Challenges in IBD Research: Assessing Progress and Rethinking the Research Agenda

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EXECUTIVE SUMMARY

U
nder the aegis of the Crohn’s & Colitis Foundation, a group of leading basic and clinical researchers came together in 1990 to assess the state of scientific knowledge and treatment for patients with inflammatory bowel diseases and to create a blueprint for the foundation’s research program. The participants produced a white paper called “Challenges in IBD Research,” naming a set of research priorities that were considered both urgent and timely.

The foundation has convened similar meetings every few years, updated its research agenda, and published a white paper accordingly. The most recent Challenges document, published in 2003 in Inflammatory Bowel Diseases, described the complex and active communication that takes place between bacterial flora, the epithelium, and the immune cells in the intestine. Perturbation of these interactions can result in chronic intestinal inflammation. These observations generated the hypothesis that “Inflammatory Bowel Disease (IBD) is due to an abnormal cell-mediated immune reaction—primarily by CD4 T cells—to the antigens and adjuvants of the enteric bacteria in genetically susceptible hosts.” Research over the past 4 years has largely supported this hypothesis.

In May 2007 a broad group of investigators convened to review progress in IBD research since 2003 and to generate a new set of research priorities for the Crohn’s & Colitis Foundation. Although our major working hypothesis has not changed, research advances have allowed us to define our priorities more precisely. Significant strides in basic IBD research have taken place principally in 4 areas:

- Identification of additional of genes associated with IBD, particularly the association of mutations in IL-23R with Crohn’s disease.
- Strengthening of the association of IBD with an abnormal immune response to commensal bacterial flora.
- A central contribution to mucosal homeostasis by the innate immune system.
- Further elucidation of the cellular populations and their mediators that drive and regulate the immune response in the gastrointestinal (GI) tract. The Th17 subset of effector T cells has recently been discovered and appears to be involved in the progression of chronic inflammatory diseases in multiple organs, including the intestine.

In considering research progress over the past few years and in planning the foundation’s research priorities for the near future, we identified the following major themes:

- The tools available for analyzing genetic information have improved dramatically. These improved tools have allowed for the rapid identification of genes associated with IBD.
- The human GI tract contains a large and complex group of microorganisms and their metabolic products. This complex has been termed the microbiome. There has been a marked improvement in the tools available for the analysis of complex microbial systems. These tools are just beginning to be applied to questions specifically related to human IBD.
- The genetic heterogeneity of Crohn’s disease and ulcerative colitis suggests that there are genetically determined subsets of patients with these diseases and that these subsets may be associated with specific responses to drug therapy and specific prognoses.
- There has been an increase in the number of therapies approved for the treatment of Crohn’s disease and ulcerative colitis, as well as in new drugs being tested for efficacy in these diseases. In all likelihood, several of these drugs will be considered for FDA approval in the near future.

These advances have opened up new avenues for IBD research and have paved the way for new therapies based on an improved understanding of basic biological mechanisms.
We therefore propose the following areas of investigation as the leading basic and clinical research priorities for the Crohn’s & Colitis Foundation.

**Genetics**

Over the past few years abnormalities in several genes, including *NOD2* and *IL23R*, have been associated with IBD. Although it is possible that the major genetic associations with IBD have already been identified, other genetic associations likely remain to be discovered.

*NOD2*, a component of the innate immune system, is an intracellular sensor for the bacterial product muramyl dipeptide. The association of Crohn’s disease with mutations in *NOD2*, a gene involved in the host response to commensal flora, supports the hypothesis that IBD involves an abnormal immune response to enteric bacteria. The most striking aspect of the association of *NOD2* mutations with Crohn’s disease was the realization that these mutations are present in only a minority of Crohn’s disease patients and that they are also seen in a small but significant portion of healthy controls. Thus, these mutations are neither necessary nor sufficient for the development of Crohn’s disease. Other factors that would allow an individual with *NOD2* mutations to develop Crohn’s disease are unknown but may include additional genetic mutations, environmental events, or both.

As other IBD-associated mutations have been described, it appears that they too occur only in a minority of IBD patients. It remains broadly unknown how these mutations interact with each other, with other genetic variants, and with environmental events, all of which are important questions for research. Even though the association of Crohn’s disease with *NOD2* mutations was identified in 2001, the mechanism by which *NOD2* variants affect the development of Crohn’s disease is still unknown. As new genetic variants are identified, a major challenge will be to establish the mechanisms by which they contribute to the pathogenesis of IBD.

**The Human Microbiome**

The human GI tract contains a large variety of microbes that interact with each other and with the host in a complex and largely unexplored manner. The full range of bacteria represented in the normal human GI tract has not been completely characterized, nor have we established how consistent the flora are from individual to individual or within one individual over time. Whether there are consistent differences in the microbiome between normal individuals and IBD patients also is not known.

There is good evidence that the basic defect in human IBD is an exaggerated immune response to some component of the microbiome. Whether that exaggerated response is to all commensal bacteria, to a subset of bacteria, or to a single strain is not clear. Moreover, the genetic heterogeneity of IBD patients raises the possibility that different groups of patients may have exaggerated responses to different subsets of the commensal flora.

Recent improvements in technology have made it possible to characterize complex microbiologic systems, such as the human microbiome. These tools will allow a genetic cataloging of the varieties of organisms present and a characterization of the biological products produced. Full characterization of the normal and IBD human microbiome is likely to give important insights into the pathogenesis of IBD and to suggest therapeutic approaches based on manipulating the microbiome itself.

**Host–Microbial Interactions: The Innate Immune Response**

Early work on the immunologic basis of IBD focused on the adaptive immune system. The demonstration that Crohn’s disease is associated with mutations in *NOD2*, a gene that codes for a protein component of the innate immune system, has brought new focus to the role of innate immunity in the pathogenesis of IBD. However, we have an incomplete picture of how the innate immune system functions in regulating the response to commensal organisms and pathogens.

Mice lacking Myd88, a central protein in the innate immune response, have a normal GI tract under baseline conditions but have an impaired response to injury. Defining the mechanisms by which defects in the innate immune system alter the host response to commensal organisms may give important insight into the pathogenesis of Crohn’s disease and ulcerative colitis.

The host response to commensal organisms is controlled not just by the bone marrow–derived cells of the innate immune system but also by the epithelium, which plays a critical role in the regulation of the intestinal immune response in that it separates the microbiome from the cells of the innate and adaptive immune systems. Toll-like receptors (TLRs)—plasma membrane proteins that respond to bacterial products—are an essential component of the innate immune system. TLRs are expressed not just on macrophages and dendritic cells but also on epithelial cells. The “cross talk” between commensal bacteria, the epithelium, and other cells of the innate immune system is likely to be important in the pathogenesis of IBD. As a consequence of the apparent importance of the innate immune system to the pathogenesis of IBD, the foundation will emphasize research that focuses on the role of the innate immune system in the host response to commensal flora in both normal individuals and patients with IBD.

**Host–Microbial Interactions: The Adaptive Immune Response**

The adaptive immune system encompasses the antigen-specific immune responses mediated primarily by T cells and
B cells. Previously, there were thought to be 2 major T-cell effector phenotypes: Th1 and Th2 cells. Recently, the Th17 subset of effector T cells has been identified and appears to be important in the progression of chronic inflammatory diseases. Th1 and Th17 effector cells are involved in mediating Crohn’s disease, whereas Th2 effector cells have been implicated in ulcerative colitis. T-effector cells drive the activation of the immune response, whereas T-regulatory cells act to shut it down.

At present, we have an incomplete understanding of the pathways involved in the regulation of the adaptive immune response to commensal bacteria and pathogens in the intestine. A better understanding of the mechanisms involved in both the activation and the down-regulation of the intestinal immune response promises to be useful in the development of improved therapy for IBD.

Recent advances in medical therapy for IBD—in particular, therapy directed against TNF—have focused on shutting down the effector arm of the adaptive immune response. It is expected that additional medical therapy aiming to shut down other components of the effector arm of the adaptive immune response and to strengthen the regulatory component will be effective in treating IBD. The foundation is interested in supporting research to define the adaptive immune response to commensal flora in normal individuals and abnormalities in the adaptive immune response associated with IBD.

Defining Prognosis

Genetic data demonstrate that Crohn’s disease and ulcerative colitis are far more heterogeneous than previously appreciated. The presence of subgroups of patients with different genetic profiles raises the question of whether it is possible to predict an IBD patient’s prognosis and probable response to therapy based on his or her genetic profile. The last few years have also seen a rapid expansion in the number of serological studies used to characterize patients with IBD. These studies may correlate, on the one hand, with genetic markers and, on the other, with the patient’s prognosis and likely response to therapy. The treatment of IBD could be dramatically improved by targeting specific therapies to individuals with specific genetic or serological characteristics.

