VERY EARLY ONSET IBD IN CHILDREN

- CAUSES, CURES, & CONNUNDRUMS -

Scott B. Snapper, M.D., Ph.D.

STATE OF THE ART RESEARCH LECTURE
October 9th, 2015
NASPGHAN Post-Graduate Course
Washington DC

www.veoibd.org

Disclosures

I have the following financial relationships to disclose:

Abbvie – IBD Advisory Board; **Cubist** – IBD Advisory Board; **Eisai** - IBD Advisory Board; **Enterome** – IBD Advisory Board; **Hoffman La-Roche** – IBD Advisory Board, Consultant; **Ironwoods** – IBD Advisory Board; **Jannsen** – IBD Advisory Board, Consultant; **Lycera** - IBD Advisory Board; **Merck** – Inflammation Advisory Board; **Pfizer** – Therapeutic Scientific Advisory Board; Grant Support; **Synlogic** – IBD Advisory Board

** No products or services produced by these companies are relevant to my presentation.*

Learning Objectives

- **Review immunodeficiencies that may present with intestinal inflammation**
- **Understand the phenotype, genetics and prognosis for IBD presenting in very young children**
- **Learn an appropriate immunological evaluation of a child with early IBD.**

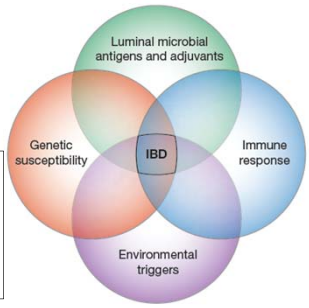
Key Point 1:

IBD is a Complex Disorder that May Require a Genetically Susceptible Host with an Appropriate Environmental Trigger(s)

Key Point 2:

IBD Results from an Exaggerated Mucosal Immune Response to Commensal Microorganisms

Pathogenesis of IBD



Incidence of IBD is Increasing Dramatically Worldwide

Sartor, Nature Clin Prac, 2006

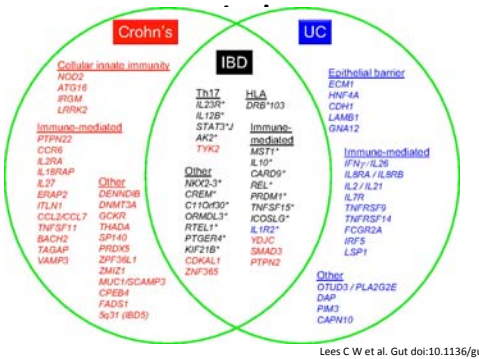
www.veoibd.org

Genetics and IBD in the Adult and Pediatric Population

- Increased risk of IBD in 1st degree relatives (26 fold increase for CD; 9 fold increase for UC)
- 30% of children have one or more family members with IBD
- Concordance rate much greater in monozygotic vs dizygotic twins
  - 10-15% in UC; 25-30% in Crohn's

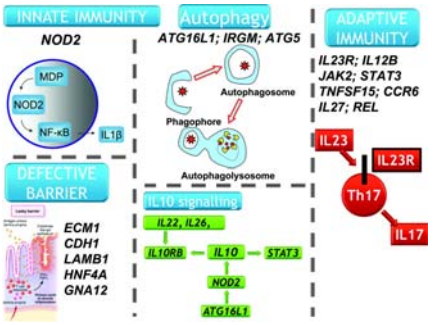
Loftus et al., Gastroenterol. 2004
Bengtson et al. J. Crohn's Colitis 2009
Brant., IBD J. 2011
Ruemmele Curr Opin Gastroenterol 2010

GWAS Studies Have Identified over 180 Inflammatory Bowel Disease Susceptibility



Lees C W et al. Gut doi:10.1136/gut.2009.

Key Pathways Arising From Gene Discovery In Crohn's Disease And Ulcerative Colitis



Lees C W et al. Gut doi:10.1136/gut.2009

Unique Aspects of Pediatric IBD

- ~20% of IBD presents in children
- Children with UC – more extensive disease
- Children with CD – upper intestinal tract involvement common
- Young children often present with Crohn's colitis with perianal involvement

Mamula P. Am J Gastro 2002
Heyman MB J Pediatr 2005

Unique Clinical Features of VEO-IBD*

VEO - IBD	Adolescent and Adult-Onset IBD
• Colonic involvement - 80% at < 10 years of age	• Colonic involvement - <20%
• Ileal involvement - less common at age < 10 yrs	• Ileal involvement – up to 80%
• Family history – 40-50%	• Family history – 14-20%
• Extension of disease – up to 40%	• Extension of disease – up to 16%

