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REVIEW ARTICLE

News from the "5th international meeting on inflammatory bowel diseases" CAPRI 2010

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Abstract

At the "5th International Meeting on Inflammatory Bowel Diseases selected topics of inflammatory bowel disease (IBD), including the environment, genetics, the gut flora, the cell response and immunomodulation were discussed in order to better understand specific clinical and therapeutic aspects. The incidence of IBD continues to rise, both in low and in high-incidence areas. It is believed that factors associated with 'Westernization' may be conditioning the expression of these disorders. The increased incidence of IBD among migrants from low-incidence to high-incidence areas within the same generation suggests a strong environmental influence.

The development of genome-wide association scanning (GWAS) technologies has lead to the discovery of more than 100 IBD loci. Some, as the Th 17 pathway genes, are shared between Crohn's disease (CD) and ulcerative colitis (UC), while other are IBD subtype-specific (autophagy genes, epithelial barrier genes). Disease-specific therapies targeting these pathways should be developed. Epigenetic regulation of the inflammatory response also appears to play an important role in the pathogenesis of IBD.

The importance of gut flora in intestinal homeostasis and inflammation was reinforced, the concepts of eubiosis and dysbiosis were introduced, and some strategies for reverting dysbiosis to a homeostatic state of eubiosis were proposed. The current status of studies on the human gut microbiota metagenome, metaprotome, and metabolome was also presented.

The cell response in inflammation, including endoplasmic reticulum (ER) stress responses, autophagy and inflammasome-dependent events were related to IBD pathogenesis. It was suggested that inflammation-associated ER stress responses may be a common trait in the pathogenesis of various chronic immune and metabolic diseases.

How innate and adaptive immunity signaling events can perpetuate chronic inflammation was discussed extensively. Signal transduction pathways provide intracellular mechanisms by which cells respond and adapt to multiple environmental stresses. The identification of these signals

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has led to a greater mechanistic understanding of IBD pathogenesis and pointed to potentially new therapeutic targets.
A critical analysis of clinical trials and of risk-benefit of biological therapy was presented. The problem of Epstein–Barr virus (EBV) and lymphoma in IBD was extensively discussed. Lymphomas can develop in intestinal segments affected by IBD and are in most cases associated with EBV. The reasons of treatment failure were also analyzed both from basic and clinical points of view.
Two very interesting presentations on the integration of research and clinical care in the near future closed the meeting. These presentations were focused on macrotrends affecting healthcare delivery and research, and the need to innovate traditional infrastructures to deal with these changing trends as well as new opportunities to accelerate scientific knowledge.

Contents

The "5th International Meeting on Inflammatory Bowel Diseases was held in Capri (Italy) from April 8 to 10, 2010, under the presidency of R. Caprilli (Italy). The meeting was restricted to 120 participants including invited speakers, authors (young investigators) of selected papers, and "thought leaders". The structure of the meeting consisted of 8 sessions, in which selected basic aspects of IBD, including the environment, genetics, the gut flora, the cell response and immunomodulation were used in order to improve understanding of and discuss specific clinical and therapeutic aspects. The meeting was designed to be very interactive and focused more on basic science rather than purely clinical topics. The key objectives of Capri 2010 were: 1) Update knowledge in key areas of IBD pathogenesis; 2) Incorporate into IBD emerging scientific concepts by inviting top experts in areas outside of IBD; 3) Ponder about the future rather than discuss already existing information; and 4) Attract and retain the brightest young investigators in the field of IBD. The aim of this article is to summarize and outline the scientific news presented and discussed at the Capri 2010 meeting.

1. Environment and disease pathogenesis

The incidence of IBD continues to rise, even in high-incidence areas. It has been estimated that the prevalence of IBD in the general population may be as high as 0.4–0.5% in North America (United States and Canada), translating into approximately 1.4 million persons with these chronic intestinal disorders.[1] In the United States, it is estimated that IBD accounts for 1.4 to 1.9 million outpatient visits, 90 to 200 thousand hospitalizations, and approximately $2.1 billion in direct and indirect costs in 2004 (E.V. Loftus, USA).

The incidence and prevalence of ulcerative colitis (UC) and Crohn's disease (CD) are also increasing in areas that historically were thought to be low-incidence areas, such as East Asia, the Indian subcontinent, the Middle East, Latin America, and Eastern Europe.[2] It is believed that factors associated with 'Westernization' may be conditioning the expression of these disorders.[3,4] The increased incidence of IBD among migrants from low-incidence to high-incidence areas, within one generation (e.g., South Asians), is also suggestive of a strong environmental influence. A North–South gradient has been reported, not just in IBD but also in other immune-mediated disorders.[5,6] Racial and ethnic differences are also present: Mexican-Americans are more likely to develop UC than CD (more proximal disease extent, fewer extraintestinal manifestations, high prevalence of pANCA), whereas African-Americans are more likely to develop CD (more colonic or perianal, less ileal, more arthritis and uveitis).[7]

The two best understood environmental influences on the expression of IBD continue to be cigarette smoking and appendectomy. Both of these factors are associated with a reduced incidence of UC, while quitting smoking is associated with an increased risk of UC. Smoking is a risk factor for CD and increases its severity, and appendectomy may be a weak risk factor for CD. Intriguing reports on the role of drinking water quality and air quality on the incidence of IBD

have recently appeared in the literature, but confirmatory studies are needed before we conclude that they represent true risk factors.

Modern lifestyle might alter another environmental factor, the enteric microflora. Thus may occur in different ways: improved sanitation, decline in endemic parasitism, decreased exposure to soil microbes, decline in *Helicobacter pylori* infection, increased antibiotic usage, less crowded living conditions, refrigeration, sedentary lifestyle, obesity, and increased consumption of refined sugars and saturated fats.[4] Diet as a risk factor is difficult to study and may act indirectly via the microflora. Future studies need to focus on dietary patterns rather than individual foods.[8]

The results of studies of early life influences and risk of IBD have been, at best, conflicting. While the hygiene hypothesis, postulating that lack of early exposure to common pathogens or commensal bacteria might result in abnormal immune response to these antigens later in life, remains attractive, this has not been borne out in a consistent fashion across studies at the clinical or population level. In regard to the relation between psychological stress and IBD, recent systematic review of 18 prospective studies examining stress as a risk factor for disease exacerbations showed a significant association, and coping behaviors appear to modulate the effect of stress.[9]

Future directions should focus more on the gut microbiota, the effect of diet on microbiota, early life events, migration from low-prevalence to high-prevalence areas, and residents of transitioning societies (developing to developed).