The rapid increase in the identification of IBD-associated genes combined with the expansion in the number of serological studies available and the anticipated increase in the number of approved therapies will enable the determination of whether genetic and serological markers are useful in directing therapy in IBD.

Improving Therapy

The optimal goal of medical therapy—to cure Crohn’s disease and ulcerative colitis—has yet to be achieved. Short of a cure, inducing and maintaining clinical remission while minimizing adverse effects to medication and preventing complications are goals worth achieving. Until now, medical therapy for IBD has focused on controlling the overactive immune response in the GI tract. This approach has been only partly effective and, even when successful, is frequently associated with worsening of disease activity when therapy is withdrawn.

Advances in our understanding of the pathogenesis of IBD and the development of new pharmacologic agents raise the possibility of being able to not simply decrease the level of inflammation but also to change the natural history of the disease. The goal would be to alter the immune response to prevent the development of inflammation and subsequent injury to the GI tract.

A precedent for such an expectation is found in the treatment of other chronic inflammatory diseases. The medical therapy for rheumatoid arthritis, for example, now focuses on early treatment with disease-altering drugs, with the goal of preventing joint destruction. We are now positioned to perform studies to determine if such an approach would be effective in IBD. There are some data to support the use of immunomodulatory drugs as first-line therapy (“top-down therapy”) in IBD. Studies are needed to test both the efficacy of this approach and the risk/benefit ratio of such aggressive therapy.

A major gap in our efforts to optimize medical therapy in IBD has been the absence of clinical trials in children. IBD frequently begins in childhood, and it is likely that the best opportunity to alter the natural history of the disease occurs at the time of diagnosis. It is expected that clinical trials in children with IBD will yield improvements in medical management.

NEW RESEARCH CONSENSUS

In updating the foundation’s Challenges in IBD Research, the meeting’s participants identified the following research priorities:

- Use genetics, immune profiles, and biomarkers (clinical, medical, genetic) to predict individual prognosis (natural history, response to therapy, toxicity of therapy).
- Identify new genes associated with IBD and perform functional studies to define the mechanisms by which genetic polymorphisms lead to chronic inflammation.
- Define functions of both known and newly discovered IBD-related genes.
- Study ethnic, age-related, and anatomical genetic variants.
- Study gene–environment interactions (bacteria, food, toxins, tobacco, etc.).
- Translate discovery into therapy, with the goal of changing the natural history of Crohn’s disease and ulcerative colitis.
- Better define the risks of medical and surgical therapies.
- Better understand age- and sex-specific risks versus benefits of established and new medical and surgical therapies.
• Focus on cost effectiveness.
• Better define the innate mechanisms (innate immunity, epithelial barrier, integrated mucosal signaling) involved in IBD pathogenesis.
• Better define the adaptive immune response (regulatory T cells, effector T cells, B cells, antigen-presenting cells, interactions with the innate immune system) involved in IBD pathogenesis.

To carry out this ambitious research agenda, the following resources will need to be developed:

• A clinical trials infrastructure (in development).
• A workshop, to take place in 2008, to focus on defining prognosis/phenotypes.
• A microbial “toolbox,” including:
  • A gene chip for commensal bacteria.
  • Bioinformatics for the microbiome project (in possible partnership with industry).
• A pediatric research network (underway).

The remarkable progress in our understanding of the pathogenesis of IBD has opened up research opportunities to expand on these observations in an effort to further define the basic mechanism of IBD and has also revealed a series of new targets for medical therapy. The foundation is eager to move this research forward.

WORKGROUP REPORTS

I. REPORT OF GENETICS SUBCOMMITTEE

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State of the Art of IBD Genetics Research

Early functional candidate gene studies found modest associations between HLA variants and IBD. Several IBD linkage regions were identified in subsequent genomewide linkage scans. Association mapping in linkage regions identified Crohn’s disease (CD)–associated polymorphisms in the chromosome 16 NOD2 gene, which encodes an intracellular sensor for the muramyl dipeptide component of bacterial peptidoglycan, and a 250-kilobase haplotype in the IBD5 linkage region on chromosome 5q31. A 2-locus risk haplotype formed by single-nucleotide polymorphisms (SNPs) in the SLC22A4 and SLC22A5 genes was reported to account for the IBD5 association, and the 2 SNPs were reported to decrease transporter activity or promoter activity, respectively. However, the reported functional effects have not been confirmed, and other studies have shown equivalent evidence for association with other SNPs spanning the IBD5 risk haplotype.

Four recent genomewide association studies have independly identified multiple confirmed novel genetic associations with CD, including a subunit of the receptor for the proinflammatory interleukin-23 cytokine (IL23R), on chromosome 1p31; the ATG16 autophagy–related 16-like 1 (ATG16L1) gene, on chromosome 2q37; a locus that may influence expression of the prostaglandin E receptor 4 (subtype 4) (PTGER4) gene, on chromosome 5p13; a region on chromosome 10q21 with no known genes; the immunity-related GTPase family, M (IRGM) gene, on chromosome 5q33; the NK2 transcription factor–related, locus 3 (NKX2-3) gene, on chromosome 10q24; a locus on chromosome 3p21 that spans many genes; and the protein tyrosine phosphatase, non-receptor type 2 (PTPN2) gene, on chromosome 18p11.

Unanswered Research Questions in IBD Genetics

What are ALL the genes that predispose to, protect against, or determine subtypes and course of IBD?. It is likely that additional IBD susceptibility loci, genetic determinants of clinical subtypes of IBD, and genetic risk factors unique to different racial and ethnic groups remain to be identified.

What are the functional mechanisms of IBD genes?. The functional mechanisms of IBD-associated genetic variants and the role of associated biological pathways in the pathogenesis of IBD need to be understood.

How do IBD genes interact with each other and with environmental factors to predispose to or modify the course of IBD?. Crohn’s disease and ulcerative colitis (UC) are complex multigenic disorders in which gene–gene and gene–environment interactions are probably crucial in disease pathogenesis. The study of gene–gene and gene–environment interactions may be important at 3 levels: first, as an approach to identify novel loci not easily detectable with methods that do not take interactions into account; second, as an approach to generate hypotheses regarding potential biological interactions; and third, as an approach to generate a model for determining an individual’s risk of developing the disease or a specific subtype of it.

What is the predictive value of IBD-associated genetic variants for the development of IBD, disease subtype and course, and response to therapies?. An important challenge is the application of genetic association information to the improvement of clinicians’ abilities to determine patient diagnosis and prognosis. In addition, as anyone who has interacted with patients or with patients’ family members knows, one of the first questions asked is, “What is the risk to my children/siblings/other relatives of also developing the disease?” Furthermore, it is important for professionals involved in developing health care policies and plans to know the true prevalence of causal variations and the risks conferred by these variants.
Recommended Research Directions in IBD Genetics

To identify additional CD-associated genetic variants through joint analysis and deeper replication studies of existing genomewide association data. Genomewide association studies have rapidly identified several confirmed novel CD susceptibility loci. However, many additional true associations are probably among the thousands of SNP loci for which there is only modest nominal evidence of association in individual studies. Joint analysis of all existing genomewide association data and deeper replication studies are likely to identify additional genetic risk factors.

To perform genomewide association studies in UC, early-onset, and minority racial/ethnic IBD cohorts. Some CD susceptibility factors probably also confer risk for UC, but it is likely that UC-specific genes also exist. Early age of onset of IBD has unique characteristics compared with adolescent and adult-onset IBD, and phenotypic characteristics differ between minority racial/ethnic groups and white, European ancestry IBD cohorts. The phenotypic differences in early-age-of-onset and minority racial/ethnic group IBD suggest that there may be genes that contribute uniquely, or more substantially, to risk in these populations.

To determine the functional mechanisms of IBD genes. A major goal of future IBD research will be to understand the functional mechanisms of IBD genes and associated biological pathways. Accomplishing this will require collaboration between geneticists and investigators in other relevant research disciplines.

To develop and apply statistical and experimental approaches to identifying gene–gene and gene–environment interactions. Analytical and experimental approaches are needed to establish the identity and nature of genes through gene–gene and gene–environment interactions. These methods can be directed toward genomewide association data sets or data sets targeted to specific biological pathways implicated by confirmed genetic risk factors. One of the key challenges in examining gene–environment interactions is the lack of standardized and validated research tools for the characterization of nongenetic factors that contribute to the pathogenesis of IBD (e.g., the intestinal microbiome, smoking).