*** Defined as Age < 10 by the Paris Classification**

Griffiths (2004) Best Pract Res Clin; Heyman et al (2005) J Ped; Ruemmele et al (2006) JPGN; Kappelman et al (2008) IBD; Louis et al (2008) Gastro, van Limbergen et al (2008) Gastro, Vernier-Massoulle (2008) Gastro: Levine et al (2011) IBD; de Bie et al (2012) IBD

Unique Aspects of Infantile IBD (< 2yo)

- Often isolated Colonic Disease
- Severe Course – refractory to multiple immunosuppressant medications, often requiring surgery, occasionally fatal
- > 40 % with one or more family members with IBD
- 25% first manifestation of underlying immunodeficiency

Ruemmele 2006 JPGN
Cannioto 2009 EJP
Heyman 2005 J Ped

Greatest Increase in IBD Incidence Very Early Onset IBD

	Percent Change in Incidence (P-value by Poisson Regression)		
Age at diagnosis	IBD	CD	UC
6mo-4yr	+56.8% (P=0.11)	+51.0% (P=N/A)*	+38.1% (P=0.95)
5-9 yr	+65.7% (P<0.0001)	+58.9% (P=0.0003)	+57.9% (P<0.0001)
10-14 yr	+34.1% (P<0.0001)	+36.3% (P=0.002)	+38.9% (P=0.09)
15-17 yr	+25.1% (P=0.009)	+12.1% (P=0.006)	+27.4% (P=0.03)

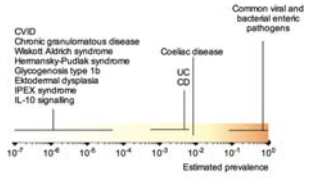
*** By Poisson regression analysis, controlling for sex**

www.neopics.org

Benchimol et al (2009) Gut 48:1490-97;
Benchimol et al (2014) Gastro ePub Jun 18.

Primary Immunodeficiencies Often Present with Intestinal Inflammation

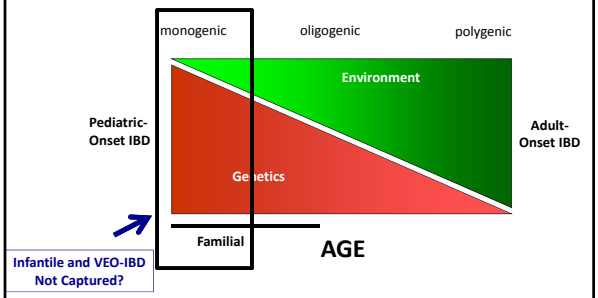
- IPEX syndrome
  - Frequent enteropathy
- Wiskott-Aldrich syndrome
  - 10% with colitis
- Chronic granulomatous disease
  - Gastric granulomas
  - Crohn's-like colitis
- NEMO (NF-kB Essential Modulator) Deficiency
  - enterocolitis
  - superficial cryptitis
- XIAP (X-linked inhibitor of apoptosis)
  - severe fistulizing perianal disease in about 20% of patients
- Common variable immunodeficiency
  - Frequent enteropathy



Estimated Prevalence of Monogenetic Disorder that Can Present with an IBD like immunopathology

Holm Uhlig Gut 2013

Have Large Scale Genetic Efforts Missed Key Dominant Pathways Causing Infantile and VEO-IBD?



Since these are Rare Diseases an International Effort is Required to Advance our Understanding

Adapted from Kaser A, Zeissig S & Blumberg RS, Dig Dis 2010

Very Early Onset IBD Consortium

NEOPICS

Care-for-Rare FOUNDATION

(www.veoibd.org)

Mission:

To diagnosis, treat, and develop new therapies for young children and infants with IBD.

>80 Centers; 250 Scientists; > 1000 VEOIBD Patients

PIs: Aleixo Muise, Christoph Klein, Scott Snapper

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Very Early Onset IBD Consortium

Care-for-Rare FOUNDATION

NEOPICS

THE LEONA M. AND HARRY B. HELMSLEY CHARITABLE TRUST

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- **Fiona Powrie**
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- **Dan Turner**
  Head of the Pediatric Gastroenterology and Nutrition Unit at Shaare Zedek Hospital, Jerusalem, Israel.

15

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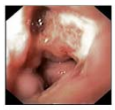
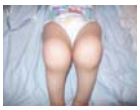
Case

- Presented in 1st year of life with severe colitis
- Persian ancestry
- Multiple enterocutaneous fistulae, recurrent folliculitis, recurrent infections, impaired wound healing

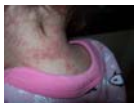


Severe Colitis

Perianal disease with multiple fistulas



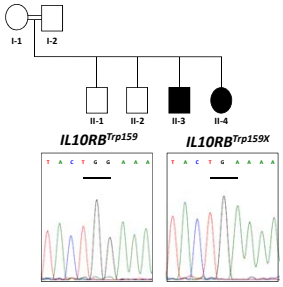
Joint effusions



Folliculitis

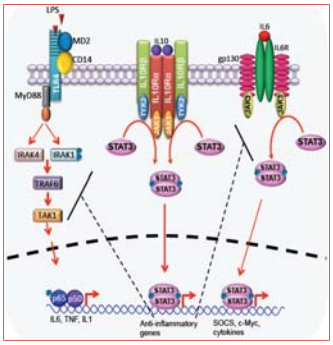
Glocker, Snapper, Grimbacher, Klein *NEJM* 2009

