IBD PATHOGENESIS AND ITS RELEVENCE TO TREATMENT

Department of Gastroenterology

PGIMER

Chandigarh

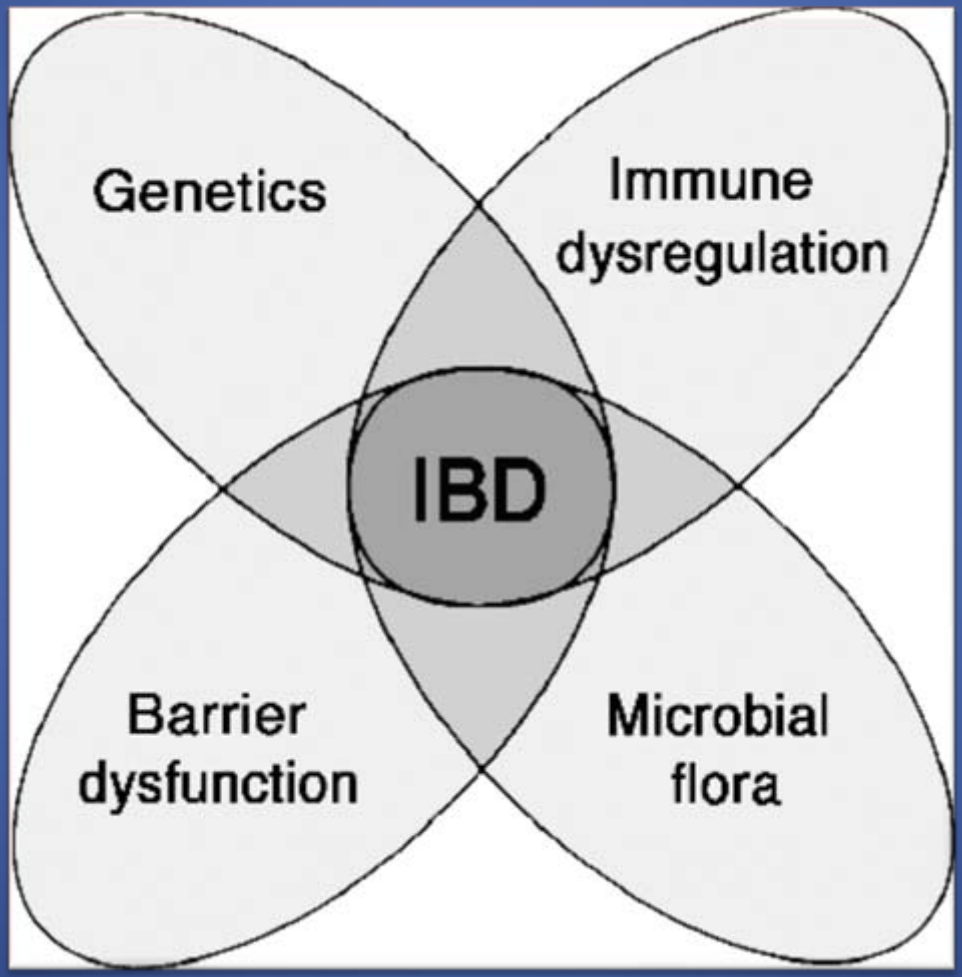
INTRODUCTION

- IBD - immune-mediated disease
- Complex pattern/interplay of host genetics and environmental influences
- Substantial progress in understanding the pathophysiology
- Translated into newer, more effective therapies
- Improved the quality of life of patients with IBD