Epidemiological studies of human diseases should not only be aimed at providing data on their prevalence and incidence, but should generate hypothesis stimulating further experimental research for a better understanding of their pathogenesis and management. Like IBD, asthma and allergic diseases have a very high and increasing prevalence worldwide (S. Bonini, Italy). Comparing epidemiological data of asthma and allergic diseases to those of IBD may help understand similarities and differences in these chronic debilitating inflammatory conditions. Among the various factors suggested to be responsible for the increasing prevalence of asthma and allergic diseases are environmental changes, declining prevalence of microbial burden, lack of physical exercise and diet,[10] all of which also apply to IBD. In particular, in regard to the tight relationship between microbial stimulation of the immune system and the prevalence of allergic diseases, the prominent role of the gut in modulating innate and adaptive immune responses appears not to be restricted to the gut but also highly relevant to other systemic inflammatory conditions.

Immune-mediated inflammatory conditions, like IBD, exert their effects through various cells and the proinflammatory mediators they secrete. Prominent among these are CD4-positiveT cell subsets and their related cytokines. In addition to the two classical T helper 1 (Th1) and Th2 cells, the Th 17 subset must also be considered (B. Stockinger, UK). IL-17 producing T cells are generated by a unique mixture of conditioning cytokines, including IL-6, IL-23 and TGF-β. IL-17 mainly mediates adaptive immune responses against pathogens (fungi, bacteria) but seems to also be involved in autoimmune syndromes and IBD.[11]

IL-17 and IL-22, both Th17-derived cytokines, are strongly up regulated in IBD but the distinction between beneficial and pathological effects for these two cytokines is still unclear. A low level of IL-17 expression is beneficial for gut homeostasis and barrier function. IL-17 has been shown to promote tight junction formation and mucin secretion. IL-22 plays a role in the induction of defensins (antimicrobial peptides) and is therefore important in the response against gut pathogens. On the other hand, excessive IL-17 and IL-22 expression correlates with intestinal inflammation.

It has been recently shown that the Th17 program is modulated by interaction with endogenous and environmental stimuli that trigger the aryl hydrocarbon receptor (AHR).[11–13] Both endogenous and exogenous AHR ligands influence Th17 cell response: this may be beneficial (induction of IL-22 for mucosal defense, wound healing) or detrimental (exacerbation of Th17-mediated autoimmunity). It is likely that endogenous AHR ligands play a role in mucosal homeostasis. A wide variety of potential AHR ligands from the commensal flora as well as dietary components may be involved. It still remains to be determined to what extent AHR activation due to interactions with gut flora or food constituents or chemical pollutants influences IBD pathology and the function of intestinal IL-17 producing T cells.

Aluminum worsens intestinal inflammation and delays mucosal repair in experimental models of colitis, suggesting that is an environmental microparticle that could participate to the dysregulation of intestinal homeostasis and IBD (G. Pineton de Chambrun, France). Aluminum is a contaminant which could be involved in IBD pathophysiology in two ways. First, for environmental reason: aluminum is a common metal with ubiquitous distribution (water, soil, atmosphere), it contaminates vegetables and drinking water, and human activities increase aluminum bioavailability (industries, intensive farming, alimentary additives, drugs, etc); after oral intake, aluminum could interact with intestinal mucosa and the local immune system. Second, for biological reason: aluminum increases immune response *in vitro* (it acts as a vaccine adjuvant), induces granulomas and epidemic granulomatous enteritis in horses.

2. Genetics and disease pathogenesis

M. Parkes (UK) emphasized that the development of genome-wide association scanning (GWAS) technologies has lead to the discovery >100 confirmed IBD loci.[14–16] Some, as the Th17 pathway genes (*IL23R*, *IL12B*, *JAK2*, *STAT3*), are shared between CD and UC, while others are IBD phenotype-specific (autophagy gene as *ATG16L1*, *IRGM* and *NOD2* for CD; epithelial barrier genes *HNF4a*, *E-Cadherin*, *LAMB1* and *IL-10* for UC). Disease-specific therapies targeting these pathways should be considered.

The capacity of genetic findings in predicting who might develop IBD in the future remains limited. A more useful application would be the detection of genetic markers which, when combined with other biomarkers and clinical data, might predict disease course. Such markers have yet to be developed but the appropriate studies are underway. Additional pharmacogenetic insights are also likely to be gleaned through the analysis of GWAS data. The hope is that genetic studies can bring to light pathways of primary importance in IBD pathogenesis, and that some of these might be amenable to therapeutic manipulation.

Only a minority of the genetic risk for IBD is explained by genetic studies (R. Duerr, USA). Where is the rest of the missing heritability? The 'common disease, common variant' hypothesis states that common complex diseases are due, at least in part, to disease loci with one or only a few common genetic risk variants, each with relatively small effects. Are there more of such loci to be found? Do IBD loci identified in GWAS of common variants also harbor low frequency IBD-associated variants that may have larger effect sizes? Do unique families with multiple IBD members carry rare disease-causing variants? What about copy number and other types of structural variants? Answers to these important questions are expected from ongoing and future studies.

Instead of working from genotype to phenotype, perhaps working backwards from phenotype to genotype in the search for IBD genes might be an alternative option, as suggested by Abreu MT, USA.

Genetically heterogeneous, dominant diseases provide a significant challenge compared to recessive syndromic phenotypes. To genetically confirm any suspected disease-causing gene, one has to identify additional mutations in families with the same phenotype. Even without power for conclusive logarithm of odds (LOD) scores, the calculation of exclusion LOD scores or shared genomic regions can be very helpful. Exome enrichment and sequencing is never comprehensive, variants will be inherently missed. Thus, it is a good strategy to study a number of families, and do not bet everything on a single pedigree.

Next generation, high throughput sequencing has many applications that are useful for the study of IBD. Exomic sequencing is here; whole genome sequencing is next. Clinicians and investigators must identify distinct (sometimes rare) phenotypes through a variety of approaches including molecular and immunological ones. Microbiologic characterization of these distinct phenotypes will be necessary for the study to be complete. To genetically confirm any suspected disease-causing gene, one has to identify additional mutations in families with the same phenotype and ideally have more than one pedigree.

Genetic variants might partially modulate linear growth in pediatric-onset CD (J.J. Lee, USA). A significant association between growth impairment in CD and a stature-related polymorphism in the dymeclin gene (*DYM*) has been found. In addition, there is over-transmission of two CD-susceptibility alleles, 10q21.1 intergenic region (rs10761659) and *ATG16L1* (rs10210302), in growth-impaired CD children. Further studies need to validate these associations and investigate other stature and CD-susceptibility loci associated with the growth-impaired phenotype.

J. Lee (UK) reported that gene expression profiling of separated CD8 T cells reveals a gene signature of prognostic utility in IBD, as previously observed in systemic lupus erythematosus and vasculitis. A common CD8 T cell gene expression signature exists in both UC and CD. This is detectable at diagnosis before any treatment is given. This signature can divide patients into two distinct groups, which are otherwise indistinguishable. Patients in each group have significantly different disease courses: significantly shorter time to need for treatment escalation, and significantly more escalations required over time. These observations may have important clinical implications: 1) Ability to identify patients at diagnosis who are likely to run a more aggressive disease course, and 2) Personalized use of aggressive medical therapies (top-down).

