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Crohn's Disease: A Case for MAP Targeted Therapy

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Abstract

Crohn's disease (CD) is a severe intestinal inflammatory disease, for which currently no full cure is possible, and of which the pathogenesis is still not fully elucidated. Intestinal bacteria are thought to play a role in the onset, combined with environmental factors, immune factors, and genetic susceptibility of the host. However, we do not fully understand the nature of the disease yet, and as a consequence, this lack in our knowledge may prevent us from developing effective and curative therapies. If we are able to revisit our views on involvement of *Mycobacterium avium ssp. paratuberculosis* (MAP) a as an important player in this disease, this might open up new options for therapeutic targets.

Introduction

Crohn's disease is an inflammatory bowel disease, a complex pathology with severe manifestations in the intestine [1], but also other organs can be affected, such as the skin, the eye, joints, and tendons [2]. Initially, this disease was described by its symptoms, as an auto-immune disease in which the immune system attacks the body's own intestinal cells. The current view on the pathogenesis of the disease is that it is of a multifactorial nature, where environmental, immune, and bacterial factors in a genetically susceptible host all play a role [3]. With the rise of GWAS techniques [4] a lot of new information has come to light which has already helped us to elucidate part of the molecular and cellular mechanisms which are important for intestinal immune homeostasis, and some of the mechanisms which are disturbed in Crohn's disease.

As there is still no consensus on the cause of CD, current therapeutic strategies are still focused primarily on dampening the damage of detrimental immune reactions by suppressing the immune system. Although this seems as the best way currently available to manage the symptoms of this disease, there may be merit in re-evaluating these strategies. Immunosuppressive therapy may be effective for a while, but oftentimes patients are forced to switch medication, due to side effects, build up of allergic responses to the drugs, or simply the loss of effectiveness, indicated by flare ups of inflammatory markers and symptoms. It might be time to consider other approaches, related to a different hypothesis about its pathogenesis and disease progression. If we consider CD not only as an auto-immune phenomenon, but an immunological syndrome with a typical pathogenic source (in a susceptible host),we can envision that treatments which either chemically interfere with the pathogen's viability, or which actually stimulate the immune system to battle this pathogen, might be better as a long term therapeutic strategy. This would require careful approaches and in-depth knowledge of the behaviour of this pathogen and its weaknesses, as a full blown a-specific immune attack may only aggravate the inflammation which is already present, leading to more damage. Strikingly though, some pioneering studies have already demonstrated the beneficial effects of innate immune stimulation in the form of granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) administration [5,6], indeed pointing us in the direction of a primary infectious agent.

Hoping to identify a causative agent for CD within the microbial population, a lot of studies have focused on the role of the intestinal commensal bacteria, demonstrating that many CD patients have an abnormal enterotype or bacterial composition in the intestine, represented by decreased diversity, and decreased numbers of members of the phyla *Bacteroidetes* and *Firmicutes* [7,8]. This however may also be a consequence of initial differences in intestinal health, intrinsic to the disease, such as increased permeability, altered glycobiome expression, mucus composition, and the subsequent (in) ability for normal taxa to find a sustained niche and become part of that person's microbiota.

Antibodies against several microbes such as *Saccharomyces Cerevisiae* have been isolated from CD patients [9], and amongst others, *Candida* [10] and Segmented Filamentous Bacteria (SFB) [11] have also been implicated as possible disease inducing microbes. However, *S. cerevisiae* has never been identified as instigator of the inflammation, and is perhaps just detected by the immune system as dangerous, because it has come in contact with immune cells of the lamina propria, because of leakage of intestinal content to underlying tissues. Candida and SBF are more likely to play a detrimental role in disease onset, but may also be part of secondary infections [12]. To get closer to identifying a pathogen which could be instigating the inflammatory reactions in CD, we need to return to the current views on Crohn's pathogenesis and symptoms. One of the first things which are thought to go wrong is that the innate immune system appears to be relatively inactive [13]. This may be related to genetic factors, but another possibility is that it is also 'pressured into submission' by micro-organisms which actively induce anti-inflammatory cytokines and suppress immune activation. Characteristics of chronically infectious organisms are in fact often immune suppression, and/or evasion or the immune system, and/or formation of cysts or spores, which enable the organism to hide from immune attacks in a resilient life form, and await its opportunity to resurface when the body's immune system is less alert.

