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MUCOSAL IMMUNOLOGY DAYS**

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Exploring All Aspects of Chronic Inflammatory Bowel Diseases

by Dr. Corinna Kolac

International experts in inflammatory bowel disease (IBD) gathered in Oxford, UK, for the 241st Falk Foundation Symposium, "Mucosal Immunology Days," to discuss the crucial interface between clinical needs and basic research. The goal was to reflect on and potentially reshape the existing framework of IBD classification. Topics included distinctions between Crohn's disease (CD) and ulcerative colitis (UC), age at diagnosis, disease location, and disease behavior as outlined by the Montreal classification [1]. Extraintestinal manifestations (EIMs) and pathways toward colorectal neoplasia were also examined. Participants concluded that a new, biology-informed IBD classification is emerging to improve clinical utility and patient outcomes.

A vision for IBD: Bridging basic research and clinical practice

Prof. Fiona Powrie (Oxford, UK) highlighted current challenges in IBD: the global rise in CD and UC incidence, significant disease heterogeneity, and the lack of effective therapy for some patients. This underscores the importance of a deeper understanding of complex biological relationships. Prof. Powrie presented insights into the complexities of IBD, focusing on gene-environment interactions that destabilize the gut microbiome, a key factor in IBD pathogenesis. Current research is centered on the interplay between a diverse microbiome and immune responses, and how specific strains can activate or inhibit inflammation [2]. For example, one study demonstrated that manipulating specific microbiota can ameliorate colitis symptoms, suggesting potential therapeutic avenues [unpublished data]. Advancements in technologies such as single-cell RNA sequencing now allow for unprecedented tracking of micro-reactive T and B cells, deepening our understanding of immune dynamics in IBD [3]. Prof. Powrie's research team used a T cell receptor (TCR) transgenic mouse model to investigate T cells reactive to *Helicobacter hepaticus*. They found that these T cells, especially those producing interleukin-10 (IL-10), interact significantly with specific macrophage types, which may have therapeutic implications for IBD [3]. Their findings suggest that modulating regulatory T cell (Treg) production could be a promising therapeutic strategy. The team identified a unique subset of antigen-presenting cells that may prime bacteria-reactive Tregs, raising questions about the relevance of these findings in humans.

Prof. Powrie emphasized the need to understand the intestinal ecosystem's niches that drive IL-10 production and the role of various chemokines. She also discussed the implications of IL-10 deficiency and the role of regulatory T cells in IBD therapy. Recent findings show that some patients with severe disease produce neutralizing autoantibodies against IL-10. Prof. Powrie also highlighted the genetic differences between Crohn's disease and ulcerative colitis, and the processes of immune dysregulation. Toward the end of her talk, she addressed stromal cell remodeling in therapy-resistant IBD, focusing on interactions between inflammatory mononuclear phagocytes and activated fibroblasts [4]. She reported that certain cellular interactions contribute to impaired responses to anti-tumor necrosis factor (anti-TNF) therapy in patients with deep ulcers. Prof. Powrie concluded by stressing the importance of a data-driven approach to understanding IBD, with a focus on cellular dynamics and the development of pathological niches over time, which may inform future treatments.

Biological classification of IBD is complex

Prof. Matthieu Allez (Montreal, Canada) addressed the complexities of biological classification in IBD. He underscored the significant heterogeneity among IBD patients, driven by varied clinical presentations, disease locations, and disease behaviors. Patients show marked variability in disease progression, with distinctions between slow and rapid progressors. The impact on quality of life can be profound, often underestimated in clinical assessments. Prof. Allez emphasized the individualized nature of treatment responses, citing cases where patients initially responded to therapies such as TNF-α blockers but later encountered treatment challenges [5]. This variability may be influenced by genetic and environmental factors. The multifaceted pathogenesis involves impaired epithelial barrier function, immune system activation, and complex genetic-environmental interactions. Inflammation may arise from insufficient regulatory mechanisms or heightened pro-inflammatory pathways, leading to tissue damage and potential surgical intervention. Advanced methodologies, such as multi-omics approaches, allow for collaborative examination of various biological samples from the same patient. Prof. Allez advocated for the integration of bioinformatics and artificial intelligence to manage IBD's complexities and called for a greater focus on precision medicine in clinical practice.