To determine the predictive value of IBD-associated genetic variants for development of IBD, disease subtype and course, and response to therapies. To accurately assess genetic risk factors and the covariates that modify those risks, it will be necessary to collect new or identify existing large population-based samples that are truly representative, have DNA samples, and have relevant clinical, ethnographic, and environmental information available. Determination of disease allele frequencies and risks in these population-based samples can then be applied for diagnostic, prognostic, and genetic counseling purposes. The study of risk alleles in extended families drawn from a representative population sampling can determine whether there are levels of risk based on degree of relatedness and whether this information can be used for genetic counseling. Prospective longitudinal studies will be needed to determine the predictive value of genetic variants for disease subtype and course and response to therapies.

Significance

Identifying genes that predispose to, protect against, or modify the course of IBD; understanding the functional mechanisms of these genes and their associated biological pathways; and determining their predictive values for development of IBD, clinical course of IBD, and response to therapies will shed light on the cause of IBD, identify targets for new therapies, and eventually provide clinicians with the enhanced ability to diagnose and treat the diseases and make prognoses for patients.

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to chronic inflammation is determined by genes that regulate innate immune responses, including mucosal barrier function and luminal and intracellular microbial killing, as well as adaptive immune responses to microbial antigens and adjuvants.

Major advances and new insights include:

- Techniques for the molecular detection of components of the complex intestinal microbiota and their localization in human subjects. These techniques can be used to identify alterations of components of the exceedingly complex bacterial and fungal microbiota of the ileum and colon in Crohn’s disease, ulcerative colitis, and pouchitis compared with normal components.

- Functional changes in commensal enteric bacteria profoundly influence intestinal inflammation and metabolic function in mammalian hosts. Functional alterations of intestinal bacteria (expression of genes that mediate epithelial adhesion, invasion, and persistence in epithelial cells and phagocytic cells) influence their ability to injure the mucosa and incite pathogenic immune responses. In addition, metabolic activities of bacteria can activate host epithelial responses and influence nutrient absorption.

- Certain species of the complex intestinal microbiota can induce pathogenic immune responses that lead to chronic, T-cell-mediated inflammation in genetically susceptible hosts. Dominant bacterial antigens exist that stimulate pathogenic immune responses. These stimuli are specific both to host and to bacterial species. These observations suggest that a manageable number of bacterial species and dominant antigens induce pathogenic responses, laying the foundation for identifying clinically important subsets of patients who will selectively respond to therapy through selective immune responses to a panel of microbial antigens.

- In the mucosa of normal hosts, bacterial components can stimulate innate immune responses that are protective. Dysregulated innate immune responses can lead to chronic intestinal inflammation driven by aggressive T-cell responses to commensal bacteria. Bacterial products can modulate innate immune responses such as NFκB activation.

- Genetic abnormalities in innate immune function lead to defective microbial killing or processing. Polymorphisms in the NOD2 gene result in defective muramyl dipeptide (MDP) binding and NFκB activation, leading to defective intracellular bacterial killing and secretion of α defensin by ileal Paneth cells. Normal ATG16L1 is necessary for efficient processing and autophagic killing of intracellular bacteria.

II. REPORT OF MICROBIAL–HOST INTERACTIONS WORKGROUP

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State of the Art and Recent Research Advances

New insights into the molecular mechanisms of host responses to microbial stimuli and novel techniques to identify microbial constituents and dominant antigens have provided further support for the hypothesis that chronic intestinal inflammation is the result of overly aggressive T-cell responses to a subset of commensal (normal, ubiquitous) intestinal bacteria in genetically susceptible hosts. Susceptibility
Unanswered Questions

What are the composition, gene expression, and metabolic function of the commensal enteric microbiota in normal humans and mice, and how do these vary in patients with ulcerative colitis, Crohn’s disease, or pouchitis and in mice with chronic immune-mediated inflammation?

What are the dominant microbial antigens that stimulate effector T-cell responses that induce chronic intestinal inflammation?

How does the host differentially recognize commensal versus pathogenic microbiota and variably respond to pathogens and commensal microbes? What different signaling pathways are preferentially used by innate immune cells to generate protective responses versus activation of effector responses to clear pathogens?

How are innate immune responses to commensal bacteria down-regulated to restore homeostasis? How are innate immune cells regulated by cells and cellular products of the adaptive immune system?

How do genetic abnormalities associated with IBD affect host responses to commensal bacteria and fungi?

Recommended Research Directions

- Develop the molecular tools and bioinformatic techniques to determine the composition, gene expression, and metabolic function of the enteric bacteria and fungi in normal humans and mice and to identify differences in these parameters in patients with ulcerative colitis, Crohn’s disease, or pouchitis and in mice with chronic immune-mediated intestinal inflammation.

- Identify the dominant bacterial and fungal antigens that drive effector T-cell responses in Crohn’s disease, ulcerative colitis, and experimental intestinal inflammation.

- Identify the mechanisms of differential host recognition and response to commensal versus pathogenic enteric bacteria that govern tolerogenic versus effector innate and adaptive immune responses.

- Identify the mechanisms by which innate immune responses to commensal microbiota are regulated to promote mucosal homeostasis.

- Understand the molecular mechanisms of how genes associated with Crohn’s disease and ulcerative colitis alter host responses to commensal microbiota and the effect of these genetic abnormalities on the intestinal microbiome.

Clinical Relevance

Identifying the bacterial and fungal species, their dominant antigens, which microbial genes are expressed, and what metabolic products unique to human IBD are produced will permit development of new therapeutic targets and diagnostic tests. Understanding the molecular mechanisms of genetic abnormalities in IBD will likewise lead to the development of therapeutic interventions that can correct these defects. Basic knowledge of normal host homeostatic responses to commensal bacteria, effective clearance of enteric pathogenic microbial agents, and down-regulation of such responses when pathogens are cleared will help to direct investigations of defective immune responses in IBD patients and of therapeutic approaches to correcting these defects.

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III. REPORT OF ADAPTIVE AND REGULATORY IMMUNE RESPONSES WORKGROUP

Charles O. Elson, MD (Chair), Lloyd F. Mayer, MD, Casey T. Weaver, MD

State of the Art of Research in Adaptive and Regulatory Immunity in IBD

Three major T-cell effector phenotypes have been defined: the T helper 1 (Th1), T helper 2 (Th2), and Th17 subsets, which are all functionally distinct. The Th17 subset has been discovered most recently and appears to be involved in the progression of chronic inflammatory diseases in multiple organs, including the intestine. Th1 and Th17 effector cells seem to mediate Crohn’s disease; Th2-like effector cells have been implicated in ulcerative colitis, but the exact role of the different effector phenotypes in ulcerative colitis remains obscure. T-effector cells initiate a cascade of cytokines, chemokines, and other molecules that mediate nonspecific inflammation, resulting in tissue injury and the symptoms and signs of chronic inflammatory bowel disease. Tumor necrosis factor alpha (TNF-α) appears to be a key molecule initiating this cascade, in that neutralization of TNF-α can reverse clinical disease and induce healing of the mucosa in many patients.

Multiple mechanisms of regulation exist, and multiple cell types contribute, including B cells and certain dendritic cell subsets. However, the dominant cell type is the T-regulatory cell (Treg). Deficient immunoregulation can lead to inflammatory bowel disease. Regulatory T cells play an important role in self-tolerance and in regulating immune responses to exogenous antigens. There are multiple subsets of Tregs, but 2 major divisions are recognized at present: natural Tregs (nTregs) and adaptive Tregs.

- nTregs are generated in the thymus and have high-affinity TCRs (T-cell receptors) to self-antigens.
- Adaptive Tregs are generated outside the thymus to antigen encountered in organs or secondary lymphoid tissues. Both types have an anergic phenotype and proliferate poorly in vitro.

Natural Tregs

- CD25 is expressed constitutively, and TGF-β and IL-2 are needed for their maintenance.
- Foxp3 transcription factor is required for their generation and continued function.
- Depletion or absence of nTregs results in organ-specific autoimmune diseases in mice (but not colitis).
- Adaptive transfer of CD4⁺CD25⁻ T cells can prevent and treat colitis in both T-cell-dependent and innate immune models. Production of IL-10 may not be required for prevention, but it is required for treatment.
- The antigen specificity of nTregs is unclear; function tested in polyclonal systems mainly, and antigen specificity needs to be defined.

Adaptive Tregs

- These can be induced from CD4⁺CD25⁻ T cells in multiple experimental systems. Some but not all may express Foxp3.
- Tr1 cells are an example: these do not express Foxp3 and produce high amounts of IL-10.