3. The gut flora: homeostasis or inflammation

The role of commensal intestinal microbiota in nutrition and health, as well as in immune diseases was discussed in depth. J. Doré (France) explained the complexity of composition and function of the intestinal microbiota, including 100 trillion microorganisms (10 times the number of cells in the human body, and containing >100 fold more genes than in the human genome), mostly still to be cultured (~70% of dominant species). Thus, the whole gut microbiome can be considered a true organ that is geared up for protecting our health and well-being throughout all stages of our life and amenable to modulation.

The key interactions between food constituents, microbes and the host derive from a long co-evolution, resulting in a mutualistic association (microbiome and human genome crosstalks). The human intestinal microbiota is diverse in composition, and appears essentially subject-specific, although its functionality is expected to be relatively homogeneous among individuals. However, it is not yet clear at which level – metagenome, metaproteome or metabolome – this functional homogeneity can be identified. At the phylogenetic level, in adults, >80% of phylotypes belong to 3 major phyla (Bacteroidetes, Firmicutes, and Actinobacteria) most of which are subject-specific.[17] A few species (2%) are altogether more prevalent (conserved among individuals) and more represented, constituting a phylogenetic core. These mainly include *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Ruminococcus bromii*, *Alistipes putredinis*, *Subdoligranulum* sp, *Bacteroides vulgatus*, *Bacteroides uniformis rel*, *Parabacteroides distasonis*, *Bifidobacterium longum*, and *Dorea formicigeneran*. At the metaproteomic level, this translates into a high proportion of conserved proteins in the microbiota (50–60%) (Fig. 1). Future studies will better define the phylogenetic, metagenomic and functional core of the intestinal microbiota.[18]

The dominant mucosa-associated microbiota appears different from the luminal faecal microbiota and at the same time highly conserved in different segments of the intestine. Molecular evaluation allows to define the normal microbiota,

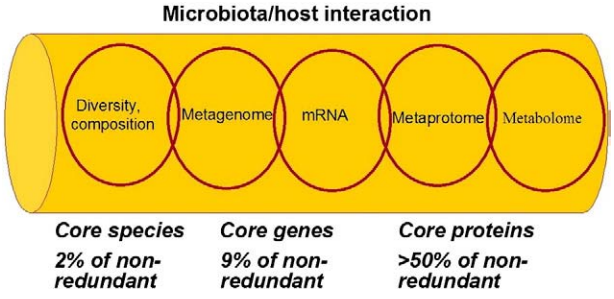

Figure 1 Core microbiome of the "normal" microbiota of healthy subjects.

or normobiosis, based on both static and dynamic parameters related to composition and function. These parameters include density, diversity, complexity, composition, core-species, dynamics (stability and resilience) of structure and functions (core microbiome). Hence, it becomes possible to explore the dysbiosis of the dominant intestinal microbiota in patients compared to healthy subjects. This opens novel fields of exploration: 1) Mechanisms by which dysbiosis of the intestinal microbiota acts in chronic, immune, metabolic or degenerative pathologies, and 2) Rationale for designing strategies to restore normobiosis/homeostasis.

Dysbiosis in CD is characterized by increased bacterial density at the mucosal level, increased proportion of immuno-agressive commensals (Gram-negative), reduced proportion of anti-inflammatory commensals (Gram-positive Firmicutes, Actinobacteria), and increased proportion of proteins potentially promoting autoimmunity. Such dysbiosis creates a vicious circle favoring aggravation and chronicity of the disease.[19,20] Very interesting is the anti-inflammatory properties of *F. prausnitzii* proved either in *in vitro* experiments (induction of high IL10/IL12 cytokine release by peripheral blood mononuclear cells, reduction of IL-1β induced IL-8 secretion by Caco-2 cells, and abolished TNF-α induced NF-κB activity in HT-29 cells) and *in vivo* experiments (both *F. prausnitzii* and its supernatant reduced blood and tissue parameters of inflammation in trinitrobenzene (TNBS)-induced colitis in Balb/c mice, and administered intraperitoneally its supernatant protected mice from death induced by TNBS).[21]

Microbiome specificities in immune-mediated diseases may allow to identification of predictive biomarkers, new targets and strategies for nutritional and/or therapeutic applications in intestinal disorders. The International Human Microbiome Consortium aims to gain an unprecedented view of the gut microbiota and validate microbial signatures of prognostic and diagnostic value. These approaches promise to identify the most redundant genomic traits of the human intestinal microbiota, thereby identifying the functional balance of this organ.

R.B. Sartor (USA) explained that since microbial composition is established in early life, a possible effect of host genetics on commensal intestinal bacteria may occur.[22,23] Genetic polymorphisms affect susceptibility to IBD by altering bacterial composition as well as altering immune responses to commensal bacteria and mucosal barrier function. The possible mechanisms for genetic regulation of enteric microbiota include altered Paneth cell function and expression of antimicrobial peptides, altered mucus production, altered secretion of IgA and IgM, and altered innate and adaptive immune responses.[24] CD could be determined by genetic influences on antimicrobial peptide expression. Genes associated with CD that affect bacterial killing include *Nod2* (defective α defensin production, clearance of intracellular bacteria), *ATG16L1* (autophagy, killing and processing of phagocytosed bacteria), *NCF4* (NADPH-mediated killing of phagocytosed bacteria), and *IRGM* (IFN-γ induced killing of phagocytosed bacteria).

B. Chassaing (France) reported that increased numbers of adherent-invasive *Escherichia coli* (AIEC) are associated with Peyer's patches of CD patients compared to those of controls. By expressing long polar fimbriae CD associated AIEC could use Peyer's patches as an open gate to induce early events of the disease pathogenesis.

S. Müller (Switzerland) analyzed the local expression of mannan-binding lectin (MBL) in the human intestine and investigated the effect of MBL-deficiency in experimental colitis with concurrent intestinal mucosal exposure to pathogenic yeast and bacteria. Deficiency of MBL is associated with increased prevalence of anti-*Saccharomyces cerevisiae* antibodies (ASCA) and with complicated phenotypes of CD. *C. albicans* and AIEC accelerate dextran sodium sulfate (DSS) colitis in MBL-deficient mice. MBL prevents excessive dissemination of *C. albicans* by supporting retention and clearance in circulation. MBL supports innate control of gut pathogens during inflammation.

D. Haller (Germany) put the gut microbiota and metabolism at the cross-road between homeostasis and chronic inflammation. He explained that the gut interface acts as a highly selective barrier and communication organ between the luminal environment including food and bacterial components and the host responsible for the regulation of metabolic and immune functions.[25] It is more and more evident that chronic degenerative disorders, including type 2 diabetes and IBD, share similar diseases mechanisms at the cellular level including endoplasmic reticulum (ER) stress and mitochondrial dysfunctions with inflammatory processes as an important disease-conditioning situation in various target tissues[26–29] (Fig. 2). Emerging evidence supports the hypothesis that the ER and the mitochondrion share common mechanisms in triggering the unfolded protein response (UPR). It was reported that the cytoplasmic double stranded RNA-activated protein kinase integrates the mitochondrial stress response into ER-associated signaling pathways, linking ER and mitochondrial UPR under conditions of chronic inflammation.[30,31]

4. Cell response in inflammation

Intestinal epithelial cells (IEC) are key regulators for the recruitment and instruction of other cells within epithelium and lamina propria as well as the response to both intraluminal commensal bacteria and pathogens. It remains to be established whether IECs can be primary source of signals for the development of intestinal inflammation.

