IBD: From Pathophysiology to Personalized Medicine

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Choosing the “right” treatment for each patient will soon be a reality for IBD

On the long, challenging path to personalized medicine in IBD

A big puzzle with many pieces

There’s certainly no lack of fascinating questions
(Prof. Dr. Markus F. Neurath, Erlangen, Germany)

Speakers, moderators and scientific organizers
Choosing the “right” treatment for each patient will soon be a reality for IBD

Personalized medicine holds the promise of effective treatment regimens that are well tolerated, as is currently being demonstrated in the field of oncology. This goal is also increasingly being pursued for the treatment of inflammatory bowel diseases (IBD). Close cooperation between basic research and clinicians will help ensure the step-by-step progression of these developments.

There is currently no lack of drugs for the treatment of inflammatory bowel disease (IBD). An increasing number of agents are now available, with targets such as inflammatory signaling molecules. Nonetheless, we are still waiting for a breakthrough in the treatment of Crohn’s disease and ulcerative colitis. Personalized medicine, in which the selection and order of drugs is optimally tailored to each individual patient, may help solve this dilemma. However, this strategy requires deeper insights into the pathophysiology of IBD, details on the immunology and genetics of the disorders, and most importantly into the interactions between these individual factors, given the complexity of the inflammation process. A number of small steps in this direction were presented during Symposium 214 in Oxford. For example, the IL-23 signaling pathway has been identified as a crucial player in the induction of gut inflammation. New technologies, such as the use of scRNA-seq to identify marker genes and monogenic gut disorders, were presented as an intriguing model for gaining new insights. Focus has also been directed toward characterizing several cytokines that have recently been proposed to be linked to IBD, including interleukin-22, and their relevance as therapeutic targets. The gut microbiota – which is undoubtedly a crucial factor in the development and form of IBD for many patients – also appears to be a potential therapeutic target. However, rapid development of therapeutic options remains plagued by the high degree of variability in microbiota between individuals as well as by the difficulties in altering the microbiota in a targeted and sustained manner. These efforts are further hampered by our incomplete understanding of the interactions between the microbiota and the immune system, which may one day provide opportunities for therapeutic strategies.

At the same time, the development of personalized medicine must also include efforts to optimally leverage the medications that are already available. For example, the combination of thiopurines with TNF-α inhibitors has now become well established. Yet, there are well-known risks of thiopurines, including myelosuppression. Going forward, a better understanding of the underlying genetics may aid in the development of targeted therapy that is better tolerated, since specific genetic variants of nudix hydrolase 15 (NUDT15) appear to be associated with a much greater risk of thiopurine-induced myelosuppression. Patients with this risk could be identified by NUDT15 genotyping before they start treatment. Calls are mounting for comparative trials on biologics and the increased utilization of biomarkers for their prescription.

Finally, completely new agents may also hold great promise, including monoclonal antibodies targeting the β7 subunit of α4β7 and αEβ7 integrins, anti-MAdCAM antibodies, oral peptides, or even S1P1 agonists. Future therapies probably will no longer be based solely on a single biologic agent, but rather on a combination of multiple biologics.

Scientific organizers
Prof. M.F Neurath, Prof. A. Kaser and Prof. F. Powrie
On the long, challenging path to personalized medicine in IBD

The appeal for personalized medicine is growing louder in nearly all fields of medicine, and inflammatory bowel diseases (IBD) are no exception. Yet, the path to personalized care of IBD will be difficult, as it will require intense basic research in the fields of pathophysiology, genetics, and immunology, as well as collaborations with clinical practitioners. However, there is no other feasible way forward, as it is quite apparent that a great unmet medical need for individualized medicine still exists despite the innovations in recent years. Many small steps in this direction were presented during the 214th Symposium of the Falk Foundation e.V. in Oxford.

Gastroenterologists hope that personalized medicine will permit highly-effective treatment for every patient that is also well tolerated. Several tenuous steps in this direction have been made in clinical practice. However, basic research will be indispensable if this progress is to be maintained, as it provides the underlying insights required to develop tailored medicine. Basic researchers have been focusing with particular intensity on the genetics and immunology underlying bowel inflammation, the precise pathophysiological processes at the mucosal barrier, and the importance of the microbiome. However, finding solutions has not proven easy. If anything has become clear to researchers over recent years, it is the complexity of inflammatory processes in IBD – and it is precisely this complexity that makes it so difficult to answer the key question: Which patient should be treated with which therapy?

H. Sokol, Paris (France), defined the pathogenesis of IBD as the “activation of the gastrointestinal immune system against the gut flora in genetically-predisposed patients under the influence of environmental factors” (Fig. 1).