For a particular group of micro-organisms these phenomena are readily described, including *Mycobacterium tuberculosis* [14] and *Mycobacterium leprae* [15]. Up to date, one of the most suspected micro-organisms isolated from patches of inflamed intestinal tissue of CD patients [16-18], which is in fact related to these, is *Mycobacterium avium ssp.paratuberculosis* (MAP) [19]. This mycobacterium causes a similar disease called Johne's disease in cattle [20,21]. Strikingly, there is considerable overlap between susceptibility loci for IBD and mycobacterial infections [22,23], indicating that CD patients are in fact more susceptible to MAP infection and persistence. The implication of MAP in CD is not very new, this hypothesis has been formulated many years ago by Dalzeil [24], however there are several reasons why this hypothesis was not unanimously supported:

a. some scientists were unable to reliably grow MAP in culture
b. MAP-specific antibodies could not be detected in CD patients
c. Some scientists were unable to visualize MAP in affected tissue samples [25].

Corticosteroids are fairly often prescribed to dampen flare ups of intestinal inflammation in this disease. In treatment for Crohn's extraintestinal manifestations, joint exacerbations are also often put to a halt with the use of oral corticosteroids. Of corticosteroids are thus primarily used to dampen the immune response and can calm an unwanted reaction to limit the damage the immune attack causes on the body. This treatment works considerably well for both intestine and joints, but it is not suitable for long term treatment due to its side effects. For several fungal infections it is known that corticosteroids not only dampen the immune response, but they also limit growth of the pathogen or even induce clearance. It would be highly interesting to study whether MAP infection is in fact also inhibited by corticosteroid use, and whether this may be a promising part of a multi-component strategy to clear MAP from an infected host.

In an article by Rutuu., *et al.*[27] on the relation between ankylosing spondyloarthritis(AS) and intestinal symptoms in a mouse model, a very strong case is made in identification of an antigen which induces both intestinal and extraintestinal, AS-like symptoms of CD. In this study, the agent used to induce these symptoms was a polysaccharide called beta-glucan. One type of the polysaccharides which are known to be produced by MAP are mannans, which protect both itself and various bacteria from phagocytosis, which causes a variety of secondary infections [28]. Beta-glucans are typically expressed by bacteria, fungi and yeasts [29], and this raises the question whether MAP expresses this also and whether it may play a role in its pathogenicity.

Each year the number of newly reported CD patients increases and there is an urgent need to clarify the mechanisms underlying the pathogenesis, so that new and better therapeutic strategies can be developed. It may be time to revisit our research and look deeper into the candidate organism MAP, just because they are difficult to detect, it does not mean they are not there; we may simply not yet have the right techniques to detect them yet. Considering all the clues pointing to MAP as an inflammatory agent in CD onset and pathology, clinical trials to study the efficacy of combining stimulation of the innate immune system with anti-mycobacterial drugs, and possibly corticosteroids as treatment for CD are highly recommended.