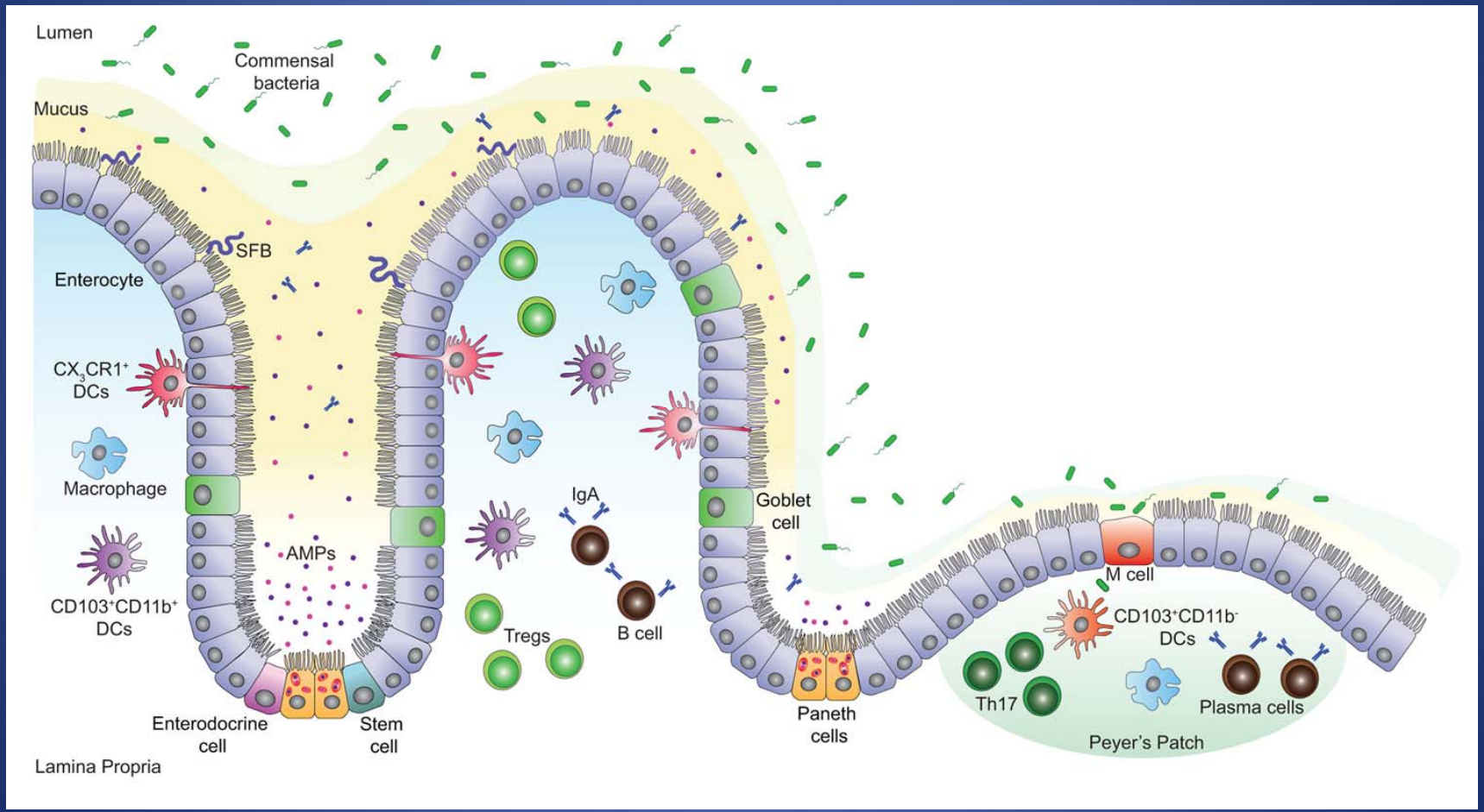
OUTLINE

- Overview of gut immunity
  - Innate immunity
    - Intestinal barrier
    - Innate immune cells
  - Adaptive immunity
- Gut microbiome
- Evidence of dysfunction in pathogenesis
- Relevance for therapy