The human microbiota is crucial for the pathogenesis and clinical form of chronic inflammatory diseases. According to P. Rosenstiel, Kiel (Germany), the microbiota is highly variable from one person to the next, as well as within each person from oral to rectal localization. The microbiota also varies over time, and its composition changes dramatically in different phases of life. The composition of the microbiome in newborns depends on the mode of childbirth, and develops in early childhood into a microbiota with a high degree of instability and rapidly increasing diversity. Adults have a unique and differentiated microbiota whose composition changes much more slowly than in children. The gut microbiota can...
be influenced by environmental factors such as diet and illness, but also by genetics. As P. Rosenstiel explained, the interactions between the host and the microbiota are dependent on “epithelial gene expression.” For example, human Paneth cells with a variant version of an autophagy gene (ATG16L1 T300A) exhibit endoplasmic reticulum (ER) stress. In a mouse model in which wild-type and ATG16L1 ΔIEC mice were given water containing antibiotics, microbiomial diversity was not restored in the transgenic mice. As P. Rosenstiel noted, “these mice lost their resilience.”

H. Sokol also pointed out that the risk of IBD correlates with the number of antibiotic therapies during childhood. The aggressive effects of environmental factors on the gut microbiota are trans-generational, as they have existed for several generations and are passed onto future generations. These changes may be irreversible and may potentially increase an individual’s baseline risk of IBD. The potential therapeutic options include fecal microbiota transplant, next-generation probiotics, and microbial metabolic products.

Gut immune cells: exciting new ground

The impact of intestinal immune processes on Crohn’s disease and ulcerative colitis has also generated excitement. The different immune cells within the intestinal milieu engage distinct metabolic signatures. While this was once considered to be a secondary consequence of cell differentiation and activation, metabolic regulation has emerged as a key driver of multiple facets of the immune response. An intriguing development in this space is the discovery of a risk gene for Crohn’s disease on chromosome 13 (C13orf31), also termed FAMIN (fatty acid metabolism-immunity nexus), as explained by M.Z. Cader, Cambridge (Great Britain). This gene plays a major role in metabolic regulation, as it controls the oxidation and synthesis of endogenous fatty acids and the levels of acyl-CoA. At the same time, FAMIN also supports a novel immunometabolic signaling pathway that is essential for the production of macrophage ATP and the generation of mitochondrial reactive oxygen species (ROS) with antimicrobial activity.

Optimizing management of thiopurine therapy

Personalized medicine is already being realized by researchers who are using genetics, immunology, and pathophysiology to improve the use of currently-available medications. Thus thiopurine monotherapy for IBD using drugs such as azathioprine is often discussed. As M.C. Dubinsky, New York (USA), emphasized, the beneficial effects of azathioprine in combination with TNF-α inhibitors (TNFi) on clinical symptoms and the mucosa are well-established: Infliximab levels are higher and ADA (anti-drug antibody) titers are lower. A post-hoc analysis of the SONIC trial confirmed that these benefits do indeed result from higher drug concentrations. M.C. Dubinsky recommended administering the lowest concentration of thiopurines required to achieve the pharmacokinetic benefits of the combination therapy. The ideal targets are 6-TGN levels of > 235 pmol/8 × 10^8 RBC with 6-MMP levels < 5,700 pmol/8 × 10^8 RBC (Fig. 2). However, the risks of thiopurines are also well-known, in particular myelosuppression and pancreatitis. Genetics may allow targeted therapy of thiopurines in the future. For example, genetic variants of NUDT15 appear to be associated with a much higher risk of thiopurine-induced myelosuppression. Patients with this risk could be identified by NUDT15 genotyping before starting therapy. A polymorphism in HLA-DQA1-HLA-DRB1 also increases the risk of pancreatitis.

M.C. Dubinsky also shared a number of practical tips for optimizing thiopurine therapy:

- Measuring TPMT levels before the start of therapy
- Frequent blood counts during the first 12 weeks and every 3 months thereafter
- Monitoring thiopurine levels
- Wearing sun hat and sunscreen recommended
- Annual skin checks and annual pap smear
- Avoid combination therapy in certain patients (e.g. elderly patients)
- Check EBV status

Thiopurine metabolite profiles: interpretation in non-responding patients

<table>
<thead>
<tr>
<th>6-TGN</th>
<th>6-MMP</th>
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<td>Low</td>
<td>Low</td>
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<td>High</td>
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- Non-Adherence
- Underdosing
- Thiopurine-resistant
- Thiopurine-refractory
- Overdosing
- Education
- Increase dose
- Allopurinol
- Another drug
- Decrease dose