R.S. Blumberg (USA) fully illustrated the relationship between ER stress, Paneth cells and intestinal inflammation mediated by the UPR.[32,33] This represents a signaling pathway from the ER to the nucleus that protects cells from stress caused by unfolded or misfolded proteins. UPR signaling is mainly driven by inositol-requiring, endoplasmic reticulum-to-nucleus signaling protein 1α (IRE1α)-X-box-binding protein-1 (XBP1) pathway (IRE1-XBP 1 pathway).

IRE1α is a transmembrane kinase/endoribonuclease which initiates the non-conventional splicing of the messenger RNA encoding a key transcription activator Hac1 in yeast or XBP1 in metazoans. XBP1 is a key component of the ER stress response, and is required for the differentiation and function of certain secretory epithelia cells.

IRE1α is ubiquitous, whereas IRE1β is specifically expressed in the intestinal epithelium. IRE1α exhibits both *endoribonuclease* activity – with XBP1 being the only known substrate – and *kinase* activity that engages both JNK and classical NF-κB pathways. XBP1 deletion causes ER stress in the epithelium, spontaneous enteritis (mainly in ileum),

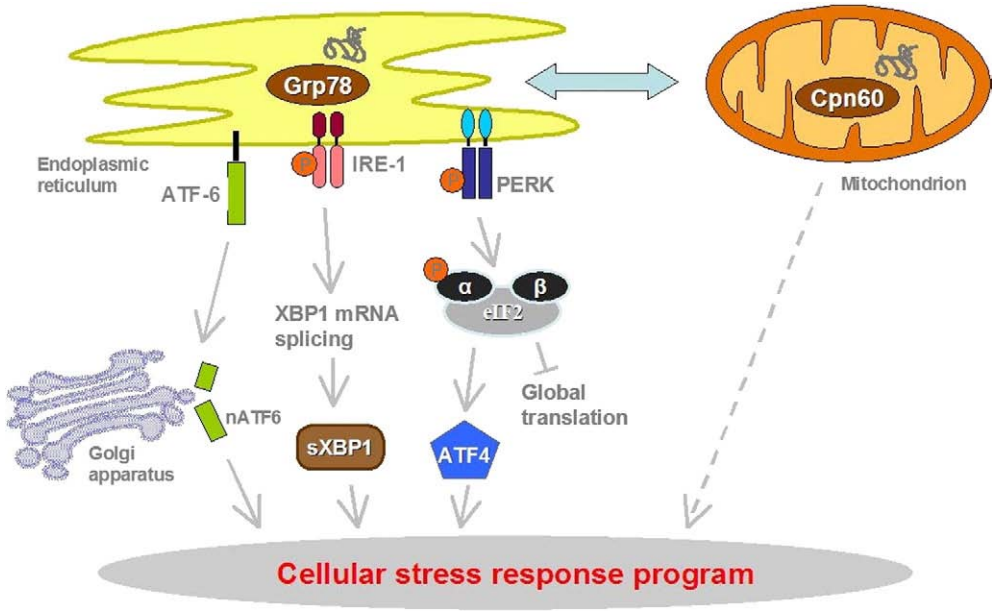

Figure 2 Signal transduction from the ER to the nucleus: highly preserved mechanisms of stress responses (Courtesy of D. Maller, Germany).

increased susceptibility to DSS colitis, lacks of Paneth cells in the intestinal epithelia, decreases crypt bactericidal function, and impaired *Listeria monocytogenes* clearance. Stressed IECs with reduced or absent XBP1 activity displayed evidence of heightened proinflammatory tone in response to TNFα and flagellin, two known inducers of gut inflammation through elevated IRE activity and JNK phosphorylation.

ER stress is common in human IBD (both UC and CD). Genetic and environmental factors can affect ER stress in the intestinal epithelium and consequently inflammation.[28,33,34] Genetic factors include either p*rimary* ER Stress (*XBP1*, *AGR2*, *ORMDL3*) or s*econdary* ER stress (*HLAB27*, Mucins, *ATG16L1*). Environmental factors include bacteria, dietary and drugs.

It is increasingly evident that autophagy has an important role in chronic inflammation and in particular in the pathogenesis of CD (R. Xavier, USA). Autophagy involves the concerted action of cytoplasmic proteins that generate curved isolation membranes to envelop cytoplasm, cytoplasmic organelles and intracellular pathogens. Autophagy represents a host defense mechanism.[35–37] Autophagy degrades and recycles cellular contents and restricts bacterial access to the cell cytoplasm. Autophagy requires the action of two ubiquitin-like conjugation (Atg5/12/16L1 and Atg8/LC3) systems. This requirement is supported by the finding that two genes involved in autophagic processes – *ATG16L1* and *IRGM* – are significantly associated with CD. Recently two independent labs have linked *NOD2* and autophagy.[38,39] NOD2 stimulation induces autophagy in dendritic cells (DCs) and requires ATG5, ATG7, and ATG16L1. NOD2-mediated autophagy affects bacterial handling and antigen presentation in DCs.[38] NOD2 recruits ATG16L1 to the plasma membrane upon bacterial entry in epithelial cells.[39]

Autophagy has been identified as a key process in host resistance to bacterial infection, but some pathogens (*Brucella*, *Francisella*, *Listeria)* can subvert autophagy and generate their own intracellular niche. So far, little is known of the steps by which pathogens manipulate the cell to evade the autophagy pathway. Type III secretion, in host–pathogen interaction, represents a potent subversion tool.[40] How do cells recognize intracellular bacteria and how is autophagy subversion/avoidance achieved is not clear. Identifying novel components of the autophagy apparatus are expected from future studies.[41]

D.M. Monack (USA) explained that multiple inflammasomes direct innate immune responses against Salmonella. NOD-like receptors (NLRs) sense intracellular pathogens and endogenous danger signals in the cytosol.[42,43] Activated NLR's assemble a multiprotein complex called inflammasome that leads to the production of caspase-1, which triggers release of proinflammatory cytokines IL-1β and IL-18. Two inflammasome receptors, Nalp3 and Ipaf, are necessary to fully activate caspase-1 in response to intracellular pathogen *Salmonella typhimurium*. Mice deficient for both Nalp3 and Ipaf are markedly more susceptible to *S. typhimurium* infection.