MULTIFACTORIAL PATHOGENESIS

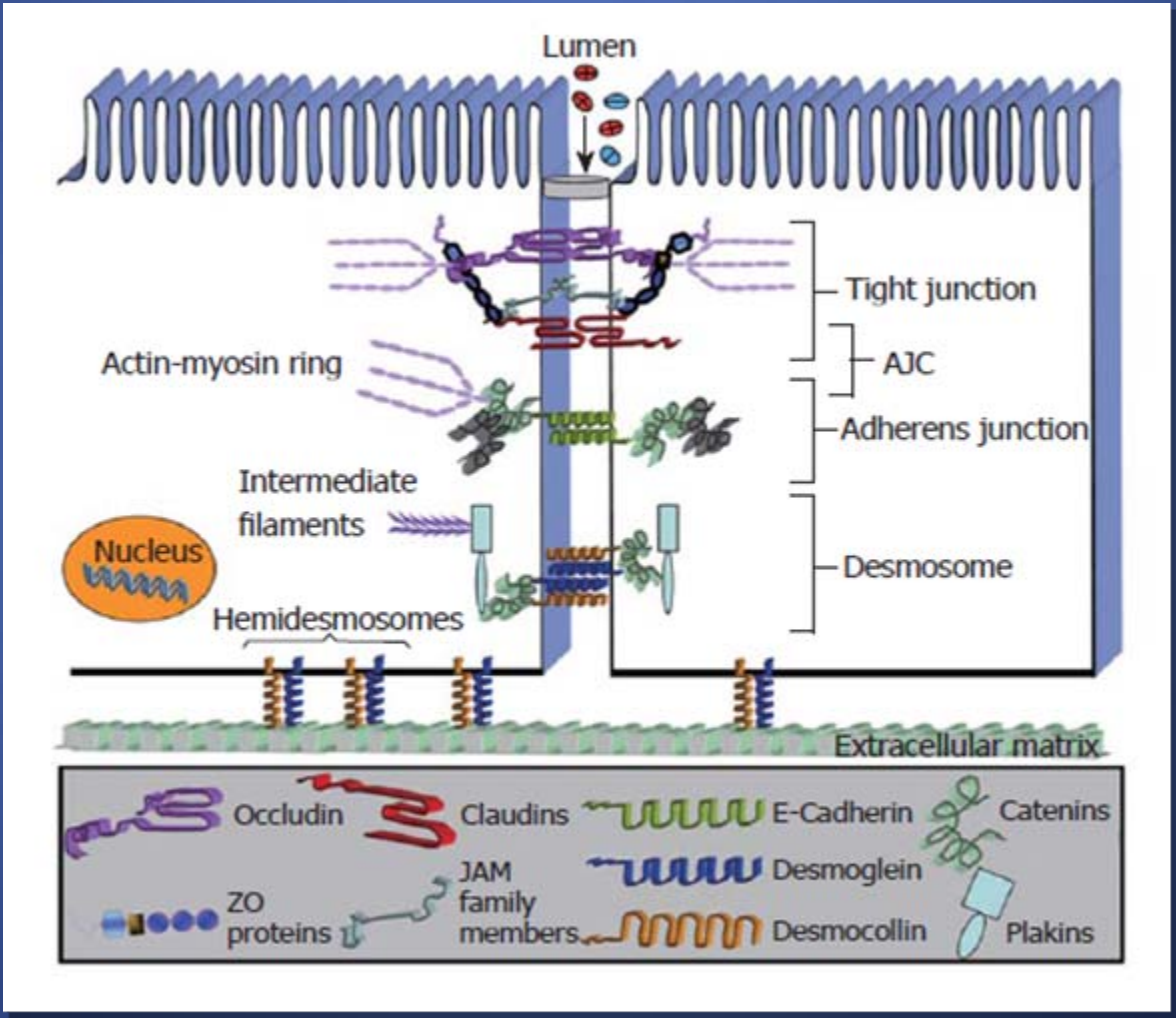


INNATE IMMUNITY
Epithelial barrier



Frontiers in immunology 2012

EPITHELIAL BARRIER

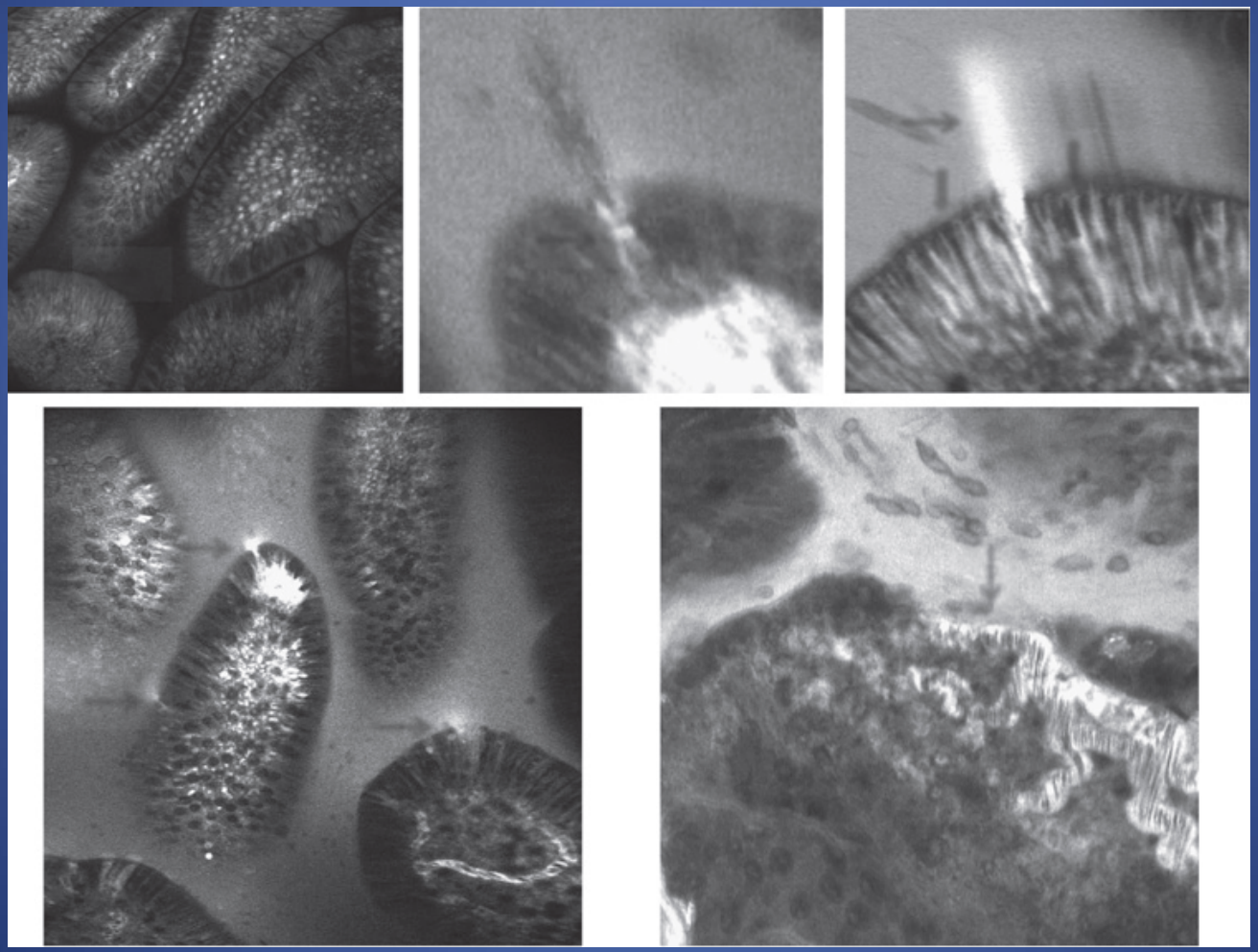


BARRIER DYSFUNTION

- Abnormal permiability established in CD patients
- GWAS studies – CD risk locus MUC 19 – intestinal mucus layer
- Barrier dysfunction directly has been observed by confocal endomicroscopy
  - Predictive of IBD relapse
- Polymorphic variations in several IBD-associated genes primary affect epithelial permiability
- Epithelial cell death(paneth cells) – caspase 8 deletion – CD in humans