He acknowledged the ongoing challenge of defining specific IBD subtypes, likening the complexity of IBD pathology to a historical battlefield—while researchers analyze the direct effects of the disease, understanding root causes requires a broader perspective. He encouraged the use of various research models to gain insights into IBD. Prof. Allez also described the postoperative recurrence of Crohn's disease following ileosigmoid resection, noting that inflammation often recurs at the anastomosis, which is detectable endoscopically before clinical symptoms appear. The composition of the microbiome after surgery significantly influences recurrence risk. Identifying specific bacterial species associated with increased recurrence, particularly adherent-invasive *Escherichia coli*, may offer insights for risk assessment [6].

Aging and the role of the immune system

Prof. Eoin McKinney (Cambridge, UK) discussed the "cliff-edge phenotype" in aging, noting that while mortality in infants and adults has declined, mortality in older adults remains unchanged, with a sharp health decline between ages 65 and 70. Variations in DNA repair mechanisms may influence aging in different tissues, suggesting an important role for the immune system [7]. Aging is highly variable, and increased variance in aging trajectories is a focus of ongoing research.

To investigate this variability, a research consortium in Sardinia, a region known for longevity, has examined a broad age range (20–120 years) over 30 years. The study includes approximately 25,000 samples from 6,000–7,000 individuals, enabling comprehensive analysis of immune aging. The aim is to integrate multiple datasets to identify and quantify immune changes with age and to determine which changes are most consequential. Aging is not linear; rather, a pronounced inflection in health occurs between ages 65 and 70, marked by a sharp decline in well-being.

Thirteen central aging patterns were identified that explain over 99% of the variance in the data. Among these, three show significant sex differences—particularly in regulatory T cell phenotypes—indicating divergent immune responses as individuals age. The research ultimately identifies two specific immune aging trajectories that are strongly associated with long term health outcomes, independent of age and sex. One trajectory, referred to as tissue factor III, is linked to worse outcomes as individuals age, particularly beyond 65.

This adverse trajectory is associated with changes in the B-cell receptor (BCR) repertoire, which undergoes notable shifts around this age. As naïve B cells decline, there is a rise in highly mutated IgM-positive memory B cells, indicating a major shift in how the immune system generates responses. This repertoire change correlates with reduced immune function and impacts overall health outcomes. While the exact causes remain unclear, there is a notable shift in class switch recombination toward IgA and away from IgG, resulting in a greater reliance on IgM memory B cells for pathogen responses.

Disease location: What distinguishes CD from UC?

Prof. Derek Jewell (Oxford, UK) focused on UC, noting that most patients have left-sided disease, while a minority have distal or extensive disease. The reasons for distal-only disease have been intensively studied since the late 1980s, with a central theme being differences in mucus composition and physiological, biochemical, and immunological differences between the left and right colon. The mucus layer is significantly thinner in the distal colon, potentially contributing to disease development. The distal colon mainly contains sialo-oligosaccharides [8-10]. High concentrations of butyrate can have a toxic effect on mucosal cells, leading to mucosal damage [11,12]. The frequency of certain immune cells in the colon varies, and genetic studies indicate that specific allelic variants, such as the HLA-D-R gene, are linked to different disease severities [13]. The colon's heterogeneity underscores the complexity of IBD, and it remains unclear what drives progression from distal to extensive disease—a significant clinical challenge. Prof. Jewell called for collaborative efforts to deepen understanding of disease mechanisms.

How diet contributes to IBD

Prof. Timon Adolph (Innsbruck, Austria) reported on the negative effects of the "Western" diet—particularly in CD—which is high in fat, sugar, and processed foods [14,15]. A meta-analysis found that ultra-processed foods are associated with an increased risk of CD, but not UC [15]. Observational studies support this, noting that adherence to a Mediterranean diet—rich in unprocessed foods—correlates with better disease outcomes in Crohn's patients [16]. High-fat diets can trigger inflammation by inducing immune responses and altering the gut microbiome, promoting dysbiosis and increasing susceptibility to colitis in animal models [17]. Research on the gene glutathione peroxidase 4 (GPX4) revealed its reduced expression in CD recurrence compared to healthy controls [18]. GPX4 plays a critical role in inflammation and wound healing, indicating potential therapeutic targets. Reduced GPX4 expression at the time of resection is significantly associated with increased risk of endoscopic disease recurrence, suggesting its potential as a biomarker for patient outcomes.

