



Commentary

Mycobacteria and Crohn's disease: The endless story

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“Happy is he who has been able to learn the causes of things”
Virgil, *Georgics* II: 490

Unfortunately Virgil would not have described us, researchers of today, as happy, because a definitive explanation of the causes of Crohn's disease (CD) is not known. In the opinion of some gastroenterologists, inflammatory bowel diseases form a mechanistic continuum that comprises, on one side Ulcerative colitis (UC) and, on the other side, CD [1]. But CD itself is not a single entity because wide variation is seen in anatomic location/extent, disease behaviour, intestinal and extraintestinal manifestations, and response to therapy.

Following the most accepted hypothesis, CD happens as a result of an inappropriate mucosal immune response to ubiquitous environmental factors such as intestinal microflora and alimentary antigens in genetically susceptible individuals [1]. The gene CARD15 or NOD2, associated with CD susceptibility, encodes an intracellular receptor involved in the host's innate immune system and the response to bacteria [2]. This discovery strengthens the prominent role of bacteria, among the other factors, in causing CD [3].

Many other genes are probably involved, and those recently discovered interfere with further inflammatory mechanisms. The interactions among different genes and various environmental factors account for the difference in location, disease behaviour, symptoms, and response to therapy. Given all these facts the hypothesis that CD is caused by a single environmental agent is pretty weak.

At this point one acceptable question that advocates of the mycobacterial hypothesis should ask is if it is possible that some cases classified as CD are mycobacterial disease. Many types of atypical mycobacteria exist: some of them are saprophytic; some others are possibly cause of disease in humans, particularly in immunosuppressed patients [4]. Among these

Mycobacteria, *Mycobacterium avium* subspecies *paratuberculosis* (MAP) is the pathogenic agent of Johne's disease (JD), a chronic illness in ruminants and other species characterized by granulomatous inflammation of the intestine. JD affects the terminal ileum and caecum, showing lesions similar to those of CD.

The MAP story starts in 1984 when a group of American researchers first isolated and cultivated, from the intestinal tissue of three patients with CD, one *Mycobacterium* similar to the agent of JD. The inoculation of this *Mycobacterium* in infant goat caused a form of CD-like lesions in this animal [5]. So far this experiment has not been repeated.

I try here to analyze from three different points of view the hypothesis that MAP is the cause of CD: (a) the presence of MAP in CD patients, (b) the epidemiological connection and (c) the response to anti-mycobacterial agents.

- (a) The identification of MAP in the tissue is problematic. MAP is a slow growing bacterium; MAP supporters cite this characteristic as the reason for the many unsuccessful attempts to cultivate it. Some studies have looked for evidence of the *Mycobacterium* in the CD tissues, through culture or DNA analysis, or for the presence of antibodies against this organism. Attempts at recovery of atypical Mycobacteria from cultures have met with variable success [6–8]. In one of the most important researches on gut mucosal flora no Mycobacteria were found in washed colonoscopic biopsies of 305 patients with bowel inflammation [9]. Moreover, since atypical Mycobacteria are ubiquitous, they can also be present as innocent bystanders passing through in the mucosal surface of CD and non-CD individuals. In fact, it is probable that MAP can be transmitted to humans through the ingestion of contaminated milk or water and, consequently, it could be found in the intestinal lumen. We know that atypical Mycobacteria can be invasive in AIDS patients. This property, as in the case of *Mycobacterium*

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tuberculosis, should be the requisite for being classified as pathogenic.

Studies of MAP antibodies have given conflicting results [10–12]. However, given that CD patients also have presence of antibodies against other bacteria and various antigens, it is scarcely credible that the presence of antibodies alone can be proof of MAP infection in CD.

- (b) From the epidemiological point of view, we know that CD is a disease frequent in developed countries and in cities and that there are no supportive data to suggest, for instance, that agricultural workers are particularly prone to it [13]. Moreover there is no increased prevalence among colleagues and spouses of CD patients, and there is a concordance of 44% in monozygotic twins in comparison with 3.9% in dizygotic [14]. All these data are in contrast with an infectious origin of CD.
- (c) The last point is devoted to the treatment of CD and its relationship with MAP hypothesis.

CD is essentially treated with immunosuppressive drugs.

Anti-TNF therapy is highly effective in inducing remission of active phases and has also shown to heal colonic and ileal lesions [15]. TNF plays a key role in the host response against tuberculosis [16] namely granuloma formation and control of disease [17]. Seventy cases of tuberculosis, 17 of them with disseminated disease, in close temporal association with the initiation of treatment with anti-TNF agents, have been reported [18].

These adverse events seem to be a strong argument against the role of MAP as infectious agent of CD, given that the anti-TNF infusion has never been associated with disseminated MAP in CD.

Moreover, many attempts have been made by using anti-mycobacterial therapy for obtaining and maintaining remission of CD. A meta-analysis of eight studies that have employed different combination of antimycobacterial drugs has shown that the treatment does not seem to be effective without a course of corticosteroids to induce remission [19]. Unfortunately, the healing of lesions, which is to be expected in a drug exerting a direct therapeutic effect on the causative agent of CD, was either not obtained [20] or not reported. The healing of lesions obtained in 56% of CD, as reported in the non-controlled study published in this Journal issue is, in fact, rather unusual [21]. Even in the case of frankly positive trials in future, we will have to exclude generic anti-bacterial and immunosuppressive effects of the employed antibiotics. But treating MAP infection by anti-bacterial agents could be unnecessary given a new possible role of MAP and other intestinal microorganism in IBD pathogenesis recently delineated.

A paper from England has suggested a link between MAP and antibody self-reactivity [22]. An anti-MAP immune response to the microbial peptide could elicit a host autoimmune response. In this case, the role of MAP could be that of triggering an autoimmune-mediated dysfunction in CD, independent of its role as pathogen. Other bacteria moreover

can be responsible of eliciting this autoimmune mechanism. This discovery renews the hypothesis of the role of MAP in CD combining the two prevalent hypotheses of CD pathogenesis: namely that it is both an autoimmune-mediated and also a bacterial disease.

Conflict of interest statement

None declared.

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