6-TGN: 6-thioguanine nucleotide; 6-MMP: 6-methyl mercaptopurine

Fig. 2: Thiopurine metabolite profiles (source: M.C. Dubinsky adapted from Gearry RB, et al., J Gastroenterol Hepatol. 2005;20:1149–57)
Overview

Migration of immune cells from the gut to joints

It would be logical to assume that rheumatoid arthritis afflicts the joints, while IBD afflicts the gut. However, the reality is somewhat more complicated: Both of these disorders are more closely intertwined than it would appear at first glance. For example, the development of targeted cytokine inhibitors – many of which are effective against both chronic disorders – has paved the way from organ-based disease classifications to mechanistic-based classifications. However, a disrupted intestinal barrier also appears to be an important trigger of joint inflammation in genetically-predisposed patients. According to G. Schett, Erlangen (Germany), a disrupted gastrointestinal barrier may be a trigger for arthritis. In this scenario, activated immune cells migrate from the bowel to the joints via the gut-joint axis. Restoring the barrier function in the gut inhibits the development of arthritis. In an animal model, larazotide could be shown to inhibit the migration of immune cells from the gut to the joints.

Optimizing TNFi therapy

As J.-F. Colombel, New York (USA), explained, the effectiveness of biologics is limited. Only about one-quarter of Crohn’s disease patients achieve complete remission after 52 weeks of TNFi therapy. Patients also need to be advised of the risk of side effects, especially lymphoma, noted J.-F. Colombel. In order to optimize treatment, he recommended an early intervention, targeted treatment, and close monitoring of the outcome of treatment (Fig. 3). However, in the end the most important decision is which drug is right for which patient. He listed several clinical factors that are predictors of non-response to TNFi, including advanced age, very early onset IBD (VEO-IDB), and biomarkers such as low albumin, as well as the intestinal expression of certain genes including TNFAIP6, S100A8, IL-11, G0S2, and S100A9TREM-1. In light of the ever-increasing number of available TNFi and other biologics, he called for more comparative data: “We need more comparative data from meta-analyses, real-world data, and direct head-to-head studies.” One objective of personalized medicine is to find the right patients for each TNFi. Antibodies targeting interleukin-12 and interleukin-23 are also used to treat IBD. According to B. Siegmund, Berlin (Germany), these antibodies are particularly effective at treating psoriasis and “psoriasis-like” lesions. The benefit of biologics that only inhibit interleukin-23 is currently under investigation.

Optimizing efficacy of anti-TNFs

![Optimizing efficacy of anti-TNFs](image)

Fig. 3: The three pillars of treatment optimization (source: J.-F. Colombel/Colombel JF, et al., Gastroenterology. 2017;152:351–61)
The gut microbiota as a therapeutic target

Fecal microbiota transplant (FMT) is one of the novel therapeutic approaches just around the corner. As A. Hart, London (Great Britain), explained, the gut microbiota plays a crucial role in determining the course of IBD for a subset of patients. It also presents an attractive therapeutic target, as reflected by the positive effects of FMT on several disorders including ulcerative colitis (Fig. 4). Nonetheless, many questions remain unanswered, including who represents an ideal donor and which methods of administration are feasible. Furthermore, as M.F. Neurath, Erlangen (Germany), explained, it remains unclear whether transplanting “normal” bacteria is sufficient, or whether these bacteria first need to be modulated in order for them to colonize and survive in the gut.

Can oral peptides compete against antibodies?

B.G. Feagan, London (Ontario, Canada), pointed out the importance of substances that are selective for the gut, such as vedolizumab, which blocks the cellular adhesion molecule $\alpha_4\beta_7$ integrin. He described etrolizumab, anti-MAdCAM, oral peptides, and S1P1 agonists as future prospects. Etrolizumab is a humanized antibody that targets the $\beta_7$ subunits of the $\alpha_4\beta_7$ and $\alpha_E\beta_7$ integrins. Approximately one-fifth of the patients in the EUCALYPTUS study achieved clinical remission. Oral peptides targeting $\alpha_4\beta_7$ are also of interest, as these represent a competitor to antibodies. Sphingosine-1-phosphate receptor modules – which have been previously used to treat multiple sclerosis – are also promising candidates, as demonstrated by studies on ozanimod. However, according to B.G. Feagan, the next generation of biologic therapy will be combination therapies. Nonetheless, he did admit that TNFi remain important agents for inducing remission.

According to G. van Assche, Leuven (Belgium), the proper role of Janus kinase (JAK) inhibitors also remains uncertain. It is difficult to predict the safety and effectiveness of the individual inhibitors due to their multifunctional roles. Tofacitinib, a JAK1/3 inhibitor, is already in clinical use, while the selective JAK1 inhibitor upadacitinib is currently in the approval process. However, data is still not available for IBD from large safety cohorts.

