Latest and Greatest in IBD Research

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Precision Medicine: Prime time?
IBD Susceptibility

Adapted from Inflamm Bowel Dis 2010:16;152
We understand more about the link between the Microbiome and IBD
THE HUMAN MICROBIOME PROJECT SAYS THE HUMAN BODY HAS 100 TRILLION MICROSCOPIC LIFE FORMS LIVING IN IT.

10x THE NUMBER OF "HUMAN" CELLS

"...the relationship between gut flora and humans is not merely commensal (a non-harmful coexistence), but rather is a mutualistic, symbiotic relationship"

The gut microbiome is different in people with IBD

A microbial signature for Crohn’s disease

Dynamics of the human gut microbiome in inflammatory bowel disease

Microgeographic Proteomic Networks of the Human Colonic Mucosa and Their Association With Inflammatory Bowel Disease
Dynamics of the Microbiome
IBD Changes More Over Time
Figure 3  Increased risk score of 11 IBD-related genetic variants in gut bacterial handling genes (NOD2, CARD9, IRGM, ATG16L1 and FUT2) is statistically significantly associated to decreased abundance of Roseburia spp. in healthy controls (false discovery rate=0.017).
Detection of IBD in Family Members

A Disease-Associated Microbial and Metabolomics State in Relatives of Pediatric Inflammatory Bowel Disease Patients
IBD is caused by dysfunction in the composition of and interactions between microbes, intestinal epithelium, and the immune system.
Genome-wide association study identifies distinct genetic contributions to prognosis and susceptibility in Crohn’s disease

Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease

ARTICLES

Exploring the genetic architecture of inflammatory bowel disease by whole-genome sequencing identifies association at ADCY7
Identification of Disease Associated Pathways

**Cellular responses**

**Autophagy**
- ATG16L1*
- IREGA
- NOD2*
- LRRK2
- CUL2
- PARK7
- DAP

**Apoptosis/necroptosis**
- PARL
- THADA*
- DAP
- PUS10
- MST1*

**ER stress**
- CPEB4
- ORMDL3
- SERINC3
- XBP1*

**Carbohydrate metabolism**
- GCKR*
- SLC2A4R6

**Intracellular logistics**
- VAMP3
- KIF21B
- TTL8
- FGFR1OP
- CEP72
- TPP1

**Oxidative stress**
- PRDX5
- BACH2
- ADO
- GPX4
- GPX1*
- SLC22A4
- LRRK2
- NOD2*
- CARD9*
- HSPA6
- DLD
- PARK7
- UT52*
- FEX13

**Cell migration**
- ARPC2
- LSP1
- AAMP

**Epithelial barrier**
- GNA12*
- HNF4A
- CDH1
- ERF11
- MUC19
- ITLN1*

**Restitution**
- REL
- PTGER4
- NKX2-3
- STAT3
- ERF11
- HNF4A
- PLA2G2A/E

**Solute transport**
- SLC9A4
- SLC22A5
- SLC22A4*
- AQP12A/B
- SLC9A3
- SLC26A3

**Paneth cells**
- ITLN1*
- NOD2*
- ATG16L1*
- XBP1*

**Innate mucosal defence**
- NOD2*
- ITLN1*
- CARD9*
- REL
- SLC11A1
- FCGR2A/B

**Immune cell recruitment**
- CCL11/CCL2/CCL7/CCL8
- CCR6
- IL6RA/IL5RB
- TSL1*

**Antigen presentation**
- ERAP2*
- LNF2
- DENND1B

**IL-23/Th17**
- IL23R*
- JAK2
- TYK2*
- STAT3
- ICOSLG
- IL21
- TNFSF15*

**T-cell regulation**
- NRDR1
- TNFSF8
- TAGAP
- IL2
- IL2R
- TNFRSF9
- PIM3
- IL7R*
- IL12B
- IL23
- PRDM1
- ICOSLG
- TNFSF8
- IFNG
- IL12

**B-cell regulation**
- IL5
- IKZF1
- BACH2
- IL7R*
- IRF5

**Immune tolerance**
- IL10
- IL27*
- SBNQ2
- CREM
- IL1R1/IL1R2
- NOD2*

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Xavier 2011
Most of our Immune System Is In The GI Tract

Baumgart Lancet 380:1590 2012
Role of Genomics Differs

Kugathasan, IBD 2014
Very Early-Onset IBD

- Diagnosed ≤5 years of age
- Frequently different phenotype and more severe disease presentation
- Often unresponsive to conventional therapy
- Rare genes
How Can We Improve Care For Our Patients?

