PROTAGONIST

Mycobacterium avium subspecies *paratuberculosis* is a cause of Crohn's disease

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Mycobacterium avium subspecies *paratuberculosis* (*MAP*) belongs to the *M avium* complex (MAC). MAC occur widely in the environment and inhabit normal animal and human intestine. MAC do not usually cause disease unless the host is debilitated. *MAP* is a pathogen and causes chronic inflammation of the intestine in many animals, including primates. *MAP* is closely related genetically to other MAC but possesses additional DNA such as IS*900*, the *hsp*X region, and the low %GC genetic element "GS", which are associated with its pathogenic phenotype. Further genetic elements related to pathogenicity may be revealed by the whole genome sequencing of *MAP* currently underway at the University of Minnesota. A recent review and extensive bibliography is available.[1]

MAP can colonise animals for years without causing disease. Chronic inflammation of the intestine (Johne's disease) may emerge after a long latent period, particularly when animals are stressed. Regional lymph nodes, liver, and lung are also involved. Histopathological features vary between animals and between different organs in the same animal.[2] *MAP* disease in animals ranges from pluribacillary to paucimicrobial, like leprosy in humans.[3] Terminal ileum and adjacent colon are commonly affected but segmental lesions in the small gut as well as colonic and rectal involvement also occur. Animals usually die of their infection and although perforation, stricture, and fistulation are not usually found in Johne's disease, these features occur in regional ileitis and colitis in dogs and pigs.[4 5] In experimental infection, *MAP* demonstrates a distinct tissue tropism and will cause chronic inflammation of the intestine if given intravenously or subcutaneously.[6 7]

With the opportunity to amplify in intensely farmed domestic livestock for over a century, *MAP* may have undergone an adaptive diversification. Genotyping of *MAP* has so far revealed 28 different strains, including those favouring a particular host such as sheep or cattle.[8] The herd prevalence of *MAP* infection in Western Europe and North America is in the range 21–70%.[9 10] Reinfection of new generations of young animals comes by passage of *MAP* from parent to offspring in milk, and from contaminated farm environments. Wildlife reservoirs contribute to environmental contamination.[11] Subclinically infected cows secrete *MAP* in their milk. *MAP* is more robust than *M tuberculosis* and can survive commercial pasteurisation conditions, commonly 72°C for 15 seconds.[1] *MAP* is present in retail pasteurised milk in Britain.[12] *MAP* survives in the environment and is probably conveyed to humans in water supplies.[1] Colonisation of the human intestine is cumulative. As with other mycobacteria, *MAP* may remain in a state of dormancy for years. Inflammatory disease develops in those who have an inherited or acquired susceptibility. Clinical disease may be triggered by intercurrent infection and by physical or psychological trauma.

In conventional media, *MAP* ranges from very slow growing to unculturable. *MAP* is more resistant to chemical and enzymatic lysis than other organisms.[1] It is present in the intestine of a proportion of normal subjects and can be detected in a majority of full thickness surgical samples of Crohn's disease gut if the correct culture and IS*900* polymerase chain reaction (PCR) methods are used.[13 14] *MAP* in Crohn's disease is present in low abundance and in a tough ZN negative form putatively coated with methylated and acetylated fucose.[1] *MAP* in humans can minimise immune recognition, and tests of antibody or cell mediated immunity using crude lysates of laboratory cultured *MAP* or other MAC, with some exceptions, have not distinguished general immune reactivity to MAC in Crohn's disease from that in normal subjects.[1] Highly significant immune recognition in Crohn's disease can be detected if molecules bearing *MAP* specific epitopes or those shared with other mycobacteria are used.[1 15]

MAP in Crohn's disease does not have a conventional mycobacterial cell wall. Pathogenic mechanisms and drug susceptibilities are not like tuberculosis. Intracellular *MAP* probably causes an immune dysregulation with transmural inflammation resulting from a perturbed immune response to leakage of enteric organisms and food residues into the gut wall. Without killing *MAP*, improvements following immune suppression or modulation, elemental diets, and antibiotics active against enteric bacteria are seldom lasting. *MAP* infection in animals is not eradicated by anti-tuberculosis drugs.[1] The failure of a lengthy controlled trial of rifampicin, isoniazid, and ethambutol to confer benefit[16] is consistent with what has long been known of the resistance of MAC to such agents in vitro and in vivo, and the non-bacillary phenotype of *MAP* in Crohn's disease. Crohn's disease is not healed by rifampicin and streptomycin which have broad activity against enteric organisms. Four outcome analyses have all shown that a substantial proportion of people with Crohn's disease improve with tissue healing when treated with a combination of

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Debate

Summary

- *Mycobacterium avium* subspecies *paratuberculosis* (*MAP*) is a member of the *M avium* complex (MAC). Unlike other MAC, *MAP* is a specific cause of chronic inflammation of the intestine of a broad range of histopathological types, affecting many species of animals including subhuman primates.
- *MAP* can colonise animals for years without causing clinical disease. Such subclinically infected animals shed *MAP* in their milk and onto pastures. The herd prevalence of subclinical *MAP* infection in Europe and North America is reported to be in the range 21–70%.
- *MAP* is present in retail pasteurised milk in Britain and is probably also conveyed in water supplies.
- *MAP* is harboured in the ileocolonic mucosa of a proportion of normal subjects and can be demonstrated in full thickness samples of gut wall in the majority of patients with Crohn's disease if the correct culture and PCR methods are used.
- As with other MAC, *MAP* infections are difficult to eradicate and the organisms are resistant to most standard anti-tuberculosis drugs. Rifabutin and clarithromycin are more active against *MAP* and about two thirds of patients with active Crohn's disease will go into remission with healing of the intestine when treated with a combination of these agents.

rifabutin and clarithromycin.[17–20] These drugs also have a broad antibacterial action but are more active against MAC and *MAP*. A controlled trial of rifabutin, clarithromycin, and clofazimine began in Australia in September 1999. Therapeutic *MAP* vaccines for immune mediated microbial clearance are needed.

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