What will the future bring?

G. D’Haens, Amsterdam (The Netherlands), provided a glimpse into the future of personalized treatment of IBD. To date, there are only a small number of evidence-based practice recommendations that account for phenotypic diversity. G. D’Haens sees patient stratification as the way forward, with diagnostic tools that allow the type of disease to be predicted becoming equally established in clinical practice as point-of-care diagnostic testing.
A big puzzle with many pieces

Basic research has uncovered a number of insights that have expanded our understanding of inflammatory bowel diseases (IBD). But achieving the overarching goal of highly-effective and well-tolerated treatment options for Crohn’s disease and ulcerative colitis will require a good eye for putting the pieces of this puzzle together. The intriguing results from new studies presented in Oxford will bring us one step closer to this goal.

IBD: overlapping polygenetic disorders

Crohn’s disease and ulcerative colitis are polygenetic disorders that share some, but not all, susceptibility loci, as M. Parkes, Cambridge (Great Britain), explained. In conjunction with environmental factors, these loci determine the localization of the disease, its course, and the extent of extraintestinal manifestations. Genome-wide association studies have identified loci with larger and smaller effects. Interestingly, as M. Parkes explained, “many of the large-effect loci are specific for ulcerative colitis or for Crohn’s disease, whereas the small-effect loci occur not only with both ulcerative colitis and Crohn’s disease, but also likely with many other immune-mediated disorders.”

IL23R R381Q: a gene variant with a protective function

Multiple different mutations in genes in the IL23-Th17 signaling pathway are associated with IBD. However, as C. Abraham, New Haven (USA), explained, some mutations can have protective functions, with one example being the IL23R R381Q variant. The IL-23 signaling pathway plays an important role in intestinal inflammation, with IL23R inducing JAK2, TYK2, and a number of STAT signaling pathways. In patients harboring IL23R Q381, macrophages exhibit reduced signaling capacity in line with a loss-of-function mutation.

Interferon-α: Is it effective or not?

Interferon (IFN)-α is one of the key mediators of inflammation processes: For example, IFN-α upregulates the anti-inflammatory molecule IL-10. However, its clinical effects are quite disappointing, as H. Tilg, Innsbruck (Austria), explained. There was no benefit of IFN-α versus placebo with regard to clinical remission of ulcerative colitis. In contrast, preclinical animal studies have shown IFN-α to be effective at treating IBD. These apparently contradictory results may be caused by opposing effects on intestinal inflammation depending on the phase of the disease: Specifically, IFN-α reduces acute intestinal damage on the one hand, but on the other hand it counteracts healing of the inflammation resulting from exposure to DSS (dextran sulfate sodium) in a dose-dependent manner.

Single-cell RNA sequencing in IBD

A. Simmons, Oxford (Great Britain), described the possibilities for IBD opened by the new technology of single-cell RNA sequencing (scRNA-seq). This talk focused on the heterogeneity of cell types in the gut and the identification of new cell populations and marker genes. She discovered that BEST4/OTOP2 cells are dysregulated in IBD and colorectal cancer. Furthermore, this technology allows specific cell pathologies to be detected in the context of IBD.

In brief

M. Parkes, Cambridge (Great Britain):

“many of the large-effect loci are specific for ulcerative colitis or for Crohn’s disease, whereas the small-effect loci occur not only with both ulcerative colitis and Crohn’s disease, but also likely with many other immune-mediated disorders.”
Dysregulated cell death leads to inflammation

The integrity of the intestinal mucosal barrier is of immense importance. When bacteria migrate into the intestinal wall in an uncontrolled manner, they can trigger severe intestinal and systemic disorders. According to C. Becker, Erlangen (Germany), “this leads to epithelial cell death and intestinal inflammation.” Controlling epithelial cell death in an inflammatory environment is a crucial step toward ensuring the integrity of the mucosal barrier. The TNF receptor plays a key role in this process as a “death receptor” that can trigger cells to undergo apoptosis. Dysregulated cell death is the primary trigger of intestinal inflammation and tissue destruction. This process is also conceivably a target for therapeutic interventions. For example, apoptosis is dependent on the STAT signaling pathway in Paneth cells, and can be blocked by JAK inhibitors. However, these pathophysiological processes are highly complex in IBD, as J. Grootjans, Amsterdam (The Netherlands), pointed out. He focused on ER stress, which triggers an unfolded protein response that leads to elevated counts of IgA-producing plasma cells in the intestinal epithelium. Immunoglobulin (Ig)A is an important molecule in IBD because it protects the mucosal epithelia and can alter the microbiota through various mechanisms, including a reduction in bacterial virulence.