It is unclear if nTregs are precursors of all adaptive Tregs or just Foxp3⁺ variants.

Infection with pathogens induces Tregs, and there may be certain microbial molecules that preferentially stimulate Tregs. Helminths stimulate Tregs as an immune evasion strategy.

The ability to induce Tregs to select antigens might be therapeutically useful. The intestinal lamina propria is enriched in Tregs, but the subsets present are not well characterized, nor are the antigens that stimulate such Tregs.

Stimulation of murine lamina propria CD4⁺ T cells with antigens of the microbiota results in IL-10 secretion, and it is likely but not proven that intestinal Tregs are reactive to the microbiota.

Most markers associated with Tregs are present in lamina propria T-cell isolates, including CTLA4, ICOS, LAG3, CD103 (α4βE), CD25, and Foxp3.

The cells and mechanisms by which intestinal Tregs are induced are unknown.

Tregs inhibit immune responses via multiple mechanisms, including production of the inhibitory cytokines IL-10 and/or TGFβ, cognate inhibition, production of IDO, and possibly via cytotoxicity. Deletion of IL-10 results in colitis in mice; deletion of TGF-β results in diffuse inflammation. Deletion of either of these genes results in innate immune defects in addition to Treg deficiency. It is not clear which is more important for the development of colitis.

CD8 T-regulatory cells exist and may play an important role in the intestine, but little is known about these cells. CD8αa T cells, which are abundant in intraepithelial lymphocytes (IEL), may have regulatory functions.

Much less is known about human intestinal Tregs, although CD4 T cells that are Foxp3⁺ or have other markers of Tregs are present there. Little is known about Treg presence and function in the inflamed intestine in IBD, although...
there have been reports of an increased number of Foxp3$^+$ cells in IBD mucosa.

**Unanswered Questions**

**T-Effecter Cells**

1. *What is the normal T-effector cell response to the microbiota in the intestine?* How is this effector response different in chronic intestinal inflammation?

2. *Which effector cells are involved in Crohn’s disease, and which are involved in ulcerative colitis?*

3. *What are the molecular events triggered by each of these effector T-cell types, and how do these differ from one another?* Moreover, can the inflammatory cascade be interrupted to therapeutic benefit?

4. *Where are the effector T cells in the intestine generated, and what dendritic cell–T-cell interactions or other innate cell–T-cell interactions are involved?*

5. *What are the microbial antigens that activate T-effector cell responses in the intestine in the normal state and during chronic intestinal inflammation?* Do these same antigens also induce Treg responses?

**T-Regulatory Cells**

6. *What are the Treg cells present in the intestine and/or mesenteric lymph node, and in which compartments do they reside?* What are their phenotypic characteristics, TCR repertoire, and other attributes? Are these Tregs the same in mouse and human intestine?

7. *Where do intestinal Tregs originate?* Are they selected in the thymus, or do they arise in the intestine itself, such as CD8aa T cells in the IELs?

8. *What is the relationship between foxp3 thymic-derived nTregs and peripheral adaptive Tregs?* Are Foxp3$^+$ nTregs precursors for all other subsets? Can Tr1 become Th3 cells and vice versa under differing conditions?

9. *Where do Tregs reside and exert their effects?* These may be different during normal mucosal homeostasis versus in the setting of IBD.

   - In GALT, regulating induction of mucosal immune responses?
   - In different regions of the intestine? The small intestine versus the colon? The IELs versus the lamina propria?
   - Are Tregs different in the colon versus in the small intestine? In mesenteric lymph nodes? In spleen and peripheral lymph nodes?

10. *What are the activation requirements for intestinal Tregs?* What are the antigens stimulating Tregs in the intestine? What are the antigen-presenting cells activating Tregs? What are the required cytokines and microenvironment?

11. *How do Tregs inhibit immune responses?* What is the molecular basis of cognate inhibition? Is this relevant to the intestine?

   - Are IL-10 and TGF-β the only inhibitory Treg cytokines, and what is the specific mechanism of their effects?

   - What is the cellular target of Tregs? If the target is mainly dendritic cells (DCs), which DCs are affected? What is the molecular basis of their inhibition by Tregs?

   - Tregs can inhibit effector T cells directly in vitro, but does this happen in vivo in the intestine? If so, how does an antigen-specific Treg find a T-effector cell specific for the same antigen in the intestine? Does bystander inhibition exist in the gut?

12. *Are defects in Tregs involved in IBD in humans?* Are they involved in mice that are not lymphopenic and have no defects in innate immunity? Are defects in Tregs in the inflamed intestine primary or secondary to the inflammation?

13. *Do the defects in innate immunity that have been described in mice and humans susceptible to IBD alter or impair Treg cell numbers or functions?* Most of the IBD susceptibility genes in humans are genes of or involving the innate immune system, such as CARD15, IL-23R, and ATG16L1.

14. *What are the non-T-cell regulatory cells and mechanisms operative in normal and inflamed intestine?* What are the roles of regulatory dendritic cells, macrophages, and B cells?

**Recommended Research Directions**

Answers to these important questions are urgently needed. Accordingly, recommended research will require the development and application of novel mouse models, such as T-effector and T-regulatory reporter mice. Such mice have already been generated for Foxp3 and IL-10 and are being applied to the identification of Treg cells in the intestine. Similar reporter mice for IFNg and IL-17 production by effector T cells are needed. Novel methodology such as Cre-lox approaches may be required.

Major goals include:

- Identification of the human T-effector cells in the intestine and determination of whether these function normally in IBD. The role of the Th17 subset in both Crohn’s disease and ulcerative colitis is of great interest. Identification of the exact adaptive pathogenic mechanisms in ulcerative colitis remains a very high priority.
• Identification of the cellular and molecular mechanisms by which genes that cause susceptibility to IBD alter either the T-effector or T-regulatory cell adaptive immune response to the microbiota. These include NOD2/CARD15, IL-23R, ATG16L1, and other genes recently described. Many of these genes encode for molecules involved in innate immunity; thus, discovering how innate immune cells alter adaptive T-cell responses in IBD is a high priority.

• Understanding the mechanisms of induction of adaptive Tregs as a treatment or preventive of IBD, with particular emphasis on those that can be translated to new therapies. Increasing the number of Tregs in the intestine may not work if they are inactivated by inflammatory cytokines. Thus, understanding the mechanisms of interruption of Treg activity in inflammatory foci and how that interruption might be reversed will be crucial.

• Identification of the microbial antigens that stimulate T-effector cells and Tregs in mice and/or humans is needed. Doing so will allow for the study of antigen-specific T-cell responses in the intestine relevant to IBD.

Clinical Relevance

A detailed understanding of the T cells that cause and prevent IBD will lead to identification of targets for new therapies that could control the disease better than is currently possible. Remission will be induced by inhibition of effector T cells and maintained by stimulation of Treg cells.

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IV. REPORT OF INNATE IMMUNITY WORKGROUP

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State of the Art and Recent Research Advances

The mammalian innate immune system consists of those defenses that are intrinsic to the organism and do not require prior exposure to the pathogen for maximal responsiveness. This immune arm contrasts with the adaptive immune system, in which exposure to antigens stimulates memory responses that can elicit protective immune responses (e.g., generation of antibodies, memory T-cell responses) on subsequent challenge with the same antigen.

The cellular components of the innate immune system in the gastrointestinal tract include, in part, the various cell types of the epithelium (i.e., absorptive cells, goblet cells, neuroendocrine cells, myofibroblasts, and Paneth cells), as well as most leukocyte populations (e.g., NK cells, neutrophils, dendritic cells, macrophages, eosinophils, basophils, and mast cells). In addition, some lymphocyte populations have “innate” regulatory function.

Previously, it was nearly axiomatic that aberrations in the adaptive immune response were responsible for the altered mucosal immune homeostasis in patients with inflammatory bowel diseases. However, the discovery that mutations in intracellular bacterial sensing (NOD2) and bacterial processing (ATG16L1) genes are associated with an increased risk of Crohn’s disease, plus the observation that a variety of human immunodeficiencies with defects in innate immune function can be associated with mucosal inflammation, led to reevaluation of the prevalent hypotheses for IBD pathogenesis. Recent advances in both human and animal model systems have supported the notion that the innate immune system may play a more critical role in maintaining intestinal homeostasis. It has become clear that aberrations in the innate immune response can lead to an overly aggressive adaptive immune response to constituents of intestinal microbiota, leading to the uncontrolled inflammatory response characteristic of patients with IBD.