The discussion also addressed GPX4's function as an antioxidant, particularly in protecting cellular membranes from lipid peroxidation. The high levels of omega-6 polyunsaturated fatty acids in Western diets may promote intestinal inflammation, especially in individuals with reduced GPX4 activity [19].

Focus on an extreme phenotype of IBD

Prof. Carl Weidinger (Berlin, Germany) discussed "extreme IBD"—severe, widespread disease often refractory to standard treatments and requiring aggressive management. He emphasized the importance of understanding extreme IBD to improve outcomes and patient care. Over 100 monogenic forms of IBD have been identified, including IL-10 deficiencies, contributing to severe inflammation and complications [20]. Somatic mutations can accumulate in IBD patients, especially in epithelial and T cells, increasing genetic variability and the clonal nature of disease. Such mutations may enhance T cell proliferation and survival, contributing to therapy resistance. Delayed treatment can lead to structural damage and worse outcomes [21], highlighting the need for timely, effective interventions. Prof. Weidinger advocated for a new IBD taxonomy based on inflammatory signatures and molecular pathophysiology to enhance treatment strategies and research quality. Rare immunodeficiencies, particularly those affecting store-operated calcium entry (SOCE) in T cells, offer insights into T cell activation. Blocking SOCE may protect against colitis, suggesting a potential therapeutic target for refractory IBD. Adipose tissue, especially leptin, also plays a role: lipodystrophic mouse models showed that absence of adipose tissue protects against intestinal inflammation, indicating that fat-derived signals are crucial for colitis induction.

Extraintestinal manifestations (EIM) in IBD

Dr. Hannah Gordon (Oxford, UK) focused on extraintestinal manifestations (EIMs) in IBD: Recent studies, including one analyzing data from over 14,000 patients, found that about 25% of IBD patients experience EIMs [22]. Crohn's disease, particularly with colonic involvement, is strongly associated with EIMs such as primary sclerosing cholangitis (PSC) and dermatological conditions. Smoking increases the risk of EIMs but appears to be protective against PSC. Over 60% of Crohn's patients have an associated autoimmune condition or EIM, highlighting IBD's multisystemic nature. Notably, behavioral and neurodevelopmental disorders (e.g., anxiety and depression) are more prevalent than rheumatological issues. These findings may prompt a reassessment of patient care in IBD.

Gut and joint inflammation – two locations, one disease?

Prof. Christopher Buckley (Oxford, UK) emphasized the interconnectedness of the gut, joints, skin, and eyes, and the need for clinicians to inquire about symptoms in all these areas. Why inflammation affects certain sites (e.g., joints vs. gut) remains unclear. Single-cell analysis reveals distinct cellular compositions in different joints, with higher vascularization and volume correlating with greater rheumatoid arthritis risk. Developmental pathways may influence susceptibility to osteoarthritis and other inflammatory diseases. Buckley highlighted research on cellular composition in CD and UC, showing that CD is associated more with T cells and enterocytes, while UC involves CD8 cells, TH-17 cells, and B cells [23]. A cellular understanding of remission—high levels of protective cells and low levels of pathogenic cells—is critical for predicting and guiding patient treatment.

Managing risks of colorectal cancer in IBD patients

As **Prof. Ibrahim Al Bakir** (London, UK) emphasized, patients with UC face an increased risk of developing colorectal cancer (CRC). He highlighted the significant challenges associated with detecting dysplasia in a scarred colon, particularly in the presence of inflamed polyps. This complexity often leads to a risk of overdiagnosis of low-grade dysplasia and, consequently, to the potential overtreatment of low-risk patients.

Recently, the surveillance guidelines in the UK were updated to adjust the frequency of endoscopic monitoring based on individualized colorectal cancer risk predictions [24,25]. Prof. Al Bakir underscored that chronic inflammation is a well-established driver of colorectal cancer in UC patients [26]. Despite substantial advances in our understanding of cancer biology, he cautioned that focusing exclusively on a limited set of mutation pathways (such as KRAS and P53) is insufficient. The heterogeneity of oncogenic pathways in CRC necessitates a broader, more integrative approach.