Resilient microbiota

A. Macpherson, Bern (Switzerland), discussed the links between nutrition, the maternal microbiota, and the innate immune system. Changes in the microbiota can be observed shortly after eating. However, the microbiota shows immense long-term resilience to changes in the metabolic environment.

IL-22 confers protection from genotoxic stress

The genomic integrity of epithelial stem cells is guarded by the DDR (DNA damage response), which represents the sum of all cellular mechanisms that are activated when DNA is damaged. According to A. Diefenbach, Berlin (Germany), IL-22 is an important regulator of this system, as it ensures potent initiation of DDR following DNA damage. Accordingly, deficiencies in IL-22 can be severe. Experiments in a mouse model utilizing IL-22^{−/−} and IL-22^{+/−} mice have shown that IL-22 deficiency can enhance the development of colitis-associated cancers, both proximally, distally, and in the rectum.

“Teaching” dendritic cells

Complex interactions between microbiota and the host immune system take place in the gut, interactions which must be tightly regulated in order to maintain the required homeostasis. The immune system must keep pathogenic microbes in check while simultaneously tolerating commensal bacteria. Disruption of this homeostasis may trigger the onset of IBD. Dendritic cells play a key role in this system. As E.J. Villablanca, Stockholm (Sweden), explained, one of the central actors in this process is retinoic acid, which is metabolized from vitamin A and acts as an immunomodulator. It is responsible for instilling tolerance in dendritic cells, among other functions.
Can T cell exhaustion provide help to predict the course of the disease?

Although the course of Crohn’s disease varies greatly between individual patients, there are currently no reliable prognostic markers. In the opinion of J. Lee, Cambridge (Great Britain), peripheral CD8 cells may potentially be of predictive value at the time of diagnosis. He investigated whether the CD8 T cell exhaustion observed in IBD may be a suitable marker for predicting the course of the disease. However, this process requires cell separation and the use of microarrays. The PROFILE (PRedicting Outcomes For Crohn’s disease using a moLEcular biomarker) study is now investigating the capabilities of a prognostic transcriptional biomarker identified based on these insights.

High levels of OSM expression are predictive of non-response to anti-TNF

OSM (oncostatin M) and OSMR (oncostatin M receptor) have been proposed as potential new IBD susceptibility genes that may be relevant in both Crohn’s disease and ulcerative colitis. As F. Powrie, Oxford (Great Britain), explained, “both OSM and its receptor are elevated in IBD, especially in patients with severe forms of the disorders.” OSM is expressed at especially high levels in myeloid cells, while OSMR is highly expressed in stromal and endothelial cells. High expression of OSM is predictive of non-response to anti-TNF-α therapy and may promote chronic intestinal inflammation. Thus, a high therapeutic need remains for these patients.

Insights gained from monogenic disorders

Intestinal inflammation may be caused by a large number of genetic abnormalities that can impair the immune system and the epithelial barrier of the intestines. As H. Uhlig, Oxford (Great Britain), explained, “more than 70 genetic disorders present clinically in the form of intestinal inflammation.” Monogenic forms of IBD are rare and exhibit a heterogeneous clinical spectrum, and typically have a very early onset before the age of six. Monogenic disorders represent natural experimental models for deciphering the network of signaling pathways that regulate homeostasis in the gut. N. Cerf-Bensussan, Paris (France), described the case of a girl who developed autoimmune enteropathy at the age of three months. The cause was identified as a mutation in PTPN2 that led to activation of the JAK/STAT signaling pathway. Further studies showed that the strict regulation of the JAK/STAT signaling pathway in resident T lymphocytes is crucial for immune homeostasis in the upper gastrointestinal tract.

Microbiota-induced B- and T-cell responses: informative indicators

O. Pabst, Aachen (Germany), focused on changes to the intestinal T cell compartment triggered by gut microbiota. Microbes and their metabolites influence the immune system in an individual manner that is different for each host and diet. Conversely, the immune system can also affect the microbiota. Studies using an adoptive transfer colitis model in mice, in which identical T cell clones were transferred into different recipients, revealed the effects of these T cell clones on microbiota-triggered intestinal pathology. These studies provided an insight into the coordination of microbiota-induced B- and T-cell responses and into the regulation of homeostasis in the gut.
How IL-10 production is triggered by Helicobacter hepaticus

One of the functions of the gut microbiota is the ability to trigger immune responses that are necessary for maintaining human health. As a result, in-depth research is required in order to understand the cross-talk between the host and its microbiota at the cellular and molecular level, according to C. Danne, Jouy-en-Josas (France). She focused her attention on the microbe Helicobacter hepaticus, which colonizes the microbiota of the mouse but is not pathogenic. Nevertheless, this microbe is still capable of activating an anti-inflammatory signature in macrophages. H. hepaticus produces a large polysaccharide that induces IL-10 production without triggering a corresponding inflammatory reaction in macrophages. This polysaccharide-specific response is dependent on the TLR2/MSK/CREB signaling pathway. The goal now is to better understand this interaction and to develop innovative therapeutic strategies based on it.