Bibliography

1. Crohn BB., *et al*. "Regional enteritis. A pathological and clinical entity 1932". *The Journal of the American Medical Association* 67.3 (2000): 263–268.
2. Danese S., *et al*. "Extraintestinal manifestations in inflammatory bowel disease". *World Journal of Gastroenterology* 11.46 (2005): 7227–7236.
3. Loddo I and Romano C. "Inflammatory Bowel Disease: Genetics, Epigenetics, and Pathogenesis". *Front Immunology* 6 (2015): 551.
4. Franke A., *et al*. "Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci". *Nature Genetics* 42.12 (2010): 1118–1125.
5. Dieckgraefe BK and Korzenik JR. "Treatment of active Crohn's disease with recombinant human granulocyte-macrophage colony-stimulating factor". *Lancet* 360.9344 (2002): 1478–1480.
6. Korzenik JR and Dieckgraefe BK. "An open-labelled study of granulocyte colony-stimulating factor in the treatment of active Crohn's disease". *Alimentary Pharmacology & Therapeutics* 21.4 (2005): 391–400.
7. Arumugam M., *et al*. "Enterotypes of the human gut microbiome". *Nature* 473.7346 (2011): 174–80.
8. Frank DN., *et al*. "Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases". *Proceedings of the National Academy of Sciences* 104.34 (2007): 13780–13785.
9. Quinton JF., *et al*. "Anti-Saccharomyces cerevisiae mannan antibodies combined with antineutrophil cytoplasmic autoantibodies in inflammatory bowel disease: prevalence and diagnostic role". *Gut* 42.6 (1998): 788–791.
10. Sendid B., *et al*. "Anti-glycan antibodies establish an unexpected link between C. albicans and Crohn disease". *médecine/sciences* 25.5 (2009): 473–481.
11. Ericsson AC., *et al*. "Segmented filamentous bacteria: commensal microbes with potential effects on research". *Comparative Medicine* 64.2 (2014): 90–98.
12. Rahier JF. "Prevention and management of infectious complications in IBD". *Digestive Diseases* 30 (2012): 408–414.
13. Marks DJB., *et al*. "Defective acute inflammation in Crohn's disease: a clinical investigation". *Lancet* 367.9511 (2006): 668–678.
14. Barth K., *et al*. "Disruption of immune regulation by microbial pathogens and resulting chronic inflammation". *Journal of Cellular Physiology* 228.7 (2013): 1413–1422.
15. Han XY., *et al*. "On the age of leprosy". *PLOS Neglected Tropical Diseases* 8.2 (2014): e2544.
16. Sechi LA., *et al*. "Mycobacterium avium ss. paratuberculosis Zoonosis - The Hundred Year War - Beyond Crohn's Disease". *Frontiers in Immunology* 6 (2015): 96.
17. Clancy R., *et al*. "Molecular evidence for Mycobacterium avium subspecies paratuberculosis (MAP) in Crohn's disease correlates with enhanced TNF-alpha secretion". *Digestive and Liver Disease* 39.5 (2007): 445–451.
18. Ren Z., *et al*. "Selective Th2 pattern of cytokine secretion in Mycobacterium avium subsp. paratuberculosis infected Crohn's disease". *Journal of Gastroenterology and Hepatology* 23.2 (2008): 310–314.
19. Kenneth Ryan. "Sherris Medical Microbiology". Fifth Edition.
20. Naser SA and Collins MT. "Debate on the lack of evidence of Mycobacterium avium subsp. paratuberculosis in Crohn's disease". *Inflammatory Bowel Diseases* 11.12 (2005): 1123.
21. Naser SA., *et al*. "Mycobacterium avium subspecies paratuberculosis causes Crohn's disease in some inflammatory bowel disease patients". *World Journal of Gastroenterology* 20.23 (2014): 7403–7415.

22. Jostins L., *et al*. "Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease". *Nature* 491.7422 (2012): 119–124.
23. Ferwerda G., *et al*. "Mycobacterium paratuberculosis is recognized by Toll-like receptors and NOD2". *Journal of Leukocyte Biology* 82.4 (2007): 1011–1018.
24. Dalzeil T. "Chronic intestinal enteritis". *British medical journal* (1989): 1076–1078.
25. Chamberlin W., *et al*. "Mycobacterium avium subsp. paratuberculosis as one cause of Crohn's disease". *Alimentary Pharmacology & Therapeutics* 15.3 (2001): 337–346.
26. Hulten K., *et al*. "Detection of Mycobacterium avium subspecies paratuberculosis in Crohn's diseased tissues by in situ hybridization". *The American Journal of Gastroenterology* 96.5 (2001): 1529–1535.
27. Ruutu M., *et al*. "β-glucan triggers spondylarthritis and Crohn's disease-like ileitis in SKG mice". *Arthritis & Rheumatology* 64.7 (2012): 2211–2222.
28. Mpofu CM., *et al.* "Microbial mannan inhibits bacterial killing by macrophages: a possible pathogenic mechanism for Crohn's disease". *Gastroenterology* 133. (2007): 1487–1498.
29. Du B., *et al*. "Skin health promotion effects of natural beta-glucan derived from cereals and microorganisms: a review". *Phytotherapy Research* 28.2 (2014): 159–166.

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