W. Marlicz (Poland) reported an increase in the number of very small embryonic like stem cells (VSELs) in peripheral blood of patients with IBD. These circulating cells are significantly enriched for mRNA for gastrointestinal lineage (lgr-5 and ASCL-2) and pluripotent stem cell markers (Oct-4, SSEA-4, Nanog) as well as CXCR4 receptor. The number of mobilized/circulating VSELs correlated in IBD patients with elevated serum levels of stromal derived factor-1 as well as hepatocyte growth factor and vascular endothelial growth factor. The biological and clinical significance as well as the true regenerative potential of these cells in regeneration of injured gut tissue is unclear.

Inflammation-induced endothelial-to-mesenchymal transition (EndoMT) was advocated as a novel mechanism of fibrosis in IBD (F. Rieder, USA). The combination of TGF-β1, IL-1β and TNF-α induces morphologic and phenotypic changes in human intestinal microvascular endothelial cells consistent with EndoMT, and these were reproduced using supernatants of activated lamina propria mononuclear cells. The changes persisted after removal of the inducing agents. EndoMT can be detected in microvessels of IBD mucosa and TNBS-induced colonic fibrosis in mice. These data suggest that inflammation induces trans-differentiation of mucosal microvascular cells into mesenchymal cells, supporting the notion that the microvessels contributes to IBD-associated fibrosis through the process of EndoMT.

5. Innate immunity

IBD is characterized by a disregulated response of intestinal T cells as well as other immune cell types. The mechanisms responsible for the induction of pathogenic T cells are still undefined, but recent progress has highlighted the critical roles of commensal bacteria, the innate immune system, myeloid cells (Dcs and macrophages), Th17 cells and regulatory T cells (Treg). In particular, analysis of Th17 responses has elucidated both pathogenic and protective roles of the cytokines produced by these cells in the development of colitis. Mounting evidence indicates that different innate signaling pathways (for example, IL-23-driven, versus TGF-β and IL-6-driven) may have differential roles in the generation of pathogenic, non-pathogenic or protective Th17 responses.[44] Furthermore, it is becoming clear that the commensal bacterial composition plays a critical role in the differential induction of pathogenic and protective T cell responses in the intestine.[45]

DCs play a pivotal role in the control of intestinal inflammation (H.C. Reinecker, USA). DCs form the major antigen-presenting cell population involved in T cell priming. In the intestine, a combination of conventional (cDCs), migratory (mDCs) and plasmacytoid-derived DCs (pDCs) create a surveillance system that is constantly engaged in sampling and processing of food antigens as well as commensal and pathogenic microbiota. Different DCs with distinct functions populate Peyer's patches, mesenteric lymph nodes and the small and large intestine immune function. DC precursors from bone marrow stem cells have been identified.[46,47] DCs play a central role in mucosal inflammation through CD40-mediated responses by directing T and B cell trafficking in the intestine, and by limiting mucosal injury through the induction of $Foxp3^+$ Tregs by $CD103^+$ DCs and lamina propria mDCs. DCs have also been linked to the induction of IL-17 secretion.

FMS-like tyrosine kinase 3 ligand (Flt3L) is a key regulator of human and mouse DC function.[48–50] Flt3L drives the differentiation of bone marrow progenitors into all DC subsets including pDCs. Flt3L is required for maintenance and expansion of lymph node and organ specific DCs. Flt3L is increased during inflammatory conditions and expressed by activated T cells and stromal cells. Stat3 is a downstream transcriptional effector of Flt3 signaling. One third of acute myeloid leukemias carry constitutive active Flt3 mutations. Flt3L directly or indirectly inhibit IL-10 production by Foxp3+ regulatory T cells.

Dendritic cell autoimmune modifiers (DCAMs) have been proposed for the treatment of intestinal inflammation. These include new series of imidazoacridinones which are based on potent FLT3 receptor tyrosine kinase inhibitors. Some of these compounds show efficiency in inhibiting experimental autoimmune encephalomyelitis (EAE) and rheumatoid arthritis, and have been optimized for oral delivery and inhibition of intestinal inflammation. DCAMs protect C57BL/6 mice from DSS-induced colitis, promote mucosal recovery from DSS colitis, inhibit proinflammatory cytokine production in mesenteric lymph nodes during chronic DSS colitis.

M. Lotze (USA) drew attention to damage associated molecular patterns (DAMPs), redox and autophagy. Pathogen or damage associated molecular pattern (PAMPs and DAMPs, respectively) are molecules that promote the inflammatory response by recognizing exogenous and self products, respectively.[51] One of the best characterized DAMPs is the high mobility group B1 (HMGB1), which is located in the nucleus, cytosol, and mitochondria. Ethyl pyruvate, which inhibits HMGB1 release, decreases inflammation, and improves survival in sepsis and hemorrhagic shock and ameliorates colitis and reduces intestinal cytokine production in $IL\text{-}10^{-/-}$ mice.[52] Anti-HMGB1 antibodies can be effective in several conditions including endotoxemia, arthritis, acute lung injury, ischemia reperfusion injury, hemorrhagic shock, colitis, pancreatitis, cerebral ischemia and cancer. HMGB1 activation of the induced receptor for advanced glycation end products (RAGE) initiates NF-κB and MAP kinase signaling, resulting in propagation and perpetuation of inflammation. The HMGB1/RAGE pathway regulates metabolism and autophagy in experimental colitis and cancer models.[53] Endogenous and exogenous rHMGB1 enhances autophagy and limits RNA viral replication. HMGB proteins function as universal sentinels for nucleic-acid-mediated innate immune responses.[54] Knockout of HMGB1 impairs mitochondrial function, causes a profound loss of oxidative phosphorylation and reduces cell survival. Induction of immunological tolerance by apoptotic cells requires caspase-dependent oxidation of HMGB1 protein.[55] DAMP molecules and reduction/oxidation appear to regulate immunity.[51,56]

DAMP micro RNAs (miRs) have been identified. miR-34c expression increases in HMGB1 wild-type lysate-exposed peripheral blood mononuclear cells (PBMC). miR-214 increases in both HMGB1 wild-type and HMGB1 knockout lysate-exposed PBMCs. miR-155 is a PAMP miR. Transfection of pre-miR-34c into human PBMCs and subsequent exposure to lysate leads to decreased IKKγ (NEMO) protein and mRNA expression.

Recent studies have suggested that epigenetic regulation of the inflammatory response may play a role in chronic inflammatory diseases (L. Backdahl, Sweden). Epigenetic modulation may account for some additional expression regulation other than genetic.[57] Specifically, epigenetic marks include histone methylation, acetylation, phosphorylation and ubiquitylation. DNA methylation is the most common epigenetic modification and occurs nearly exclusively at cytosines in CpG dinucleotide enriched areas, which are often located in the promoter region of many genes. For

instance, hypermethylation of promoter regions often results in gene silencing, while promoters of transcriptionally active genes are typically hypomethylated.[58] DNA methylation is considered to be a specifically suitable epigenetic mark to assess terminal reprogramming in chronic inflammation.[59] DNA methylation provides the main link between the genetics of the disease and the environmental components that plays a decisive role in the aetiology of IBD. Possible triggering environmental factors are nutrition, smoking, hygienic conditions, or medical treatments.