Genetic Evaluation Identified Mutation in IL-10 Receptor



IL10R Pathway

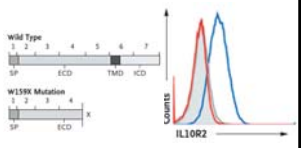
- IL10 restricts excessive immune responses
- Inhibits secretion of pro-inflammatory cytokines
- IL10 Receptor has two subunits:
  - Alpha – IL10
  - Beta – IL10, -22, -26
- Acts through JAK1, TYK2, and STAT3
- **IL10, TYK2, and STAT3 have been identified in IBD GWAS**

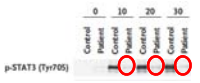


Shouval, Muise, Snapper, Adv. Immunol. 2013

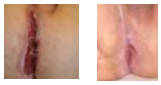
IL10R Deficiency Results in Infantile-Onset IBD

- IL10RB and IL10RA mutations have now been found in numerous locations within each gene – to date each having similar presentations and similar signaling defects





- Hematopoietic stem cell therapy can be curative



Glocker, EO. Klein, C. NEJM. 2009; EO Glocker Lancet 2010; B Begue Am J Gastro 2011; Moran CJ, et al, IBD Journal 2012; Engelhardt et al, J Allergy Clin Immunol. 2013.

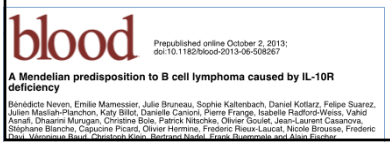
Case 2 – IS THIS ONLY RELEVANT TO VEOIBD?

- Patient presented with severe diarrhea and perianal fistulas in first weeks of life → diagnosed with IBD
- Didn't respond to various immunosuppresive medications
- Colectomy at age 5 years
- Severe perianal fistulizing disease persisted

Shouval DS, *JPGN*, 2014

CG – Clinical Presentation

- At age 12 years presented with 2 months of abdominal pain and enlarged liver and spleen
- CT – multiple focal liver lesions; hypermetabolic on PET
- Biopsy – Large B cell lymphoma
- Responded well to chemo but relapsed after 3 years
- Awaiting **autologous** stem cell transplant



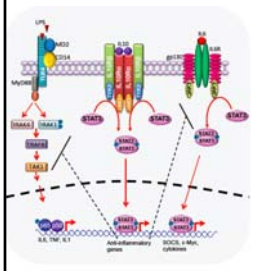
blood

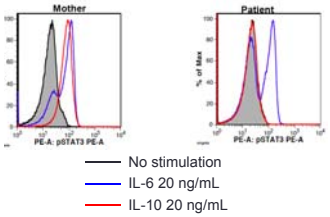
Prepublished online October 2, 2013; doi:10.1182/blood-2013-06-508267

A Mendelian predisposition to B cell lymphoma caused by IL-10R deficiency

Bénédicte Neven, Emilie Mamessier, Julie Bruneau, Sophie Kaltenbach, Daniel Kotlarz, Felipe Suarez, Julien Masliah-Planchon, Katy Billot, Danielle Canioni, Pierre Frange, Isabelle Radford-Weiss, Vahid Asnafi, Dhaarini Murugan, Christine Bole, Patrick Nitschke, Olivier Goulet, Jean-Laurent Casanova, Stéphane Blanche, Capucine Picard, Olivier Hermine, Frederic Rieux-Laucat, Nicole Brousse, Frederic Davi, Veronique Baud, Christoph Klein, Bertrand Nadel, Frank Griesmayr and Alain Fischer

Functional IL-10R Testing

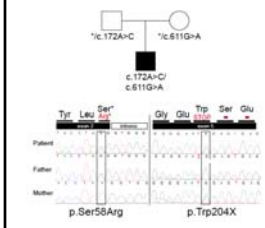


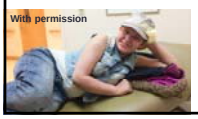


Shouval DS. Adv Immuno 2014

Shouval DS, *JPGN*, 2014

Targeted Sequencing of *IL10RB*





Diagnosis of loss of function mutations in *IL10RB*

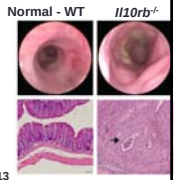
treatment changed to allogeneic SCT

>12 months s/p SCT – no signs of colitis or lymphoma recurrence

Functional Studies in Mice and Man Can Lead to Novel Therapeutic Approaches

- IL-10R patients develop **severe** infantile IBD
- IL-10R knock-out mice (*Il10rb*$^{-/-}$) develop colitis
- Recent studies have shown that IL10-induced signals is important for T cells

What is the role of IL-10R signaling in innate immune cells in the intestine ?