Major Advances and New Insights

• Continued demonstration of an important role for maintenance of barrier function by epithelial cells in regulating mucosal homeostasis. Alterations in this innate function can lead to intestinal inflammation.

• Recognition of microbial products by extracellular and intracellular protein receptors expressed on resident cells in the intestinal mucosa plays a central role in coordinating the response to commensal organisms. Tonic stimulation of these receptors by microbes appears to be important for down-regulating immune responses. Cross talk exists between signaling pathways evoked by intracellular (e.g., NOD2) and extracellular (TLR2) microbial sensors.

• Innate immune leukocytes (e.g., dendritic cells) are found with abundance in the noninflamed lamina propria of the intestine and are capable of sampling microbial constituents through an intact epithelium.

• Secretion of antimicrobial peptides by Paneth cells contributes to maintenance of intestinal homeostasis. Paneth cell function may be regulated, at least in part, by the ability to sense microbial products through intracellular innate immune receptors.

• Innate immune cells secrete a variety of nonpeptide products (e.g., leukotrienes, reactive oxygen metabolites) that are key mediators of inflammation.

• Mutations in a variety of recently discovered genes that control the innate immune response have been identified in patients with inflammatory bowel diseases, including...
genes that regulate IL-23R signaling and the autophagy pathway.

Unanswered Questions

What are the dominant cell types (e.g., epithelial cells, Paneth cells, leukocytes) that regulate innate immune responses in normal individuals and in patients with inflammatory bowel diseases?

How does the innate immune system individually and in concert with the adaptive immune system respond to the intestinal microbiota globally?

How are innate immune cells regulated by cells/products of the adaptive immune system (and vice versa)?

What are all the relevant peptide and nonpeptide mediators of inflammation secreted by innate immune cells, and how are these mediators regulated in states of health and inflammation?

Recommended Research Directions

- Identify and characterize the relative contribution of cells of the innate immune system to maintenance of intestinal homeostasis.
- Identify and characterize the specific signaling pathways in cells of the innate immune system that regulate mucosal health.
- Identify and characterize the mechanisms by which signaling events evoked by innate immune receptors (intracellular and extracellular) are integrated within the cell and lead to alterations in protein and gene expression.
- Identify and characterize all peptide and nonpeptide mediators/regulators of inflammation secreted by innate immune cells.
- Determine the unique and redundant mechanisms by which the innate immune system responds to commensal and pathogenic microorganisms.
- Characterize the mechanisms by which the innate immune system regulates the adaptive immune response and vice versa.

Clinical Relevance

Innate immune dysfunction has already proven to be an important contributor to inflammatory bowel diseases. Mutations in a variety of genes that regulate cells of the innate immune system have been associated with disease pathogenesis. Nonetheless, it remains unclear precisely how the intestinal microbiota communicates with each cell type that encompasses the innate immune system and how these cells interact with the adaptive immune system in health, ulcerative colitis, and Crohn’s disease. A broader understanding of the role and regulation of innate immune cells—identifying the complete set of genes involved, their signaling pathways, and secreted products—in intestinal health and disease will undoubtedly lead to newer therapies and the potential for prevention and cure of these chronic debilitating diseases. If a subset of IBD patients, particularly those with Crohn’s disease, have defective innate responses and bacterial killing, therapies designed to enhance rather than suppress their function should be effective, which is a fundamental change in treating IBD.

REFERENCES


V. REPORT OF EPITHELIAL BIOLOGY WORKGROUP

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The simple columnar epithelial cell sits at the interface between the luminal and subepithelial compartments of the intestine and mediates or strongly influences almost all interactions between these 2 environments. Such interactions are currently thought to have decisive effects on the pathobiology of inflammatory bowel disease.

Unanswered Questions in Intestinal Epithelial Cell Biology

The workgroup has identified the following issues and questions in epithelial cell biology, which are relevant to the pathogenesis, treatment, and prevention of IBD.

What induces and controls epithelial cell transformation in IBD (inflammatory cancer)? IBD patients have an increased propensity to develop epithelial malignancy of the gastrointestinal tract. Genetic predisposition, chronic inflammation, altered epithelial barrier function, and the bacterial microflora are contributing factors.

Malignant transformation of epithelial cells seems to universally require mutations in multiple tumor-promoting and tumor-suppressing genes and the loss of normal cell–cell contacts. The continued survival of such transformed epithelial cells involves evasion of an immune response. Recent (and exciting) studies show that engagement of intercellular junction proteins at epithelial cell–cell contacts stimulates intracellular signaling events associated with the downstream regulation of growth and survival pathways, intercellular communication, and epithelial cell polarity. Focal interactions between the epithelial cell and subepithelial protein matrix critically affect epithelial physiology and phenotype. Somehow, factors induced by long-standing inflammatory bowel disease must affect these events, which are intrinsic and fundamental to the phenotype and function of the intestinal epithelial cell.

What factors and mechanisms affect the intestinal epithelial barrier? Epithelial barrier malfunction is widely considered an important pathophysiologic basis for inflammatory bowel disease. The epithelial barrier constitutes one “portal” through which the host interacts with the normal intestinal microflora and noncellular components of the intestinal lumen. The 2 most critical components of the epithelial barrier are the intercellular junction complexes, which regulate transport of solutes, particles, and cells via the paracellular pathway, and the much more highly resistive epithelial cells themselves, which regulate active, passive, and facilitated transport into and across the cell via the transcellular pathway.

The intestinal epithelium also maintains a much less resistive extrinsic barrier consisting of the glycocalyx and secreted glycoproteins, antimicrobial peptides and enzymes, and antibodies.

How do the commensal microbes and intestinal epithelium interact? Another aspect of intestinal barrier function managed almost exclusively by the intestinal epithelial cell has to do with the way that many pathogenic intestinal microbes interact with the host: by entering the cell itself; or by sending microbial products into the cell via mechanisms of membrane insertion, endocytosis, phagocytosis, or membrane transport.

Also typical of the interaction between the commensal microflora and epithelial cells are the diverse means by which microbial pathogens have co-opted host cell signal transduction pathways, such as:

- By molecular mimicry for binding cell surface receptors, releasing bacterial products that affect the host cell plasma membrane (pore formation, hydrolysis of lipids, oligosaccharides, and proteins); and
- By producing “toxins” that enter the host cytosol.

Presumably, the commensal microflora share many features of microbe–host interaction, especially considering the strong influences of convergent evolution and the ability of microbes to share genetic elements horizontally as well as vertically.

Intestinal epithelial cells also interact with microbes via pattern-recognition molecules that function in signal transduction that is critical for innate immunity. Here, the TLR and NOD family members are now most well recognized.

How do epithelial cells regulate the inflammatory response? Intestinal epithelial cells (IECs) are uniquely positioned to serve as a direct line of communication between the immune system and the external environment. In their
normal state, mucosal surfaces of the alimentary tract are exposed on the luminal surface to high concentrations of foreign antigens. At the same time, these mucosal surfaces are intimately associated with the immune system via subepithelial lymphoid tissue. Consequently, IECs serve as central coordinators of the mucosal immune response.

The observation that IECs express and respond to cytokines has contributed significantly to the burgeoning area of mucosal immunology. IECs also serve as sources of chemokines and as chemokine targets. Moreover, epithelial-derived lipid mediators generated at sites of inflammation contribute significantly to disease outcome in IBD.

**What impact does IBD have on epithelial physiology and the pathogenesis and treatment of diarrhea and malabsorption?** It is already well established that absorption and secretion of water, ions, nutrient solutes, and lipids are mediated and regulated ultimately by the intestinal epithelial cell (with regulatory input from all other cell types, along with noncellular physiologic factors present in the mucosal environment). This is basic intestinal physiology. Each of these processes is affected by factors induced during both acute and chronic inflammatory responses, such as those found in IBD, manifesting themselves clinically as malabsorption, diarrhea, or both.

People with IBD can present with diarrheal disease caused by defects in net salt and water metabolism (absorption, secretion, or both) or with nutrient deficiencies exemplified by growth failure in children, iron-deficiency anemia, or vitamin D–dependent and –independent osteopenia. Moreover, epithelial-derived lipid mediators generated at sites of inflammation contribute significantly to disease outcome in IBD.

