Intestinal inflammation and extraintestinal disease: understanding dynamic risk

James J Ashton[1,2], Jack Satsangi [3], Holm H Uhlig[3,4,5]

1. Department of Human Genetics and Genomic Medicine, University of Southampton, Southampton, UK.
2. Department of Paediatric Gastroenterology, Southampton Children's Hospital, Southampton, UK.
3. Translational Gastroenterology Unit, University of Oxford, Oxford, UK
4. Biomedical Research Centre, University of Oxford, Oxford, UK
5. Department of Paediatrics, University of Oxford, Oxford, UK

Conflict of interest statement

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When established concepts fail, a paradigm shift is required to advance *scientific models and practices*[1]. Among the puzzles in the field of inflammatory bowel disease (IBD), is to explain the phenomenon that some patients with IBDs also develop extraintestinal manifestations (EIMs). Indeed, between 6% and 47% of patients with IBD present with conditions that may involve the skin (such as erythema nodosum, pyoderma gangrenosum and psoriasis), eye (such as episcleritis and uveitis), joint (including enteropathic arthritis, spondyloarthropathy), liver (primary sclerosing cholangitis, autoimmune hepatitis) but also additional systemic symptoms such as tiredness and pain[2]. A gastroenterology-centric view of EIM's provides little inside into the mechanisms of the immune-mediated multisystem involvement. At the heart of the association between IBD and comorbidities is the question of whether patients experience 'extraintestinal manifestations' (an immunological consequence gut disease) or rather 'extraintestinal disease' that coexists with IBD due to shared genetic susceptibility and shared environmental trigger. Up to 26% of 'EIMs' occur before the onset of intestinal inflammation, questioning a role of intestinal inflammation as a direct driver [2][3]. Whilst some manifestations including erythema nodosum, peripheral arthritis, or oral aphthous ulcers, are associated with active intestinal inflammation, others such as uveitis, ankylosing spondylitis, and primary sclerosing cholangitis are not [3].

Understanding the underlying genetics can offer some insight, since some of the hundreds of loci drive IBD disease susceptibility overlap with that of extraintestinal manifestations [2,4]. A further indication for shared mechanisms is indicated by overlapping therapeutic efficacy of medications such as JAK inhibitors (IBD, atopic dermatitis, arthritis), anti-TNF agents (IBD, psoriasis, arthritis, uveitis) and anti-IL23 agents (IBD, psoriasis, arthritis)[5], while others such as primary sclerosing cholangitis has been challenging to treat by current IBD targeting therapies. One of the limitations for our understanding of extraintestinal disease is the lack of large-scale longitudinal data across organ manifestations.

In their manuscript, Khrom *et al* take an interesting approach to the problem, by correlating hepatic, rheumatological, dermatological and ocular disease in patients with IBD with genetics, a

range of serology parameters and environmental factors[6]. This study brings together data from 12,083 individuals with IBD across cohorts of European ancestry. Factors including gender, IBD subphenotypes, or cigarette smoking were associated with extraintestinal disease. Genetic association signals in the MHC region, alongside numerous nominally significant loci, and gene-enrichment analysis implicate shared innate immune responses including IL-6 signalling, TNF-signalling and JAK-STAT signal transduction. Importantly, serological markers including antineutrophil cytoplasmic antibodies, anti-Saccharomyces cerevisiae antibodies, the I2 component of Pseudomonas fluorescens (anti-I2), and anti-flagellin (CBir1) antibodies, point towards host-microbe responses.

Whilst the study of Khrom *and colleagues*[6] illustrates the power of large dataset approaches, it also highlights open questions. The study is focused on patients with European ancestry and might be only partially translatable to other ethnic groups since differential genetic risk factors[7–9] extraintestinal disease associations apply (pyoderma is more frequent in people of Black African heritage) [10]. The relatively low prevalence of EIM compared to previous studies [2] could be due to number of factors including disease definitions, the incompleteness of coding of the electronic health records and differences in follow-up duration. The effects of treatment as dynamic immune modifiers are difficult to assess since some treatments may induce extraintestinal disease (such as psoriatic skin disease in anti-TNF treatment), while biological and immune modifying treatments might also prevent occurrence of extraintestinal disease.

The puzzle of extraintestinal diseases in patients with IBD is far from being solved. The question is how to challenge the paradigm. Phenome-wide association studies might help to address some genotype-phenotype associations[11,12]. The potential for significant progress comes from novel technologies to study immune phenotypes. A mechanistic understanding of environmental factors such as cigarette smoking is required to understand its differential role in Crohn's disease, ulcerative colitis and extraintestinal disease[13]. Fine mapping of MHC alleles, identification of MHC bound peptides, with the longitudinal analysis of shared and diverse T cell response repertoires in

the gut and extraintestinal sites via single cell transcriptomic technologies offers to understand T cell responses at different tissue sites. A granular analysis of anti-bacterial and anti-viral responses offers the ability to understand the impact of trigger events by determining the bacteria targeted by host immunoglobulin[14].