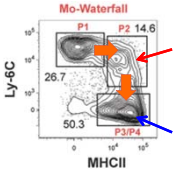


Glocker EO NEJM 2009, Kotlarz D. Gastroenterology 2012, Moran CJ IBD 2013
Murai M. Nat Immuno 2009; Chaudhry A. Immunity 2011
Huber S. Immunity 2011; Kamanaka M. JEM 2011

This is mouse!

Macrophages (Mϕ) Can Differentiate into Pro and Anti-inflammatory Subsets

Intestinal Macrophages



Pro-inflammatory

Anti-inflammatory

Bone Marrow Derived Macrophages (BMDM)

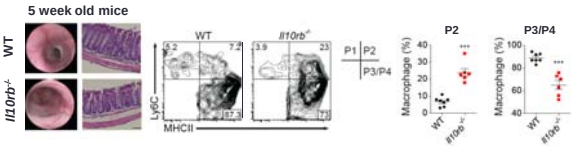
Pro-inflammatory

Anti-inflammatory

Hypothesis: IL-10R-dependent signals are required for the generation and function of pro- and anti-inflammatory Mϕ

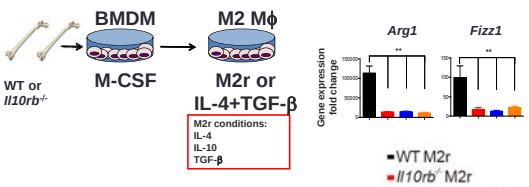
Tamoutounour S EJL 2012
Martinez FO Front biosci 2008

Reduction of Anti-inflammatory Mϕ in the Intestine of *Il10rb*$^{-/-}$ Mice



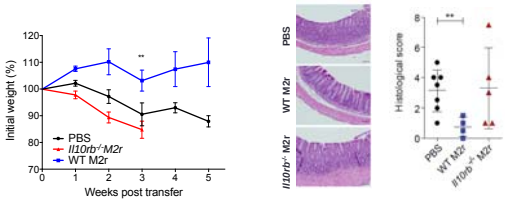
Shouval DS, Immunity 2014

Reduction of Anti-inflammatory Mϕ in the Bone Marrow of *Il10rb*$^{-/-}$ Mice



Shouval DS, Immunity 2014

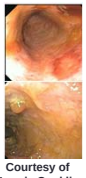
Transfer of WT Macrophages (M2r) Prevents Colitis in *Il10r* mice



Shouval DS, Immunity 2014

Animal Models Informing Human Studies

Patient	Age of Onset (months)	Current age (months)	*IL10R* mutation	Clinical features
1	3	48	*IL10RB* c.*52T (3' UTR)	Colitis, perianal abscesses, arthritis, folliculitis
2	<1	130	*IL10RA* c.585delT p.S196fs	Colitis, perianal abscesses, folliculitis, recurrent respiratory infections
3	<2	154	*IL10RB* c.477G>A p.W159X	Colitis, perianal and renal abscesses, folliculitis, arthritis
4	<6	31	*IL10RB* g.17030_22177 del5148	Colitis, perianal abscesses, folliculitis
5	<1	184	*IL10RB* c.278A>C p.S58R/ c.717G>A p.W202X	Colitis, perianal abscesses, B cell lymphoma
6	2	3	*IL10RB* c.114G>A p.W3X	Colits, recto-vaginal abscess
7	3	21	*IL10RB* c.438-604del167 p.Y59_D110del (Δexon3)	Colitis, perianal abscesses



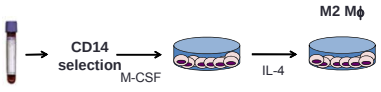
Courtesy of Laurie Conklin

NEOPICS

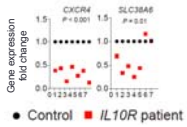
Is Mϕ generation and function abnormal in these patients ?