**Recommended Research Directions**

- A fuller understanding of the processes implicated in the epithelial cell transformation seen in IBD is both timely and urgently needed. In all cases, well-designed mechanistic and translational studies would contribute meaningfully to that understanding.
- The many factors and mechanisms that influence the function (and malfunction) of the intestinal epithelial barrier are ripe for further investigation. The outcome of such studies will have important clinical applications. We also encourage studies in the following critical areas of epithelial cell biology: (a) the biology of intercellular junctions; (b) epithelial restitution and wound repair; (c) epithelial cell–microbe interactions; and (d) epithelial uptake and intra- and transcellular transport pathways.
- The pattern-recognition molecules that facilitate the interaction between microbes and IECs need to be fully identified and understood. Almost all the studies in this area have been produced by geneticists, and very little is known about the cell biology that dictates their function. Tremendous opportunity exists in this field, and all findings will be directly relevant to IBD. It is also highly possible that manipulation of the intestinal microflora by use of probiotics or other means might have clinical utility in treating or preventing IBD.
- The identification of endogenous pathways that promote the resolution of ongoing inflammation is an emerging area of intense investigation. Continued interest in and development of lipoxins—archidonic acid–derived anti-inflammatory lipids—have revealed new and important inflammatory targets in IBD. More recently, omega-3 fatty acid–derived lipids, termed resolvins, have shown promise in promoting resolution of inflammation associated with murine IBD models. Such findings suggest that endogenously generated anti-inflammatory lipids hold particular promise as therapeutic modalities for intestinal inflammation.

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VI. REPORT OF SPECIFIC IBD DIAGNOSES WORKGROUP

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Present State of Knowledge

Inflammatory bowel diseases (IBD) are now recognized as heterogeneous disorders with a wide variety of clinical presentations and manifestations. Current diagnostic approaches attempt to fit most patients into the broad categories of Crohn’s disease (CD) and ulcerative colitis (UC). However, it is increasingly recognized that these labels do not adequately encompass the variety of forms of inflammatory intestinal conditions. Moreover, diagnosis and classification of patients based purely on existing clinical tools such as standard endoscopy, contrast X-rays, and conventional histopathology are insufficient for decision making at the clinical and research levels. For example, colonic IBD remains something of an enigma among possible diagnostic considerations [i.e., does the patient have CD, UC, IBDU (inflammatory bowel disease–unclassified), or some other category not yet described?].

Current studies evaluating genetic markers illustrate the tremendous heterogeneity in IBD. For example, the NOD2 gene has clearly been shown to be related only to small-bowel CD (but not in Asians), and other recent successes in IBD genetics (IL23R and ATG16L1) were also discovered in an ileal CD cohort. Conversely, pANCA serology and HLA or HLA-associated genes are important in colonic IBD.

Novel diagnostic techniques have recently been developed, and these are providing new information to us. For example, the findings of wireless capsule endoscopy and double-balloon enteroscopy suggest that a reappraisal of our current diagnostic schema is required due to the subtle small-bowel involvement in patients thought to have purely colonic CD, or even small-bowel disease in patients with otherwise “classic” UC.

Of great relevance to the question of diagnosis and classification is the prevailing concept that there is a great diversity in the natural history of IBD. Not all IBD patients will progress to an aggressive or complicated disease course, and some may remain relatively well on minimal medical therapy or no therapy at all. At present, there is a lack of validated markers for an aggressive disease course defined in IBD. Genetic and serological markers as well as RNA and protein expression patterns will likely enable us to define the cohorts of patients at risk for a more severe disease course so that they can be identified for specific targeted therapy. In addition, such markers will be useful in the identification of those at risk for specific extraintestinal complications of IBD, which, while rare, contribute substantially to the morbidity and mortality associated with IBD.

Although not strictly an IBD “diagnosis,” it has been long recognized that response to therapy is largely genetically determined. Moreover, the design and interpretation of clinical trials at present does not take into account the type of disease heterogeneity that likely affects response to a given therapy. There are now numerous studies in the literature illustrating differences in therapeutic response based on characteristics such as disease location and disease behavior, in addition to variable response based on time since diagnosis or level of inflammatory markers. However, it is likely that more sensitive and specific biomarkers, such as genetic polymorphisms, will be important in understanding the response to therapy.

Unanswered Questions

Will novel diagnostic tools such as wireless capsule endoscopy, double-balloon enteroscopy, and MR enterography modify our approach to diagnosing and classifying IBD (in particular, in relation to entities such as IBDU/indeterminate colitis and pouchitis)?

Can biomarker [genetic, RNA (gene expression), serological, proteomic] profiles improve the characterization of IBD with respect to identifying those at risk for rapidly progressive and severe disease, those at risk for serious complications (e.g., cancer or primary sclerosing cholangitis), and those more likely to respond to specific therapies with fewer adverse events?

Will biomarker profiles assist in identifying the healthy, high-risk individuals most likely to develop IBD such that preventive strategies can be developed?

Recommended Research Directions

Studies of the small bowel utilizing capsule endoscopy in CD/UC/IBDU. Capsule endoscopy findings may necessitate a reappraisal of how we define IBD and how we document anatomical disease location. Is small-bowel involvement in CD more common than previously assumed based on radiological imaging? Do findings in the small bowel predict a different disease outcome or require different approaches to therapy? It would be valuable to characterize the phenotype of small-bowel disease in UC/IBDU, to determine how this changes our clinical approach to diagnosis and therapy, and to see whether this alters the data with respect to the prevalence of particular genetic polymorphisms or serological subtypes.
Evaluation of models of IBD onset such as pouchitis/pre-pouch ileitis. This entity occurs in those with confirmed UC as well as in those with misdiagnosed CD. It also may have the phenotype of UC or CD and therefore represents an excellent model of de novo onset of intestinal inflammation in a genetically susceptible individual previously rendered surgically free of disease. Numerous approaches to studying this model are recommended and may include genetics, gene expression, serology, and microbiology.

Evaluation of ileal recurrence following ileocolic resection in CD. This is another model of de novo development of IBD, specifically CD, after a surgically induced disease-free state. This model is also important in studying biomarkers capable of predicting early aggressive recurrence compared to late-onset, indolent disease.

Evaluation of IBDU/indeterminate colitis. This entity may represent a true “overlap” syndrome, in which it may be valuable to identify whether there is more commonality with classic UC or classic CD in geneticserological markers. Is IBDU a unique entity in IBD, and if so what are the unique diagnostic markers associated with it? Because of the relative scarcity of this patient population, collaborative/consortial approaches would be required.

Prospective studies to identify genetic, proteomic, or serological markers that predict those at risk for rapidly progressive or severe disease or IBD-associated complications. Existing and future maintenance therapies for IBD are expensive and have nonnegligible adverse event profiles. It is clear that not all patients with IBD will progress to severe disease, and indeed, some manage without any medical therapy at all. Advances in the ability to predict those at risk for severe or aggressive disease will be critical to the clinical management of IBD. Similarly, having tools to identify those at risk for IBD-associated complications such as colorectal cancer, venous thrombosis, and PSC would be enormously helpful for clinicians. These studies will require multicenter collaborative approaches.

Prospective cohort studies of healthy but high-risk individuals to determine penetrance of specific genetic, proteomic, or serological factors and to identify possible environmental triggers. Clearly, this is a critical step toward our ultimate ability to prevent the onset of IBD. It will require large, long-term collaborative efforts to follow at-risk individuals to determine the factors that lead to the onset of IBD.

Significance
Advances in the field of IBD diagnostics and the study of biomarkers will lead to improved understanding of IBD etiology and pathogenesis, the ability to accurately select which patients to treat and with what therapies, and ultimately to the goal of IBD prevention.

REFERENCES

VII. REPORT OF MEDICAL THERAPY SUBCOMMITTEE

Bruce E. Sands, MD (Chair),
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Present State of Medical Therapy in IBD
The optimal goals of medical therapy—to cure Crohn’s disease and ulcerative colitis—have yet to be achieved. Short of a cure, inducing and maintaining clinical remission while minimizing adverse effects of medications and preventing complications are goals worth achieving. Medical induction and maintenance of remission are successful in many patients with ulcerative colitis (UC) and Crohn’s disease (CD), but there is considerable room for improvement.

Effective induction agents include 5-aminosalicylates (5ASAs), corticosteroids, infliximab, and cyclosporine for ulcerative colitis and corticosteroids (including budesonide), infliximab, and adalimumab for Crohn’s disease. The 5ASAs, long used as inductive agents for mild to moderate Crohn’s disease, continue to be used widely despite recent trials calling into question their efficacy. It has become clear that corticosteroids are neither safe nor effective for long-term use. In ulcerative colitis, rectal therapy with 5ASA enemas or suppositories can be added to oral therapy with additional benefit to patients. Other new anti–tumor necrosis factor–α biologics have been shown to be effective in CD and will offer additional options.