The crucial role of exposure to microbiota early in life

It is not clear how disruptions in the symbiosis between the host and its microbiota in early life affect the immune system later in life. G. Eberl, Paris (France), demonstrated several years ago that the microbiota regulates the type 2 immune response via RORγt T cells. He could now show that exposing germ-free mice to a bacterial cocktail during weaning triggers a major immune response which, however, only occurs during this window of opportunity. This immune reaction is important for immune defenses later in life. Mice not exposed to this bacterial cocktail developed an increased sensitivity to immune system disorders later in life.

Inhibiting bacterial respiration

Inflammation-associated dysbiosis of the gut microbiota has been demonstrated for a number of disorders, including IBD but also colorectal cancer, necrotizing enterocolitis, HIV enteropathy, parasitic infections such as toxoplasmosis, or infections with enteric pathogens such as Salmonella and Citrobacter spp. As S.E. Winter, Dallas (USA), explained, the metabolic environment of the gut undergoes changes during inflammation, with accumulation of ROS (reactive oxygen species) and RNS (reactive nitrogen species) in the inflamed gut. Respiratory processes promote the expansion of pathogenic and commensal enterobacteria. In the mouse model, mucosal inflammation is improved when bacterial respiration is inhibited, for example using tungstate, a potent inhibitor of anaerobic respiration.

The inflammasome as a therapeutic target

“Danger” signals activated by the innate immune system are frequently observed in inflammatory disorders. One possible mechanism by which these “danger” signals are triggered is via activation of inflammasomes, especially NLRP3, which has been particularly well studied. According to E. Latz, Bonn (Germany), NLRP3 is now considered to be a promising therapeutic target.

Strategies for fighting fibrosis

“Although fibrosis is relevant to IBD, we still aren’t able to treat it,” remarked G. Rogler, Zurich (Switzerland), on the topic of fibrosis. “It remains an unsolved clinical problem in Crohn’s disease.” Because inflammation and fibrosis manifest independently of each other, fibrosis cannot be prevented by anti-inflammatory treatment. G. Rogler hopes that a heterologous transplantation model will provide a suitable in vivo setting for studies on intestinal fibrosis. Established anti-fibrotic agents such as pirfenidone (which has been used to successfully treat pulmonary fibrosis) as well as the anti-MMP9 antibody are effective in this model. To the question of whether it will be possible to prevent or treat fibrosis in IBD, G. Rogler responded “yes, we will get there, but it will still take at least another 10 years.”
In brief

“Don’t operate too soon”

According to S. Fichtner-Feigl, Freiburg (Germany), physicians often rely on their gut feeling when deciding whether or not surgery is indicated. “Which is not good,” he added. He listed the following indications for elective surgery of ulcerative colitis:

- drug failure,
- cancer,
- dysplasia,
- strictures.

Emergency surgery is indicated in cases of ASUC (acute severe ulcerative colitis), especially if patients do not respond to intravenous steroids and do not improve within four to seven days of salvage therapy. However, he also argued against operating too early, since the course of the disease may not yet be known.

Molecular endoscopy: more than just pretty pictures

R. Atreya, Erlangen (Germany), presented fascinating images of fluorescent anti-TNF-α antibodies from molecular endoscopy that also have a practical benefit in routine clinical practice. The mucosal expression of target molecules such as TNF-α, which is visualized by topical application of a fluorescent anti-TNF-α antibody, has predictive value for a patient’s response to targeted therapy. In vivo, molecular endoscopy has demonstrated that expression of mucosal membrane-bound TNF (mTNF) is associated with the clinical effectiveness of a subsequent anti-TNF therapy in patients with Crohn’s disease. Preliminary data from 25 patients revealed clinical response in 13 patients, 2/13 of whom had low mTNF and 11/13 high mTNF. “Molecular endoscopy has now made the leap to clinical trials”, remarked R. Atreya.