Shouval DS, Immunity 2014

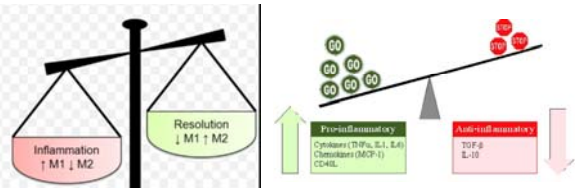
IL-10R Signaling is Required for the Generation and Function of Human Anti-inflammatory Mϕ



Generation of M2 Mϕ



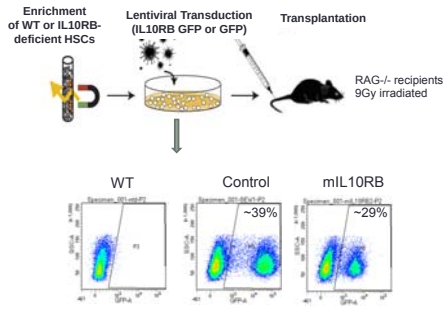
IL-10R-Signals in Macrophages Regulate Intestinal Inflammation



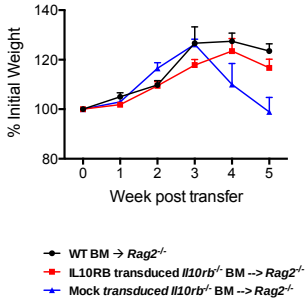
Developing Gene Therapy Approaches for VEOIBD

Dror Shouval, MD
Sandra Frei, Ph.D.
Jeremy Goettel, Ph.D.
Christian Brendel, PHD
David Williams, MD PHD

Preclinical Model of IL10RB Gene Therapy



Transduction of *Il10rb*$^{-/-}$ Bone Marrow Precursors With IL10RB Expressing Lentiviral Vectors Protect Mice from Colitis



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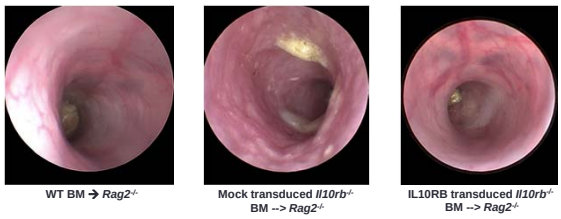


WT BM → *Rag2*$^{-/-}$

Mock transduced *Il10rb*$^{-/-}$ BM --> *Rag2*$^{-/-}$

IL10RB transduced *Il10rb*$^{-/-}$ BM --> *Rag2*$^{-/-}$

Case 2

NEOPICS

- Patient ET
  - Presented at 2 months of age:
  - Blood in stool
  - Diagnosed with cow's milk protein allergy
- Diagnosed < 1 yo with Crohn's colitis.
- Developed perianal and small bowel disease < 2 years of age.
- No evidence of chronic infections or immunodeficiency.
- No family history of IBD, parents not consanguineous.
- Has abnormal low normal reactive oxygen species (ROS) production (3x).

All images are used with the permission of the patient and family

Muise, et al Gut, 2011

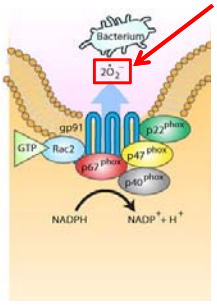
Hypothesis:

Defects in the NADPH oxidase genes that do not cause overt Chronic Granulomatous Disease (CGD) are associated with susceptibility to IBD.

Muise, et al Gut, 2011

NADPH Oxidase Genes and CGD

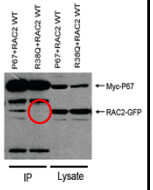
Gene	Inheritance	Frequency
CYBB: gp91phox	X-Linked Recessive	~65%
CYBA: p22phox	Autosomal Recessive	<5%
NCF1: p47phox	Autosomal Recessive	~25%
NCF2: p67phox	Autosomal Recessive	~5%
NCF4: p40phox	Autosomal Recessive	< 1%



Lam et al., 2010

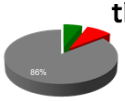
Sequencing of NADPH Oxidase Genes in Infantile and VEO-IBD Patients Identifies Deleterious Mutations

- Identified a novel NCF2 variant - (c.113 G/A) resulting in a mutation in p67phox R38Q
- Variant results in aberrant Rac2 binding
- Patient responded to antibiotic treatment
- Examined this mutation – 2 independent VEO-IBD cohorts
  - 4% of VEO-IBD patients (11/268)
  - 0.3% of older IBD patients (1/330)
  - 0.2% of healthy controls (1/480)



Muise, et al Gut, 2011
Dhillon et al, Gastro 2014

How do we assess the heritability of the remaining fraction?



- IL10RA (n = 5)
- IL10RB (n = 7)
- unknown (n = 71)

1. Deep sequencing of GWAS loci for identification of rare variants
2. Immunochip analysis of selected genes in similar cohort
3. Whole Exome Sequencing (WES)/Whole Genome Sequencing (WGS)

WES in VEO-IBD patient leads to identification of mutation in XIAP

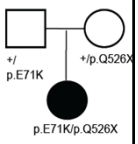
Exome Sequencing Analysis Reveals Variants in Primary Immunodeficiency Genes in Patients With Very Early Onset Inflammatory Bowel Disease

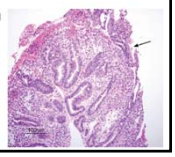
Dissecting Allele Architecture of Early Onset IBD Using High-Density Genotyping