It is now known that compliance with long-term therapy is a key factor in maintaining a durable remission. Discontinuation of maintenance therapy results in substantial rates of relapse. Over time, medical therapy is insufficient in many patients, with 30% of UC patients requiring colectomy by 30 years and 80% of CD patients requiring at least 1 surgery by 20 years, with many requiring 2 or more surgeries.

Treating and ultimately preventing complications of CD and UC—including strictures, fistulas, and cancer—are key therapeutic goals that would provide major benefits and improve disease outcomes. Therapeutic strategies to prevent these complications are needed and are more likely to be successful than medical approaches in reversing them once they have occurred. Studies have yet to determine whether
early intervention with the most potent therapies (the top-down approach) will change long-term outcomes (intestinal resection, colectomy, colon cancer, and disability) compared with the use of standard (step-up) strategies of escalating potency of medical therapy, or whether the additional benefits of early intervention will outweigh potential risks and costs associated with this treatment strategy.

Unanswered Questions in Medical Therapy in IBD

Treatment Strategies

Is a top-down strategy (versus standard step-up strategies)

- More effective in inducing remission?
- More effective in maintaining remission?
- Able to change long-term outcomes (surgery, disability, quality of life)?
- More cost effective?
- Safe?

What medical therapies can prevent or delay recurrence after segmental resection for Crohn’s disease: AZA, MTX, low-dose metronidazole, other antibiotics, TNF antagonists?

Disease modification—can early, aggressive intervention soon after diagnosis change the course of disease, with withdrawal of very potent therapy and maintenance of long-term benefits from being off medication?. (That is, can disease modification be achieved?)

Combination of Immunomodulators and Biological Therapy

What is the appropriate role of immunomodulators as combination therapy with biological therapies?. How do the tradeoffs between the potential for additional efficacy and safety concerns of combination therapy balance out?

Immunogenicity of Biological Therapy

How can the immunogenicity of biological therapy—which limits safety and long-term efficacy—best be mitigated?. Can novel methods be developed to induce long-term immunologic tolerance to biologics?

SurrogateEndpoints of Remission

What are the optimal endpoints for medical therapy in UC and CD? Specifically, are surrogate endpoints (such as endoscopic healing, absence of inflammatory markers in the stool, and histologic quiescence) more predictive of superior long-term outcome than clinical remission? Do the benefits associated with achieving these outcomes outweigh the costs and risks (i.e., is this approach cost effective)?

Predictors of Relapse

Can tests be developed to differentiate between patients on an effective maintenance therapy versus those in a clinically quiescent phase of disease who will flare within a year? (That is, can we develop reliable predictors of relapse?)

Markers of Disease Progression

Can prognostic markers of disease progression be developed in order to select certain patients for more potent medical therapies who would derive sufficient benefit to justify the costs and risks?

Recommended Research Directions in Medical Therapy in IBD

Definitive randomized, controlled trials to determine whether top-down medical therapy strategies are superior to step-up medical therapy strategies in Crohn’s disease. Early intervention with very potent medical therapy might change the natural history of disease, preventing long-term complications. However, top-down approaches may also entail increased costs and risks. Previous studies of top-down therapy have been limited in power and length of follow-up. These and other methodological limitations in the few existing studies of top-down therapy prevent a definitive assessment of the advisability of top-down approaches. It is essential to evaluate these strategies with randomized, controlled, double-blinded prospective studies.

The risks and costs of each strategy need to be weighed carefully against the benefits if top-down strategies are to be adopted in clinical practice. If a top-down strategy adds an incremental benefit at great cost, it will not be cost effective. It will also be important to include baseline measures of disease severity, disease duration, demographics, and biological (genetic, serological, stool inflammation) markers. These may be able to be used in secondary analyses to risk-stratify patients and to identify a subgroup that would benefit sufficiently to justify a top-down strategy. This benefit should be confirmed in a prospective randomized, controlled trial of patients who match this high-risk profile. It should also be noted that top-down strategies may be applicable to ulcerative colitis as well.

Investigation of the appropriate roles of immunomodulators as concomitant therapy for biological therapies.

Appropriate studies include large-scale, prospective investigations of withdrawal of immune modulators after remission, bridge therapy (short-term biological therapy as a bridge to maintenance with an immunomodulator), and monotherapy with a biological versus combination biological and immunomodulator therapy. Such studies need to be powered sufficiently to answer questions of the efficacy of these strate-
gies, whereas questions about safety may be better addressed in prospective cohort studies of immunomodulators with and without biological therapy while adjusting for other factors predictive of adverse outcomes.

Randomized controlled trials of postoperative prophylaxis for Crohn’s disease after segmental resection. Segmental resection in Crohn’s disease is an opportunity to intervene at a time when the burden of disease is least. Studies thus far have provided disappointing results for 5-aminosalicylates, thiopurine agents, and probiotics, whereas studies of biological agents have rarely been undertaken. Studies are needed to define optimum approaches to preventing recurrent disease after resection.

Studies of novel strategies for disease modification. Short of curative therapy, the ultimate goal of medical therapy is to improve on the natural history of disease. Anti-TNF antibodies have been demonstrated to be capable of healing the mucosa in some patients and more reliably so than other therapies. Opportunities exist to study the longer-term effects of achieving mucosal healing in both Crohn’s disease and ulcerative colitis. For example, a study comparing treatment pushed to achieve mucosal healing and clinical remission versus clinical remission alone could determine whether long-term outcomes are improved by applying objective (endoscopic) remission criteria to guide therapy. Such a study would also provide some data regarding the risk/benefit ratio of this approach. Another study design might explore the possibility of withdrawing therapy in patients who have achieved “deep” remission—endoscopic healing, clinical remission, and off steroids—to explore the risk of relapse.

Studies of whether prognostic (clinical, biologic) markers can truly predict the course of disease in IBD. The most effective therapies available to treat IBD include agents that have rare but potentially serious adverse effects. Directing such agents toward the treatment of patients who are at greatest risk for poor outcome (rapidly progressive/aggressive disease) should improve the risk/benefit assessment of treatment. As noted above, this issue is directly relevant to questions regarding top-down strategies, where the risk/benefit analysis could be improved by being able to identify at diagnosis individuals at greatest risk for rapid progression of disease, a group for whom more effective but riskier therapies may be worthwhile. Identification of genetic and other markers associated with the efficacy or risk of adverse events with specific therapies would be an important intermediate step in predicting outcomes.

Useful prognostic markers must be cost effective, and biological markers must always be compared to more inexpensive markers acquired from the clinical history. Likewise, surrogate markers that are sensitive and specific in predicting relapse would be of great clinical utility. Prospective cohorts are needed to discover and validate such markers.

Studies of novel immunologic approaches for tolerization to biological therapies. As new biological agents continue to be developed, the immunogenicity of parenterally delivered biologics will continue to be a concern for long-term use. Future studies should focus on methods of reducing the immunogenicity of biological agents without additional systemic immune suppression. In addition, the development of small-molecule therapies that target pathways currently targeted by biological therapies should eliminate the issue of immunogenicity of biological agents and should be a research priority.

Clinical Relevance
Finding better treatment strategies with existing classes of medications and translating novel basic insights into new classes of therapeutic agents will have an immediate impact on the quality of life of all people with IBD.

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VIII. REPORT OF SURGICAL THERAPY WORKGROUP

Victor Fazio, MD (Chair), Susan Galandiuk, MD, Walter A. Kotun, MD, Scott A. Strong, MD

State of the Art in Surgical Therapy
Medical therapy for Crohn’s disease has undergone significant advances, with a number of new therapies now available—especially immunomodulators and biologics.
However, most patients will require surgical treatment at some time during the course of their disease.

Advances in surgical treatment of Crohn’s disease have taken place in the following areas:

- Selecting the appropriate operation, especially in light of the need to practice “bowel economy” via conservative procedures aimed at maintaining intestinal length. These measures include using limited margins of resection (removing only macroscopically significant disease segments), using nonresective techniques (strictureplasty and its variants) where appropriate, and conserving colonic length.
- Making the operative experience as safe as possible by reducing surgical site infection rates, optimizing nutritional status, and selectively using temporary fecal diversion.
- Reducing recurrence rates via postoperative medical therapies and smoking cessation.
- Preserving intestinal continuity and function, including surgical treatment of perianal disease.

In ulcerative colitis, surgical advances have included:

- Widespread use of restorative proctocolectomy.
- Selective use of laparoscopic approaches.
- Identification of risk factors for postoperative sepsis.
- Salvage surgery for the apparently failed ileoanal pouch.
- Identification of predictive models for outcome of pouch surgery.
- Revival of continent ileostomy for selected patients where permanent end ileostomy is the alternative.