Epigenetic reprogramming is critical in the activation and differentiation/maturation of the immune response.[60] Differentiation of Th1/Th2 cells is determined by changes in epigenetic status at their signature loci. This is particularly true for Treg cells where demethylation in the Foxp3 promoter is a hallmark for this T cell population. Also B cells and the cells involved in innate immunity show differences in their epigenetic profile after stimulation with certain immune response triggers.

Regulation of cell differentiation depends on both the gene expression profile and the epigenetic profile. Epigenetic variation can be responsible for the ultimate phenotypic expression (disease). Therefore, identifying disease-specific epigenetic marks in the genome would provide excellent clues to disease pathways as well as serve as potential therapeutic targets. Epigenetic modifiers such as histone deacetylase inhibitors and inhibitors of DNA methylation seem to have therapeutic effects in chronic inflammatory diseases.[59] 5-AZA-cytidine, an inhibitor of DNA methyltransferases (DNMT1) seems to be a promising compound in this respect.

E. Cario (Germany) showed that deletion of TLR2 promotes Th1-mediated inflammation in MDR1 deficiency. Loss of TLR2 dramatically aggravates commensal-dependent colonic inflammation in MDR1−/− mice. This study identifies TLR2 as an important inhibitor of aberrant −Th1 cell activation in the absence of MDR1. Thus, UC patients with combined genetic defects in TLR2 and ABCB1 (MDR) may exhibit a more severe disease phenotype.

O. Brain (UK) reported the molecular mechanism by which NOD2 induces autophagy in DCs, using a combination of proteomic approaches. CD patients expressing *NOD2* or *ATG16L1* variants have defective NOD2-mediated autophagy, which influences antigen presentation and bacterial handling. This may result in deficient bacterial clearance. DCs from CD patients expressing *NOD2* variants exhibit failure in muramyl dipeptide mediated autophagy and LC3 localization with HLA DR. ATG7 and HMGB1 may be potential links to NOD2-mediated autophagy induction.

6. Adaptive immunity

The role of the microbiota and transcriptional regulators in Th17 cell differentiation was analyzed in detail by D.R. Littman (USA). IL-17-producing CD4$^+$ T lymphocytes, while important for mucosal immunity, have also been implicated as major contributors to tissue inflammation and are thought to be involved in human autoimmune diseases, including IBD.[61] Lymphoid lineage cells that share the property of producing IL-17, IL-17F, and IL-22 include $\alpha\beta$ T cells (CD4 cells primarily, but also some CD8 cells), $\gamma\delta$ T cells, LTi cells, and NK-like cells. All of these cell types express IL-23R, RORγt, and AHR (and CCR6?). In the absence of RORγt, T cells do not make IL-17 or IL-22 and LTi and NK-like cells do not develop. In the absence of AHR, none of these lymphoid cells make IL-17 or IL-22 and clearance of pathogenic bacteria is impaired.

RORγt is a key transcription factor regulating Th17 cell development. Although critical for Th17 cell differentiation, RORγt function is integrated with that of other nuclear factors, namely STAT3, IRF-4, and BATF, that have also been demonstrated to be essential; and AHR and Runx-1, that contribute in a more restricted manner to Th17 cell differentiation. RORγt appears to be a promising target for anti-Th17 therapy. In fact, small molecule inhibitors of RORγt activity, by blocking Th17 cell differentiation, improve mouse models for autoimmunity. RORγt-deficient T cells fail to induce EAE or transfer colitis.

A fine balance between Th17 and Treg phenotypes exists and appears to be governed by the concentration of TGF-β and by an interaction of RORγt with Foxp3, as well as by the composition of the commensal microbiota.[62,63] Antibiotics reduce Th17 cell differentiation in the small intestinal lamina propria. In germ-free mice, Th17 cells are absent and the proportion of Treg cells among the CD4$^+$ T cells is substantially increased.[63] Gram-positive spore-forming anaerobes closely related to *Clostridia*, namely segmented filamentous bacteria (SFB), appear to be responsible for the accumulation of Th17 cells in the intestine.[64,65] SFB colonization protects host from *Citrobacter*-induced colitis from one hand, but also correlates with increased susceptibility of mice to autoimmune disease from the other (Fig. 3). SFB colonization of germ-free mice enhances frequency of Th17-mediated spontaneous arthritis (K/BxN model). All these findings illustrate the importance of maintaining an appropriate commensal bacterial-regulated balance between effector T cells and Treg cells. How specific microbial products influence the differentiation of the lamina propria RORγt- and AHR-expressing lymphoid cells as well as Treg cells is an area that is increasingly recognized to be of central importance in pathogenesis of IBD.

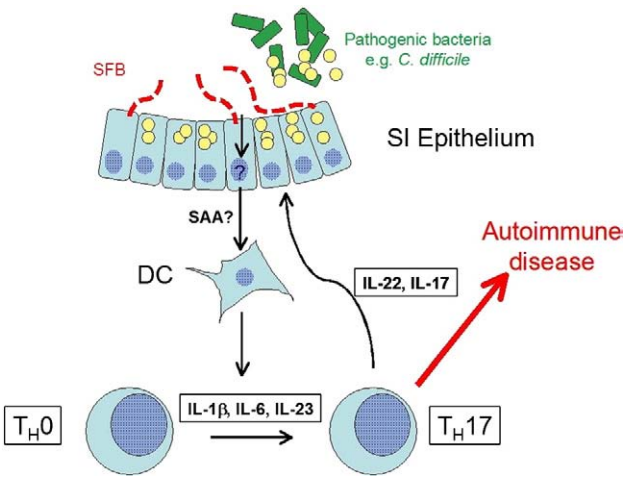

Figure 3 Microbiota, Th17 cells, and mucosal protection (Courtesy of D.R. Littman, USA).

The presentation by F. Powrie (UK) mainly focused on the role of IL-23 and STAT-3 pathways in influencing the balance between tolerance and immunity in the intestine.[66–69] Intestinal homeostasis is a balancing act between effector and regulatory T cells. The intestine is a preferential site for differentiation of Foxp3+ Treg cells . Functionally distinct DC subsets promote Treg development via TGF-β and retinoic acid dependent mechanism. During inflammation, IL23 produced by DCs restrains regulatory T cells and promote Th17 effector cells. The importance of the IL23/IL17 pathway in IBD is supported by several findings: multiple SNPs in genes involved in this pathway are associated with IBD, Th17 cytokines are increased in colon and blood of patients and drive T cell dependent colitis. IL-23 drives colitis by promoting the development of IFN-γ and Th17 cells and inhibiting Foxp3 Treg cells. A conserved IL-23/RORγt inflammatory axis in innate and adaptive lymphoid cells in the intestine appears to be present.