EA Worthey *Genetics in Medicine* 2011
Kelsen JR et al, Gastro 2015
Cutler, Kugathason et al, PLOS ONE 2015

Case 3 – WES
Multiple Intestinal Atresia (MIA), SCID and Apoptotic Enterocolitis

- A female patient born at term
  - Unrelated parents
  - Presented with high output secretory hematochezia af birth
  - Lymphopenia and hypogammaglobulinemia
- Colonoscopy demonstrated
  - chronic inflammation with severe friability
  - sloughed mucosa within the colonic lumen
  - **crypt apoptosis** and exploding crypts
- WES





Mutations in Tetratricopeptide Repeat Domain 7A Result in a Severe Form of Very Early Onset Inflammatory Bowel Disease

Gastroenterology 2014

JACI 2013

Whole-exome sequencing identifies tetratricopeptide repeat domain 7A (*TTC7A*) mutations for combined immunodeficiency with intestinal atresias

TTC7A mutations disrupt intestinal epithelial apicobasal polarity

JCI 2014

JMG 2013

Exome sequencing identifies mutations in the gene *TTC7A* in French-Canadian cases with hereditary multiple intestinal atresia

TTC7A Mutations Cause Apoptotic Enterocolitis

- Little is known about the function of the Tetratricopeptide Repeat Domain 7 (*TTC7A*) gene
- Studies suggest it plays a critical role in PI4KIIIα regulation
- Defects in murine *Ttc7* gene
  - result in the flaky skin (*fsn*) mutant mice
  - develop pleiotropic abnormalities, including runting syndrome, anemia, psoriasis, diarrhea, and intestinal apoptosis

Conclusions: TTC7A-Deficiency and VEOIBD

- Severe intestinal inflammatory process likely at least partially driven by a primary epithelial defect
- Associated with multiple intestinal atresia (and recurs post-resection)
- Associated with SCID (severe combined immunodeficiency)
- Intestinal disease seems to not respond to hematopoietic stem cell transplant

Case 4

- Pulm:
  - Bronchiectasis; Pulmonary nodules
  - rec. sinusitis, rec. URTI
- Heme:
  - Autoimmune **thrombocytopenia** & hemolytic **anemia**
  - Infiltration of BM by $CD8^{+}\gamma\delta$ T cells
- CNS
  - Seizures
  - Infiltrative lymphocytic lesions
- GI
  - Enteropathy
  - Increased lamina propria and intra-epithelial lymphocytes

Dascha Weir/Alan Leichtner

GI Manifestations

- Presented at age 12
- Inflammation of upper & lower GI tract
- Biopsies – villous atrophy, crypt hyperplasia and absent Paneth and goblet cells, increased enterocyte apoptosis and lymphocytic inflammation
- Resistant to 5ASA, steroids, 6-MP, rituximab, prograf, cyclophosphamide, infliximab & sirolimus; Dependent on PN
- Recurrent C. difficile colitis and recurrent herpes zoster infections
- Passed away at age 22 - MRSA sepsis

Zeissig S; Gut 2014

Identification of *CTLA4* Mutations

Immune dysregulation in human subjects with heterozygous germline mutations in *CTLA4*

ORIGINAL ARTICLE

Early-onset Crohn's disease and autoimmunity associated with a variant in CTLA-4

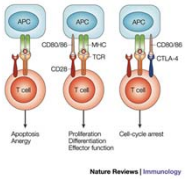
Sebastian Zeissig,[1,2] Britt-Sabina Petersen,[3] Michal Tomczak,[2] Espen Melum,[2,4,5] Emilie Huc-Claustre,[1] Stephanie K Dougan,[2] Jon K Laerdahl,[6,7] Björn Stade,[3] Michael Forster,[3] Stefan Schreiber,[1,3] Dascha Weir,[8] Alan M Leichtner,[8] Andre Franke,[3] Richard S Blumberg[2]

Autosomal dominant immune dysregulation syndrome in humans with *CTLA4* mutations

Kuehn HS; Science 2014
Schubert; Nat Med 2014
Zeissig S; Gut 2014

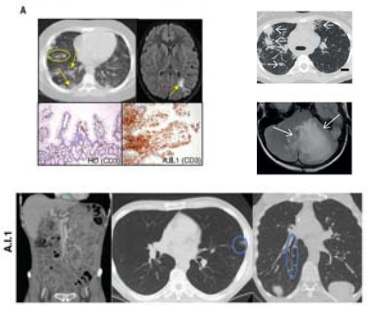
What is CTLA-4 ?