• Combine our genomic information with our clinical knowledge
Candidate Causative Variants in VEO-IBD?

Buchanan, New studies failing to explain the genetics of common disease, 2012
Whole Exome Sequencing
VEO-IBD Pathways

Epithelial Barrier
- ADAM17, IKBKG, COL7A1, FEMT1, TTC7A, GUCY2

Phagocyte Defects
- NADPH Complex

Immuno-regulation
- IL10, IL10RA, IL10RB, FOXP3, CTLA

T & B Cell Defects
- RAG1/2, IL7R, PTEN, WASP

Hyper-inflammatory
- XIAP, STXBP2, LYST, RAGB27a

VEO-IBD
Link Between Immunology and IBD

- IL-10, IL-10R
- XIAP
- Severe dyskeratosus congenita
- Trichohepatic enteric syndrome
- IPEX
- Multiple intestinal atresia
- NEMO (IKBKG)
- ADAM17
- CGD
- Glycogen storage dis 1b
- LAD I
- Hermansky Pudlak

- Leaky SCID
- PLCG2
- WAS
- DOCK8
- XIAP
- NEMO
- ADAM17
- CGD
- Glycogen storage dis 1b
- LAD I
- Hermansky Pudlak

IBD often a presentation
Whole exome sequencing performed in infant with VEO-IBD

A mutation is identified in NLRC4

Functional assays reveal IL-18 overexpression

Functional assays

Novel IL-18 inhibitor is used to treat patient

Novel Therapeutics

Extraordinary patient care

Unresponsive to conventional medical therapy

Genomics

Mutation

Clinic
Gut Microbiota Development

Factors affecting the microbiome:
- Genetics
- Birth route
- Geography
- Hygiene
- Stress
- Diet/nutrition
- Drugs

Microbiome complexity and stability

Healthy

Perturbation

Infectious diseases, metabolic diseases, and inflammatory disorders

- Protect against pathogens
- Train/stimulate immune function
- Supply nutrients, energy, vitamins, SCFA

- Inflammation (local > systemic)
- Oxidative stress
- Increase in Gram negative bacteria
- Infection (opportunist/c pathogenic)
- Altered metabolite production

Disease

Early onset

Adult onset

Late onset

Birth
3 years
Adult
Elderly

Kostick et al, Gastro 2014
Relative Abundance in VEO and Healthy Controls
From Studies to Therapies

De Lange, Nature Genetics 2017
What have we learned?

Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease

Maire A. Conrad, MD, MS,* Ronen E. Stein, MD,* Elizabeth C. Maxwell, MD, MS,* Lindsey Albenberg, DO,*† Robert N. Baldassano, MD,*† Noor Dawany, PhD,‡ Andrew B. Grossman, MD,*† Petar Mamula, MD,*† David A. Piccoli,*† and Judith R. Kelsen, MD*†

The NEW ENGLAND JOURNAL of MEDICINE

Ustekinumab as Induction and Maintenance Therapy for Crohn’s Disease


The NEW ENGLAND JOURNAL of MEDICINE

Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn’s Disease

ORIGINAL ARTICLE

ORIGINAL ARTICLE
Ustekinumab as Induction and Maintenance Therapy for Crohn’s Disease

Mongersen, an Oral SMAD7 Antisense Oligonucleotide, and Crohn’s Disease
Fecal Transplant

Provide donor stool to affected patient in effort to alter microbiome

Effective and safe treatment for C. diff

Efficacy in IBD not established yet
Combination of oral antibiotics may be effective in severe pediatric ulcerative colitis: A preliminary report

Dan Turner a,*, Arie Levine b, Kaija-Leena Kolho c, Ron Shaoul d, Oren Ledder a
And More
Mission: Remission

Synergy of Care

Science → Patient

Onset of Disease → Comprehensive Evaluation

Patient Care

Translation Research

Patients → Therapy

Novel Therapies

Genetics & Microbiome → Novel Therapies
Thank you!