A pivotal concept in this context is clonal evolution, whereby mutations confer a selective advantage to cancer cells, enabling them to outcompete normal cells—an especially relevant mechanism in IBD-associated carcinogenesis. Prof. Al Bakir drew attention to the frequent presence of chromosomal copy number alterations, not only in neoplastic tissue but even in non-neoplastic mucosa. He proposed that low-coverage genome sequencing represents a valuable and practical tool for assessing chromosomal alterations and microsatellite stability in clinical practice [27].

To illustrate this, he referenced studies comparing endoscopic biopsies from patients who developed cancer or high-grade dysplasia within five years to those who did not. These studies revealed significant differences in copy number alterations, indicating a higher degree of genomic instability in progressive lesions. Importantly, the detection of such chromosomal alterations in biopsies of phenotypically normal tissue may serve as a predictive marker for future cancer risk. Prof. Al Bakir concluded that this approach warrants further exploration and validation in prospective studies.

Interview with Prof. Britta Siegmund,

Lively discussions and open exchange bring the community of IBD researchers together

Gastroenterologist Prof. Britta Siegmund (Berlin, Germany) co-organized the symposium on mucosal immunology in IBD, drawing numerous leading experts. The event featured in-depth discussions on many aspects of mucosal immunology. Currently, a new IBD classification system is under review. We interviewed Prof. Siegmund during the symposium.

The Montreal classification for chronic inflammatory bowel disease (IBD) dates back to 2006 [1]. For Crohn's disease (CD), for example, it considers age at diagnosis, disease location, and disease behavior. The classification is now being revised. What factors might be important in the future?

Unfortunately, I can't share specific details yet. However, it's becoming clear that disease localization will play a significant role and needs to be better defined—something we've learned from oncology and immunological research. Only by refining how we define localization can we truly understand its relevance and build on it. We'll also integrate perianal classification. The new system for clinical practice likely won't be overly complex—it needs to be practical and user-friendly. The Montreal classification isn't fundamentally wrong; the new version will simply be more granular. We're making sure these changes are practical—otherwise, the classification won't be adopted widely. At the same time, we're considering a research-focused classification that goes beyond clinical needs, allowing for more detailed data collection.

There's a lot of discussion around new models. How relevant are organoids in clinical practice today? Could patients with severe disease expect personalized treatment using these models soon?

Organoids are an excellent tool for studying certain aspects of IBD. However, the intestinal wall contains many different cell types, while organoids are purely epithelial—all the supporting structures are missing. If the defect is in the epithelium, organoids can provide valuable insights. But once other cell types are involved, things get much more complicated. So, while organoids are a useful model, they have their limitations.

There's ongoing debate about whether biomarkers could indicate IBD long before symptoms appear. Does this suggest potential for screening?

The idea of using biomarkers comes from studies of blood samples from US veterans, who regularly give blood and receive healthcare, creating large datasets. It's relatively easy to identify people who later developed IBD and analyze their earlier blood samples. There's a set of blood markers associated with a higher risk of developing IBD, but how meaningful these markers are is still unclear. Initial efforts are underway to identify individuals at increased risk and to treat those at very high risk before clinical symptoms appear, with the hope of preventing intestinal inflammation. These are exciting, but still experimental, approaches.

Monogenic IBD is receiving significant attention at this symposium. What's the current state of research?

There are two types of monogenic IBD. The condition is more common in children and adolescents, especially before the age of one—here, the likelihood of a monogenic cause is very high. Pediatricians are therefore much more familiar with this topic. But there's also a second form in adults, often characterized by a particular phenotype or severe disease. In these cases, genetic sequencing is warranted.

How important is nutrition in the development of IBD?

Nutrition is important not only in the development of IBD but also in its management. For example, research has shown that an emulsifier-free diet can help control mild to moderate Crohn's disease. Regarding the onset of IBD, we know that a "Western diet" is strongly associated with increased risk. Of course, diet likely plays a role in many other diseases as well. In my opinion, we, as a society, should do more to reduce our intake of processed foods and focus on fresh, unprocessed foods with as few emulsifiers as possible.

What has your personal highlight of this symposium been?

For me, the highlight is the many lively discussions. I find them incredibly enriching. Everyone brings unique perspectives, and we can only make progress by sharing ideas and weighing options together. Identifying where the true gaps are and what needs urgent attention is invaluable. Moving forward requires collaboration. I really value the openness among researchers and the dialogue with clinicians. For all these reasons, I'm already looking forward to the next symposium, which will take place in Gothenburg in 2027.

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