Special Lecture
The genetic architecture of IBD in different populations

“We still don’t have a good understanding of the differences in the genetics of Crohn’s disease and ulcerative colitis between different populations” explained J. Cho, New York (USA). Ulcerative colitis is considered to be the “more typical” of the two inflammatory disorders. The most important and most validated disease locus is the HLA region (MHC class II). As J. Cho explained, “the genetic architecture at this locus is nearly identical between European and east Asian regions.” In contrast, much larger differences are observed in Crohn’s disease. The most important disease locus in Europe is NOD2, which is predictive of ileal localization and a stricturing disease phenotype. However, this locus is rarely relevant in patients from Africa, the US, or East Asia. An association between Crohn’s disease and IL23R and PTGER4 has been observed in patients in Africa and the US as well as in patients of European descent. The situation for patients in East Asia is particularly interesting, because there is a clear association between Crohn’s disease and the HLA class II locus as well as the TNFSF15 risk locus. The genetic architecture at these loci differs greatly between European and Asian patients.
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G. Rogler, Zurich (Switzerland)
B. Vucelic, Zagreb (Croatia)
There is now a long-established tradition of awarding poster prizes to young scientists at the international symposia of the Falk Foundation e.V., a tradition that was continued at Symposium 214 in Oxford. Prizes were awarded to the following researchers:

**D. Aschenbrenner**, Oxford (Great Britain), for the project: “An IL-1-dependent IL-23 inflammatory monocyte signature correlates with disease severity and treatment response in patients with inflammatory bowel disease”.

**L. Martínez-Sanchez**, Erlangen (Germany), for the project: “Rac1-mediated maintenance of epithelial integrity in the gut”.

**P. Pavlidis**, London (Great Britain), for the project: “The interleukin-22 transcriptional programme is activated in human colonic inflammation and associated to anti-TNF-α primary non-response in Crohn’s disease”.

From left to right: Prof. M.F. Neurath, Dr. D. Aschenbrenner, L. Martínez-Sanchez, Dr. P. Pavlidis, Carola Falk (for the Falk Foundation e.V.)
“There’s certainly no lack of fascinating questions”

“Personalized medicine” is the new buzzword that nearly every field of medicine seems to be embracing. But what does this term actually mean, what are the implications for IBD in particular, and what is the state of current research? We posed these questions to Prof. Dr. Martin F. Neurath, Erlangen (Germany), who was the scientific organizer of Symposium 214.

Editor.: The development of innovative therapeutic principles has advanced the treatment of inflammatory bowel disease in recent years. How large is the need for even more improvements?

Prof. Neurath: I think we still have a lot of room for improvement. At present, 70% of Crohn’s disease patients and about 30% of ulcerative colitis patients still require surgery at some point due to complications of their disease. Moreover, many patients also suffer from the side effects of the drugs they are currently taking. Hence, we need an optimized treatment strategy that we can initiate early in the course of the disease.

Why is optimization needed at this point in time?

We have only recently gained deeper insights into the genetics, pathophysiology, and immunology of inflammatory bowel disease, and we now have a better understanding of the progression of these disorders and of the mechanisms we need to interfere with in order to treat them effectively. Genetic studies have shown that the pathological processes are much more complex than we could have imagined 10 or 20 years ago. We need to pay much more attention to each patient’s individual genetic predisposition when selecting treatments.

You mentioned personalized medicine, which is taking root in an increasing number of medical fields. What exactly does the term mean?

Personalized medicine is the concept that physicians should try to select the treatment that is most suitable for each individual patient and his or her disease, with the highest likelihood of effectiveness and the lowest likelihood of problems and complications possible. The current outlook is that we will one day perform a panel of diagnostic tests that will guide our therapeutic decisions.

Is there any area of IBD therapy where personalized medicine is already being implemented, at least in part?

We are currently taking only small steps. Measuring fecal calprotectin, serum trough levels, or ADAs (anti-drug antibodies) in patients on TNF-α inhibitor therapy, for example, is a good start. If serum trough levels are too low, we can raise the dose. If a patient develops ADAs, a different TNF inhibitor can be used or the patient can be switched to a different class of drugs. However, these strategies have yet to be widely embraced in routine clinical practice.

What options for optimizing treatment can be implemented today using the treatment strategies that are currently available?

In addition to TNF inhibitors, a number of other drugs are now available, including integrin blockers, JAK inhibitors, and other cytokine inhibitors. However, we still have no idea what the best order of these drugs is. There are also a large number of other unanswered questions: Should we always start with TNF-α inhibition or is this decision insignificant? Do we have any opportunities to decide which patients would be better off starting with a TNF inhibitor and which patients should start with an integrin blocker? The first clinical trials comparing these different mechanisms are now underway, but even they won’t really bring us any closer to the goal of personalized medicine. We would like to be able to tell patients “based on your current situation, we recommend this or that strategy.” That aspect of personalized medicine is currently one of the most important.
**The CALM study attempted to provide individually-optimized therapy by orienting patients' treatment according to the biomarkers CRP and calprotectin. Is that the right direction?**

It’s at least one step toward personalized medicine. CRP levels do not have much predictive power, since many patients with severe intestinal inflammation have normal CRP levels. So a normal CRP level doesn’t mean that a patient has no inflammation. Calprotectin has a greater predictive value, but also has the limitation of only reflecting inflammation in general. In other words, elevated CRP might also just be a sign of an infection occurring as a complication of treatment. Nonetheless, the use of biomarkers still represents the first steps toward improving our analysis of each individual patient’s situation, and toward using that information to decide whether he or she should be more closely monitored or needs more intensive treatment. It is difficult to rely on symptoms alone.