- Suppressive immunoregulatory surface protein
- Activation of T naïve cells induces expression of CTLA4 → binds CD80 or CD86 → inhibitory signal to activated T cells
- Shares homology to CD28

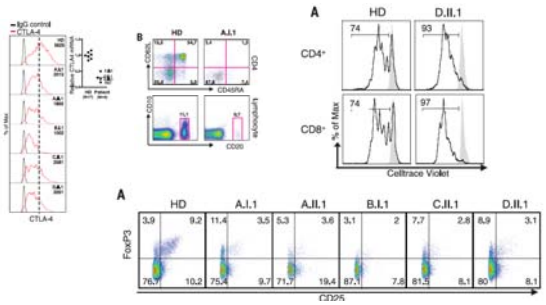


Nature Reviews | Immunology

CTLA4 Deficiency



Immunological Analysis of Patients with CTLA4 Mutations



Immunologic And Genetic Evaluation

- All patients with low immunoglobulin levels
- Thyrombocytopenia, Hemolytic anemia
- Fewer regulatory T cells; markedly fewer naïve T cells; many activated T cells
- Autosomal dominant inheritance; Incomplete penetrance

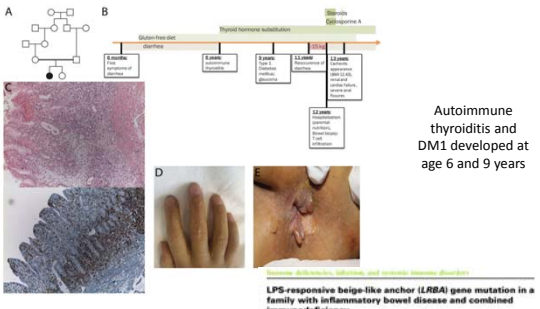
Treatment: ? BMT

Not all patients young! Some diagnosed in 40's

Conclusions – When to suspect CTLA4 Mutations ?

- Multiple autoimmune features
- Low immunoglobulins
- Pulmonary/CNS involvement
- Positive family history

LRBA Mutations Can Initially Present as VEO-IBD +/- CVID



Autoimmune thyroiditis and DM1 developed at age 6 and 9 years

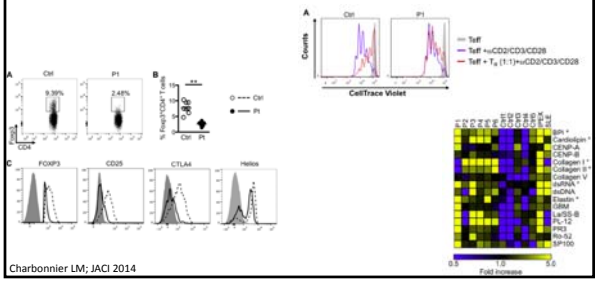
Serwas NK; IBD 2015

LPS-responsive beige-like anchor (*LRBA*) gene mutation in a family with inflammatory bowel disease and combined immunodeficiency

Lopez-Herrera G; Am J Hum Gen 2012; Alangari A; JACI 2012

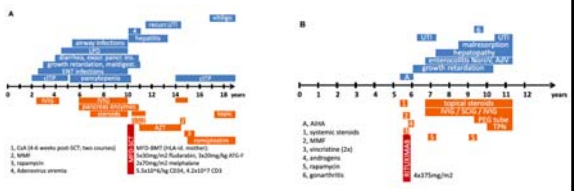
Extended Spectrum of LRBA Deficiency

- Not all have low immunoglobulins
- Report of a family with IPEX-like phenotype



Charbonnier LM; JACI 2014

Treatment Options for LRBA Deficiency



AUTOIMMUNE DISEASE

Patients with LRBA deficiency show CTLA4 loss and immune dysregulation responsive to abatacept therapy

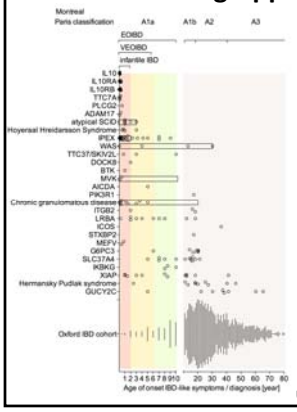
Lo et al, Science 2015

Seidel MG; JACI 2014

Conclusions – When to suspect LRBA Mutations ?

- Multiple autoimmune features (pulmonary, endocrine, GI)
- Low immunoglobulins
- Can present with IPEX-like phenotype
- Positive family history

Evolving Approach to VEO-IBD



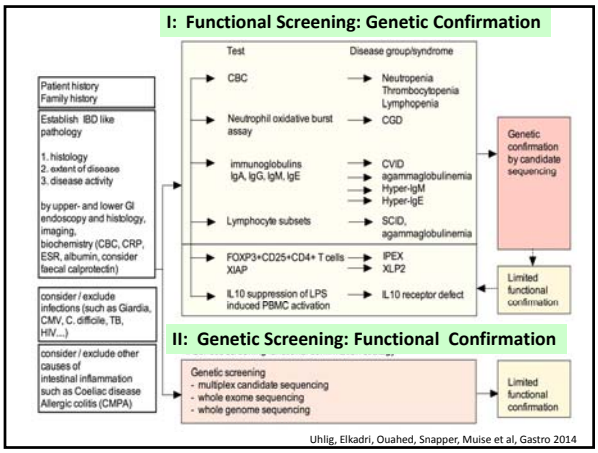
First – Screen for Genes know to Cause VEOIBD

