University of Florida, College of Veterinary Medicine, Gainesville, FL, United States