**The road from the pathophysiology studies you cite to actual clinical practice is a long one. What do you think currently has the highest chance of being implemented in the near future?**

The ability to modulate the immune system through completely new mechanisms is relatively tangible at the moment. IBD research is also a few steps ahead of dermatology and rheumatology in this regard, since we are already able to manipulate the entry and exit of immune cells into and out of the gut. This is a very exciting field where we can expect quite a few new developments. Research is also focusing on the microbiome, although it is still in its infancy, meaning that our analyses are still more descriptive than anything else. The first studies attempting to isolate, purify, and characterize specific bacteria have now begun, in the hopes of perhaps re-introducing these bacteria into patients in a controlled manner that would restore the proper balance between bacterial species. When these studies are complete, we will know whether this strategy is effective and if so, in which individual situations. At the same time, we still don’t know whether transplanting “normal” bacteria is sufficient, or whether these bacteria first need to be modulated in order for them to colonize and survive in the gut. We also need to find out which patients are suitable for the manipulation of microbiota, and which patients would be better off with classical TNF inhibition. Moreover, we will also have to examine local inflammation more closely to determine where we can intervene. In my view, this will be one of the key questions.

**The use of genetic tools is also a topic of discussion. How far has research advanced in this direction?**

There is no doubt that genetic studies have advanced our understanding of the disease considerably, and that we have discovered a number of novel pathophysiological mechanisms. For example, we now know that certain mutations, such as mutations in the IL-10 receptor gene, lead to very early onset IBD. This has led to strategies that focus on treating these patients with IL-1 inhibitors. However, genetic testing is not a routine diagnostic instrument and it remains unclear whether it ever will be. It might also be necessary to combine multiple sources of information, like genetics and the microbiome, to reach an answer.

**What is your own field of research?**

My main focus has always been immunology. We are currently studying cells that mediate inflammation, which are primarily antigen-presenting cells, macrophages, and T cells. My main focus has been on the JAK-STAT pathway. I started thinking about the idea of inhibiting IL-12/23 more than 20 years ago. It now seems very likely that we will soon have specific IL-23 inhibitors in addition to the IL-12/23 inhibitors already available, and once we do we will start to study the importance of these new drugs. JAK inhibitors are also an interesting class of drugs. A large number of cytokines are activated by JAKs, with 15 activated by JAK1 alone. In other words, if you inhibit JAK1, you’re inhibiting 15 cytokines at once. That’s why these drugs are so potent, but also why they might potentially cause side effects.

**Does personalized medicine also hold hope for patients with mild IBD?**

Absolutely, because it is conceivable that IBD with an initially mild onset may progress, meaning that locally-restricted ulcerative colitis may eventually develop into pancolitis. Personalized medicine should inform us about which patients can be expected to develop an aggressive form of the disease, allowing us to treat aggressively at early stages.

**If you could hazard a guess about the future, where do you think treatment of IBD will be in 30 years?**

My assumption is that in 20 to 30 years, we will have a diagnostic system that will allow us to analyze patients very precisely and to tell them which medications are most suitable for them specifically. But in order to get there, we will need to answer a number of fascinating questions – there is certainly no lack of those.
Scientific Dialogue in the Interest of Therapeutic Progress

Symposium 219
IBD-Patients – In the Center of Care
Copenhagen, Denmark
May 22–23, 2020

Symposium 220
XXVI International Bile Acid Meeting: Bile Acids in Health and Disease 2020
Amsterdam, The Netherlands
July 10–11, 2020

Symposium 221
IBD Management in the New Decade: Old Myths and New Realities
Athens, Greece
October 2–3, 2020

Symposium 222
Eosinophilic Esophagitis – Advanced Science for Everyday Challenges in Clinical Practice
Zurich, Switzerland
November 20–21, 2020

Workshop
Primary Liver Cancer – Emerging Concepts and Novel Treatments
Mainz, Germany
February 13–14, 2020

Symposium 218
Current Challenges of Inflammatory Bowel Disease
Mexico City, Mexico
March 6–7, 2020

Workshop
Microscopic Colitis – New Insights and Recommendations
Copenhagen, Denmark
May 21, 2020

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