Next Examine Genes in Common Pathways

Examine Novel Variants

Functional Examination of Variants

Uhlig, Elkadri, Ouahed, Snapper, Muise et al, Gastro 2014



Uhlig, Elkadri, Ouahed, Snapper, Muise et al, Gastro 2014

VEO-IBD: Take Home Points

- **GWAS have shown that genetics in adult and adolescent pediatric IBD overlap considerably.**
- **Immunodeficiencies account for a significant percentage of patients presenting with infantile IBD**
- **Unique genetic abnormalities may be more dominant in VEO-IBD (e.g., IL-10R; NCF2); however, data is limited**
- **Whole exome sequencing (and ultimately whole genome sequencing) will greatly expand our ability to detect rare variants in individual patients**

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www.veoibd.org

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There is an Urgent Need to Develop *In Vivo* Models to Study Basic Biology of Human Cells and Disease

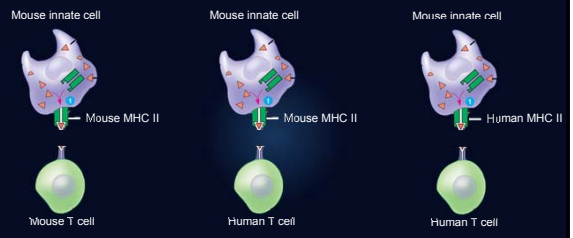
Unknown patient risk
Multifactorial

Hematopoietic stem cells (HSCs)

Jeremy Goettel, PhD

Tractable model
No risk to patient
Controlled environment

CD4 T cells interact with MHC class II



Good Immune Response

Poor Immune Response

Immune Response??

Goettel et al, Blood 2015

Generation of immune-humanized mice using CD34⁺ HSCs

Hematopoietic stem cells (HSCs)

huDR1

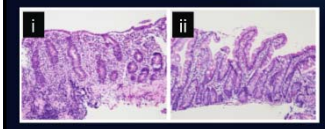
Enhanced T cell and B cell responses!

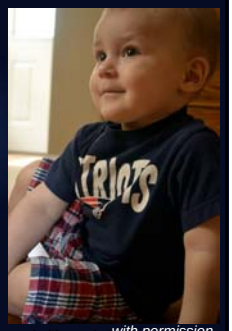
HLA-DR1*01:01 donor

Goettel et al, Blood 2015

IPEX: (immunodysregulation, polyendocrinopathy, enteropathy, X-linked syndrome)

- Due to loss-of-function mutation in *FOXP3* (critical for regulatory T cells)
- Autoimmune enteropathy, eczema, type-1 diabetes, elevated IgE
- Often fatal in the first 2 years of life
- *Foxp3*^{sf} mice also develop systemic inflammation, autoimmunity, and premature death





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Can human HSCs from an IPEX patient transfer clinical phenotype to humanized mice?

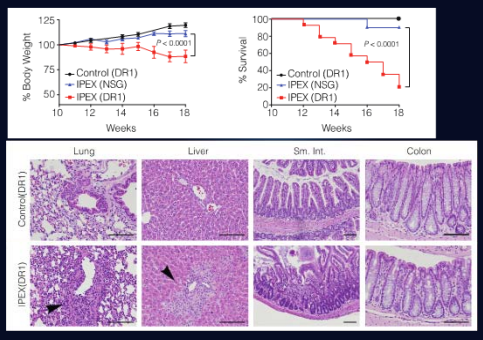
Hematopoietic stem cells (HSCs)

huDR1

Patient CD34⁺ cells or IPEX CD34⁺

Goettel et al, Blood 2015

Increased mortality and mulisystem organ failure in IPEX(huDR1) mice



Goettel et al, Blood 2015

Summary

- huDR1 mice exhibit greater T cell diversity, T cell recall responses, B cell maturation, and antibody class switching compared to NSG mice.
- $CD34^+$ HSCs from a patient with IPEX syndrome cause multi-organ inflammation, development of autoantibodies, and increased mortality in huDR1 mice similar to that observed in *Foxp3*^{sf} mice.

Future directions

- Evaluate $CD34^+$ HSCs from very-early onset IBD patients (e.g.,IL10R deficiency, Wiskott-Aldrich syndrome, CGD) in huDR1 mice.
- We have re-derived huDR1 mice into germ free conditions to evaluate the role of specific microbes, byproducts, and metabolites in regulating mucosal immune function and promoting homeostasis.