A key problem that all studies face is the delay between the impact of early life environmental factors and the onset of disease ranging typically 2 to 4 decades of life. Prospective follow up of patients is challenging but might allows to identify early immune responses in patients with IBD[15] while harnessing biobanks for historic samples can inform on exposure to microbes, or the presence of autoantibodies [16]. New approaches to understand the development of intestinal and extraintestinal immunopathology might involve learning from nature and medical practice. Monogenic forms of IBD often present with distinct pattern of extraintestinal disease providing strong causative genetic evidence for molecular and cellular disease mechanisms[17]. Intestinal and extraintestinal disease can be triggered by medications that target immunoregulatory networks such as so-called checkpoint inhibitors (anti-CTLA4 or anti-PD1/PDL1) causing dermatitis, thyroiditis, hepatitis as well as enteropathy and colitis[18]. Since those medications are now used in thousands of patients with malignancy, this setting presents not only a group of medical adverse effects to be understood (and avoided for patient benefit) but also potentially a human time lapse experiment with defined time point as a trigger of the disease, the opportunity to collect genetic, epigenetic, metagenomic, and lifestyle exposure data (including diet and smoking) before onset and during follow-up. Most importantly outcome can be studied in a defined time frame, with intestinal and extraintestinal complications arising a magnitude shorter as compared to classical IBD. Studies show the impact of the microbiome such as Faecalibacterium or Bacteroidales abundance to modulate effectiveness of the anti–PD-1 therapy checkpoint therapy[19]. Although, only a surrogate of IBD, this experimental human model might inform on key modifier of disease and serve as a paradigmatic shift to study susceptibility of multiorgan immunopathology.

Current evidence points towards a very dynamic model were risk of intestinal and extraintestinal disease cannot adequately be captured without combining the largely static genetic susceptibility with study of dynamic processes (infection and microbiome, epigenetics, antigen specific responses, cigarette smoking) and its interlinked biology via epigenetics, innate and anti-gene specificity immune responses (**Figure 1**).

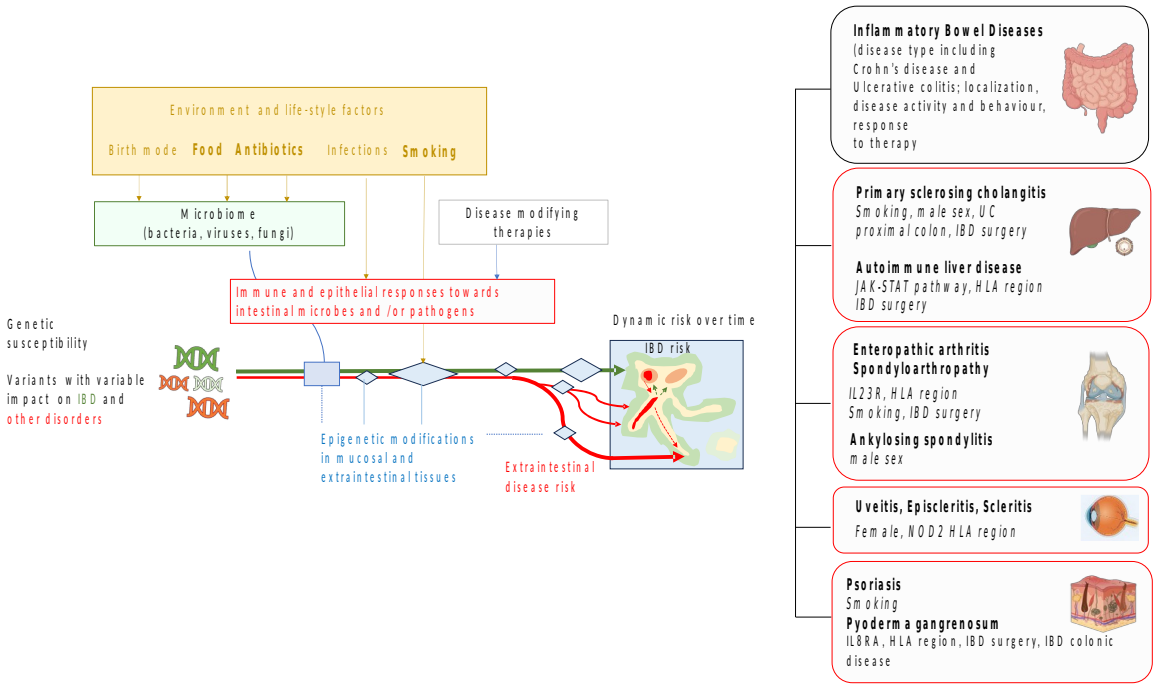

Figure 1 A dynamic model of risk factors associated with occurrence of inflammatory bowel disease and extra-intestinal disease.

Genetic susceptibility and environmental factors such as food or antibiotics modulate the microbiome and imprint epigenetic signatures that impact on disease susceptibility to IBD and extraintestinal disorders [2,6]. Intestinal and extraintestinal disease onset and activity is driven by shared and differential susceptibility factors that determine the disease trajectory and therapy response pattern of individual patients as a probabilistic process.

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