The role of effectors T cells in IBD was discussed by M. Neurat (Germany). Differences in T cell subsets, effector cytokines, transcription factors, and perpetuating cytokines have been found between CD and UC[70–73] (Fig. 4). In CD T cells produce large amounts of Th1 cytokines such as IFN-γ and IL-12, while in UC colitis produce more Th2 cytokines such as IL-5 and IL-13. IL-13 has been suggested to alter barrier function and epithelial integrity in UC. Th1 associated transcription factor T-bet was found to be induced in CD but not UC, where the GATA3 factor prevails. T-bet transactivates the IFN-γ promoter, induces chromatin remodelling at the IFN-γ locus, and induces IL-12 receptor β2 chain expression. Recent studies suggest that IBD is associated with Th17 cells and Th17-associated cytokines (IL-17A/F, IL-21 and IL-22).[61,66] An upregulation of the Th17 associated transcription factors RORA and RORC has been found in IBD patients and seems to play an active role in intestinal damage.

The IL-6/sIL6R system shows a crucial role in experimental colitis with both proinflammatory and protumorigenic functions. Both IL-6 and sIL-6R blockade suppresses tumorigenesis in the DSS/AOM model.[74,75] The nuclear factor of activated T cells (NFAT) family of transcription factors controls calcium signaling in T lymphocytes. NFATc2 plays a critical role in experimental colitis by controlling T cell derived cytokines.[76] NFATc2 controls IL-6 production and subsequently T cell apoptosis and Th17 cytokines. NFATc2 emerges as an attractive target for therapy of IBD.

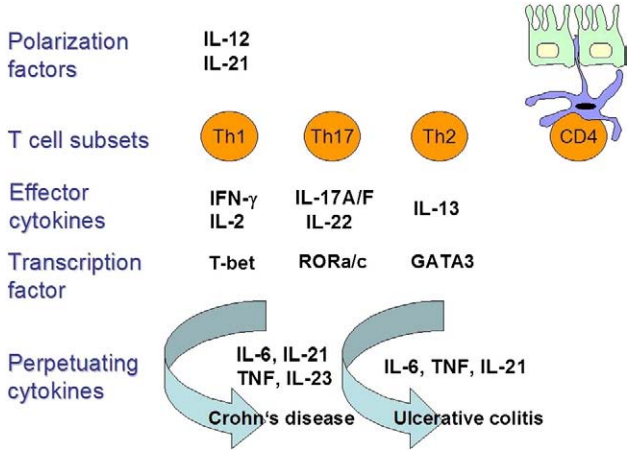

Figure 4 Key cytokine targets in IBD (Courtesy of M. Neurath, Germany).

Interferon regulatory factor (IRF)-4 selectively controls cytokine gene expression in chronic intestinal inflammation.[77,78] IRF-4 controls T cell dependent experimental colitis. IRF-4 knockout mice are protected from experimental oxazolone and TNBS colitis. IL-6 treatment prevents the protective effects of IRF-4 deficiency.

Retinoic-acid-related orphan receptor (ROR)γ deficient T cells lack colitogenicity. Neither IL-17A, nor IL-17F or IL-22 expression alone in T cells is necessary for colitis induction.[79] IL17A and IL17F seem to have redundant functions in the gut. Neutralization of both IL-17A and IL-17F protects animals from colitis. IL-17A rescues colitis in RAG−/− mice transferred with RORγ−/− T cells. Th17 are also important in the T cell transfer colitis model.

R. Alaniz (USA) presented a humanized mouse model of IBD and microbial immunity. The results of the study support the notion that HLA-DQ8-restricted CD4+ T cell responses to microbial targets exacerbate the severity of IBD after enteric bacterial infection, and the evaluation of HLA-restricted antigens in a humanized mouse model are important for IBD research.

M.C. Fantini (Italy) reported that Smad7 expression in T cells protects from colitis-associated colorectal cancer even in the presence of strong colonic inflammation. Protection is at least in part due to IFN-γ expressed by Th1, cytotoxic T cells (CTL) and NK/NKT cells into the tumoral and peritumoral areas of the colon. Accumulation of IFN-γ-expressing CTL and NK/NKT cells correlates with high expression of the cytotoxcity markers (i.e. perforin1, granzyme B and FasL) and induction of apoptosis in dysplastic epithelial cells.

7. Developments in clinical IBD

A critical overview to improve understanding of clinical trials in IBD was presented by M. Lémann (France). Clinical trials aiming at supporting a new first line indication should always include comparison with the accepted first line treatment. The trial aiming at demonstrating superiority should (when ethically justifiable) also include a placebo arm to provide internal validation of the study. A three-armed trial with test, reference and placebo is the recommended design (EMEA 2005). The critical points of induction (4–12 weeks) and maintenance (6–24 months) clinical trials in IBD were examined. In induction trials in IBD is crucial: 1) demonstrate efficacy (the test product arm is superior to placebo or is superior (or non inferior) to an active comparative drug), 2) define the target population ('active' disease susceptible to be improved by the test product without interactions with concomitant medications); 3) define endpoints (definition and timing of primary, secondary, exploratory).[80] In maintenance trials in IBD the selection of remitters and/or responder to study drug, as well the long term remission are crucial.

Trials combining induction treatment and maintenance treatment should preferably only enter patients that have achieved remission (in either the trial drug or comparison group), into maintenance phase and preferably a re-

randomisation should be done. Clinical trials are mainly devoted to demonstrate efficacy and safety of new products, but the rules are strict and the selection of patients and endpoints must be optimized. It should be remembered that clinical trials do not reflect real life because of the short time and black and white endpoints. Others studies are needed to define the best strategies, including comparative studies, prospective cohorts, sequential or combined therapies, and more practical endpoints.

G. D'Haens (Belgium) performed a critical analysis of risk-benefit in biological therapy. The risk-benefit ratio is conditioned by modality ("over" treatment in mild disease or "under" treatment in severe disease) and type of treatment (combination of drug such as corticosteroids, immunosuppressants and biologics). Adverse events with immunomodulators and biologic therapies for IBD are common. Fortunately, the majority of these events are mild and transient. Clinicians need to be aware, however, that serious problems can occur including agranulocytosis and sepsis, potentially dangerous opportunistic infections, malignancy (cancer or lymphoma), immunogenicity and loss of response, injection and cytokine release reactions, autoimmunity, heart failure, and demyelination. In particular, patients who use biologic therapies in combination with classic immunomodulators appear to carry an elevated risk for these problems.[81] In general, the benefits of biological therapies outweigh the risk in properly studied patients. Adherence to the European Crohn's and Colitis Organization (ECCO) guidelines will probably further reduce the risk of complications.[82] The efficacy of the treatment needs to be balanced against the severity of these adverse events. The presence or absence of therapeutic alternatives also needs to be taken into account. IBD therapies do not always need to be continued lifelong; withdrawal strategies need to be refined. Monotherapy regimens usually give fewer adverse events in the long run. Prolonged corticosteroid use and deep immunosuppression should be avoided.