Unanswered Questions

In Crohn’s Disease

What is the optimal management of perianal Crohn’s disease, especially anal fistulas?

When to use and when to discontinue setons and when to use definitive reconstructive surgical treatments? These surgical decisions are of particular importance in light of recent data (ACCENT II) showing that only a third will benefit at the end of 1 year with infliximab therapy.

How can clinicians better characterize patients in terms of who will benefit most from surgery?

To minimize postoperative recurrence, should patients be placed on top-down therapy?

Can ileoanal pouch surgery be applied to selected patients with Crohn’s disease?. How can we determine which patients will benefit from this procedure?

In Ulcerative Colitis

How does infliximab affect outcomes of colectomy? What interval of abstinence from the drug prior to restorative proctectomy is appropriate?

What is the optimal management of DALM and adenoma in patients with ulcerative colitis?

How can problematic pouchitis be better predicted and treated?

How can fecundity be enhanced during and after surgery for ulcerative colitis?

Recommended Research Directions

- Investigate the value of combined biological and surgical treatment of fistulas in Crohn’s disease as possible “curative therapy.”
- Explore the value of top-down postoperative therapy in Crohn’s disease to prevent or delay recurrence.
- Explore the pathology of segments of Crohn’s disease–affected intestine treated by strictureplasty. Most surgeons have noted that it is common for such treated sites to undergo a return of the mucosa to apparent normalcy.
- Focus on ways to improve fertility in women undergoing restorative proctectomy by the use of antiadhesion products or other means.
- Compare cesarean section versus vaginal delivery in the context of the need to minimize anal sphincter injury.
- Investigate the role of minimally invasive surgery for ulcerative colitis.
- Characterize the metabolic and genetic features of patients best treated by surgery. Such research is especially important given that 25%–35% of patients with Crohn’s disease do not experience significant clinical recurrence.
- Study pouchitis as a model for “new-onset IBD.” This would allow for the study of normal small bowel that progresses to inflammation.
- Investigate the predictors of pouchitis.

Clinical Relevance

Predictive models of the outcome of IBD surgery—whether clinical, biochemical, histologic, genetic, or a combination of these—would allow for informed choices by the patient affected by Crohn’s disease or ulcerative colitis.

Improving the quality of life of patients remains one of the major goals of investigators. Research along recommended lines would provide critical information to help surgeons prevent nutritional disturbances and short bowel syndrome, reduce the number of ileostomies, and better assess cancer risk.
IX. REPORT OF PEDIATRIC WORKGROUP

Francisco A. Sylvester, MD (Chair), Athos Bousvaros, MD, Marla Dubinsky, MD, William Faubion, MD, Stephen Guthery, MD, Jeffrey Hyams, MD, Subra Kugathasan, MD, D. Brent Polk, MD, and Eva Szigethy, MD, PhD

Current State of IBD Therapy in Children

Modern treatment paradigms for IBD call for interventions that achieve more than symptomatic relief. The advent of novel therapies and new uses of established therapies offer children the prospect of decreased corticosteroid use and better disease outcomes, including symptom control, mucosal healing, improved growth, timely sexual maturation, and better quality of life overall. However, the long-term risks of these therapies are unknown in children. Recently reported cases of fatal lymphoma in young patients with Crohn’s disease treated with a combination of thiopurines and infliximab highlight the need for ongoing monitoring of possible complications of therapy. The true prevalence of adverse effects of conventional and newer therapies needs to be better understood in children with IBD.

For children with IBD, especially Crohn’s disease, growth delay significantly impacts quality of life. Although established therapies, including corticosteroids, antibiotics, mesalamine, and immunomodulators, effectively improve gastrointestinal symptoms, there is emerging evidence to suggest they do not induce catch-up growth in children with IBD. Biological therapies may be more effective in enhancing growth and physical maturation, but this requires additional study. Primary nutritional therapy is effective in the treatment of Crohn’s disease, with 50%–60% of patients responding in the setting of clinical trials. Although this therapeutic modality is routinely used in Western Europe and Canada, it is seldom offered to patients in the United States. The mechanisms by which enteral formulas heal inflammation and improve symptoms of IBD are not well understood.

Finally, the psychological effects of IBD and of current therapies have not been well studied in children. Preliminary data suggest that depression rates are higher in children with IBD and that depression in turn affects disease outcomes and response to therapy. There is a growing body of literature showing that certain cytokines may be responsible for some of these depressive symptoms. In addition, therapies like corticosteroids can aggravate depression (both directly and by lowering self-esteem because of cosmetic side effects) and have negative effects on mood, concentration, and short-term memory. Moving forward, it is important to better understand the etiology of emotional and cognitive symptoms in youth with IBD. It is also critically important to determine which subgroups of youth with IBD respond to psychotherapy and which subgroups may benefit from adjunctive antidepressant therapy for depression or anxiety.

Unanswered Clinical Questions in Pediatric IBD

What is the incidence of short- and long-term adverse effects of medications? It is urgent to identify therapeutic regimens that offer the prospect of safe and effective induction and maintenance of remission in children with IBD. For example, for children with moderate to severe Crohn’s disease, glucocorticoids followed by azathioprine/6-mercaptopurine, methotrexate, infliximab alone, or enteral nutrition need to be compared. The best options for children with severe ulcerative colitis facing the possibility of colectomy need to be investigated. Risk factors associated with serious side effects need to be identified and prevented, if possible.

Are there clinical or biological variables that predict treatment outcome? Can children be stratified according to these variables prior to therapy? Preliminary evidence in children suggests that a combination of clinical variables and serological biomarkers may be predictive of disease behavior. Antibodies to Saccharomyces cerevisiae in particular appear to be predictive of more aggressive disease and early surgery. Additional disease biomarkers need to be identified.

How are growth and pubertal development best measured as an outcome variable in the context of a clinical trial? There is a critical need to understand the effects of established and newer therapies on growth and sexual maturation in children. Despite its importance to pediatric patients with IBD, this issue has been largely overlooked in previous trials.

Recommended Research Directions in Pediatric IBD

Therapy for IBD in children must be considered separately from therapy for adults with the diseases. Although many questions remain unanswered in pediatric IBD, the following were identified as the top 3 priorities based on feasibility and importance:

- A national multicenter registry to record the safety of current IBD therapy.

The adverse effects of immunosuppression in children is likely distinct from its effects in adults. For example, the risk of posttransplant lymphoproliferative disorder is greater among young children undergoing liver transplantation. Recent reports of hepatosplenic T-cell lymphoma in young individuals with Crohn’s disease receiving thiopurines and infliximab justify the need for surveillance programs in the pediatric age group. The industry-sponsored TREAT registry and Vaccine Adverse Events Reporting System (VAERS) may serve as models for such a registry. Although interested pharmaceutical companies, especially those that manufacture biological therapies, may take the lead in these efforts, it is
important that pediatric specialists and patient advocates be involved from the outset in registry design and monitoring to ensure appropriate scope and reporting moving forward. From this registry we hope to gain information about frequency and severity of adverse effects of therapy, rates of tachyphylaxis, and sensitization to biologics and possible ways to prevent them.

● Risk stratification to guide therapy.

Clinical trials in children with leukemia have identified specific risk factors that predict response to therapy. A similar paradigm could evolve in pediatric IBD. For example, recent data from prospective registries in children with Crohn’s disease suggest that about 20% of patients have aggressive stricturing and fistulizing disease, needing surgery within 2 years of the initial diagnosis. Preliminary data suggest that several immune and genetic markers can identify this group of patients. Such variables may help to guide therapy in new-onset IBD to identify those who are likely to develop aggressive disease, hospitalized patients with ulcerative colitis, pouchitis, growth-delayed patients, and/or very young patients with IBD.

● Infrastructure to support clinical trials in children with IBD.

Over the past 40 years, pediatric oncologists have formed multicenter collaborative networks to improve survival for children with cancer. An astounding 95% of children with cancer, as of 1997, were registered in a trial network. The parallels between pediatric childhood cancer and pediatric IBD cannot be ignored. Both are diseases of low incidence. Both represent disorders with significant burden despite their low incidence. Both fields have experienced advances in molecular biology, genomics, biostatistics, and pathophysiology that now must be translated into clinical medicine. The clinical trial networks will provide the sample sizes necessary to characterize relevant clinical outcomes, improve those outcomes, and identify biological and/or clinical variables that are correlated with those improved outcomes. Pilot and feasibility studies must be implemented as a first step toward establishing collaborative networks.

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