L. Beaugerie (France) extensively discusses the problem of Epstein–Barr virus (EBV) and lymphoma in IBD. Lymphomas often develop in intestinal segments affected by IBD and are in most cases associated with EBV.[83] Chronic intestinal mucosa inflammation constitutes a risk factor for subsequent lymphoproliferative disorders (LD) like for high-grade dysplasia or adenocarcinoma. If confirmed, a sustained mucosal healing of intestinal lesions could be associated with a reduction in the risk of intestinal inflammation-associated LD. EBV infection could be an important cofactor, especially in patients receiving immunosuppressants that promote reactivation of latent EBV infection. Therapy is associated with a moderately increased risk of LD. Patients receiving thiopurines have a 3 to 5-fold increase in the risk of LD compared with patients naïve to thiopurines or those who discontinued the drug,[84] even though the overall risk is very low. Most of the excess cases of LD affect young adults. It should be assessed whether a progressive increase in the systemic EBV viral load may precede in some cases the clinical onset of LD in IBD. If this is confirmed, the sequential measurement of systemic EBV viral load could emerge as a routine clinical tool for managing the risk of EBV-associated LD in IBD patients receiving thiopurines. The recently identified risk of hepatosplenic T cell lymphoma in young male IBD patients co-treated with anti-TNFα and thiopurines is low and does not appear as associated with EBV infection.[85]

The reasons of treatment failure during IBD therapy were analyzed both from basic and clinical points of view. From a basic point of view a distinction between primary (failure at initial trial) and secondary (failure after initially responding) failure of medical treatment was made (C. Elson, USA). Primary failure may be related to heterogeneity of IBD as supported by the large number of risk alleles identified in GWAS studies of IBD; drugs effective for one gene defect might not work for another. More risk alleles and modifiers are associated to more severe disease and lower response to therapy.[86] Primary failure may also be related to metabolism of the drug by various enzyme systems or membrane transporters, i.e. cytochrome P 450 system and multi-drug resistance gene 1. Secondary failure of medical therapy is more common with the biologic therapies than with non-specific immune modulator therapy. The mechanisms of secondary failure are presently unknown, although may, in part, be related to the formation of antibodies (immunigenicity). However, one potential mechanism has been revealed in recent findings of plasticity of the adaptive CD4 T cell immune response. Although CD4 Th1 and Th2 cells are reasonably stable, Th17 and Foxp3 Tregs can turn into other subsets, i.e., exhibit plasticity.[87] The molecular basis of this appears to be interactions between the transcription factors RORγt for Th17 cells and Foxp3 for Treg cells. Another possible mechanism could be the micro RNA (miR) system, small sequences of RNA that interact with genes and alter their transcription.[88] Altered miR expression under the pressure of biologic therapy may result in escape from the beneficial effects of the therapeutic agent. A third possible mechanism for secondary failure could be the shift in the microbiota toward microbes with more proinflammatory effects that make the immune system less responsive to biological agents. It is likely that a better understanding of the mechanisms involved in drug failure ("biologic escape") would help shape better therapeutic strategies.

From a clinical point of view, mechanisms of failure include sub-therapeutic blood concentrations, symptoms without evidence of active disease by laboratory, endoscopic, and radiographic criteria, and undiagnosed and untreated co-morbidities (W. Sandborn, USA). Co-morbidities that cause symptoms in patients with IBD, in particular with CD, include disease complications (strictures, fistulas, abscesses), complications of surgical resection (bile acid diarrhea, steatorrhea, small bowel bacterial overgrowth), irritable bowel syndrome, infections (*Clostridium difficile*, Cytomegalovirus), and depression. In documented active disease (presence of clinical symptoms, endoscopic and radiological findins, as well as positivity of biomarkers), sub-therapeutic concentrations of steroids, immunomodulators and biological agents may be the cause of medical failure.

The clinical impression of gastroenterologists based on the patient's history is frequently incorrect and is insufficient to make proper therapeutic decisions. Colonoscopy and CT or MRI enterography should be routinely employed prior to any major changes in therapy: 1) Before starting steroids, immunosuppressives or biologicals; 2) When patients fail to respond to steroids, immunosuppressives or biologicals; 3) When patients receive maintenance therapy with immunosuppressives or biologicals relapse; 4) Before surgery. Treatment of patients who have no documented evidence of active disease with steroids, immunosuppressives, or

Figure 5 Paradigm for Integration of Research & Clinical Care (Courtesy of D. Podolsky, USA).

biological agents will not address the cause of the symptoms and will expose the patients to risks that may be unnecessary. These patients with persistent symptoms should be systematically evaluated for bile acid diarrhea, steatorrhea, bacterial overgrowth, and depression.

W. Van Moerkercke1 (Belgium) showed that mucosal healing in CD is associated with high infliximab trough levels. Measurement of infliximab trough levels is therefore useful in optimizing therapy since they may allow dose adjustment in patients with low drug levels.

C. Rousseaux (France) presented the preclinical and toxicological assessments of the novel orally bioavailable PPAR ligand GED-0507-34-Levo for the treatment of IBD. GED-0507-34-Levo molecule has strong intestinal anti-inflammatory and analgesic properties. Its attractive safety profile allows a phase 1 study scheduled in healthy volunteers with GED-0507-Levo tablet coated with the colonic drug release Multi-Matrix (MMX) system.

8. Integrating scientific knowledge

A very interesting tandem presentation was done by D. Poldosky (USA) and D. Hommes (The Netherlands) on the integration of research and clinical care in the future. The presentation was focused on macrotrends affecting healthcare delivery and research and the need to innovate traditional infrastructures to deal with these changing trends as well as the opportunities to accelerate scientific knowledge.

Hospitals are symptom-based and organized around curative care. In the future we will be looking for a shift from curative medicine to preventing care. A revolutionary change is expected that involves the transfer of power and authority from physicians to patients and third parties like health-insurers. The physician/patient relationship will move from paternal to collaborative. The traditional family doctor will likely become obsolete in the future. Rapid translation of scientific progress will be crucial for optimizing of healthcare service. This can be achieved if hospitals integrate medical research and daily care in order to ensure continuous innovation and personalized care (Fig. 5). Large biobanks, fully integrated into the hospital infrastructure, will become essential in the near future. Integrating the vast molecular information will identify disease subtypes and potential strategies for diagnosing and treating disease in new and more effective ways.

9. Capri lecture

The Capri lecture 2010 was given by Carlo Croce, Director of the Institute of Genetics and Director of the Human Cancer Genetic Program, the Ohio State University, Columbus, Ohio (USA). Prof. Croce gave a brilliant lecture entitled "From observation to discovery in art and science". He went along the path of his research activity demonstrating that cancer is a genetic disease due to somatic changes. He stressed the fascinating common link between art and science in the discovery of new findings. He concluded by showing some of his discoveries in the field of classical painting using the same methodology used for scientific research.

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