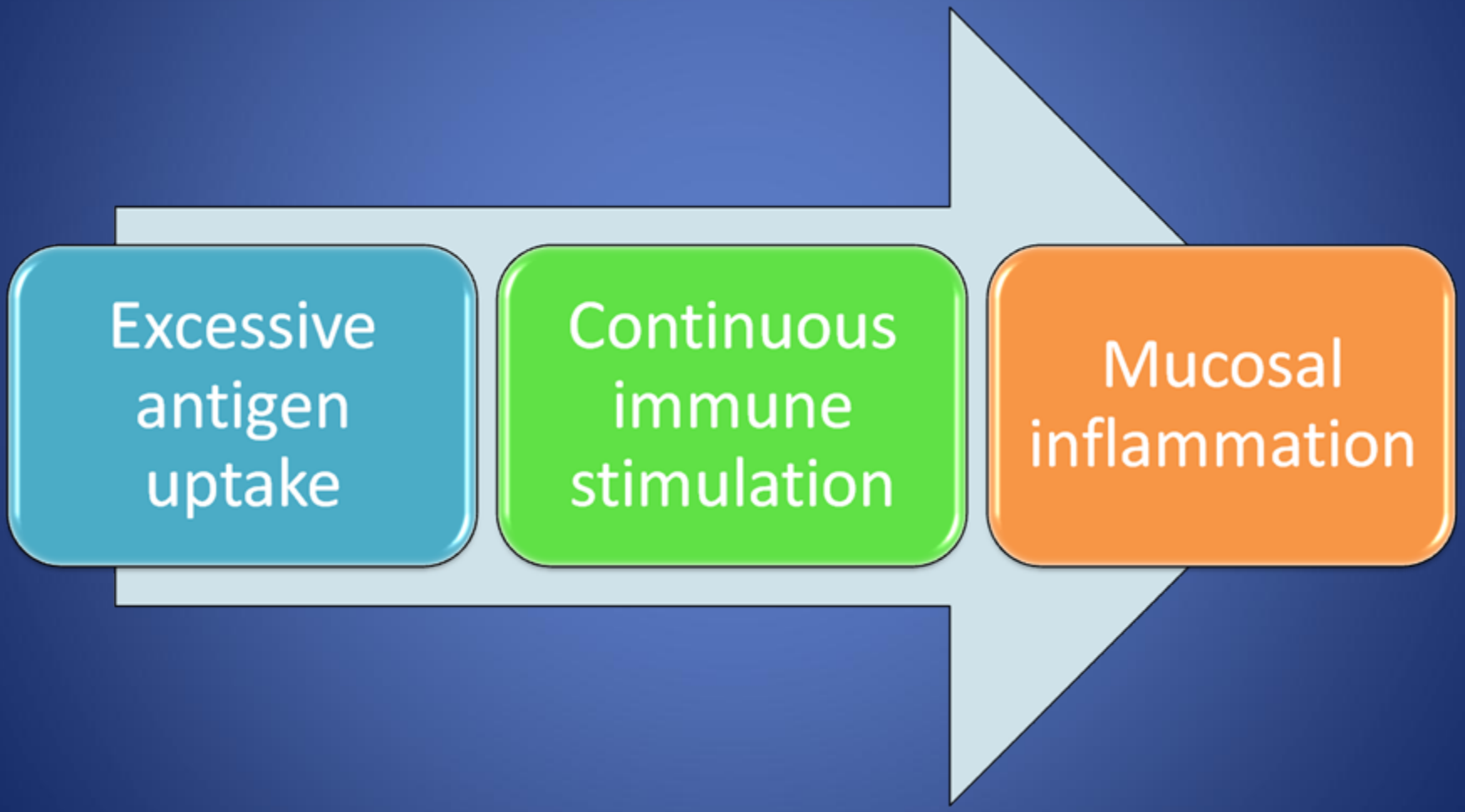
Am J Gastroenterol 1997, Nature 2012, Gut 2012, Int J Colorectal Dis 2012, Nature 2011

LOSS OF BARRIER FUNCTION
Confocal endomicroscopy



Gut 2012

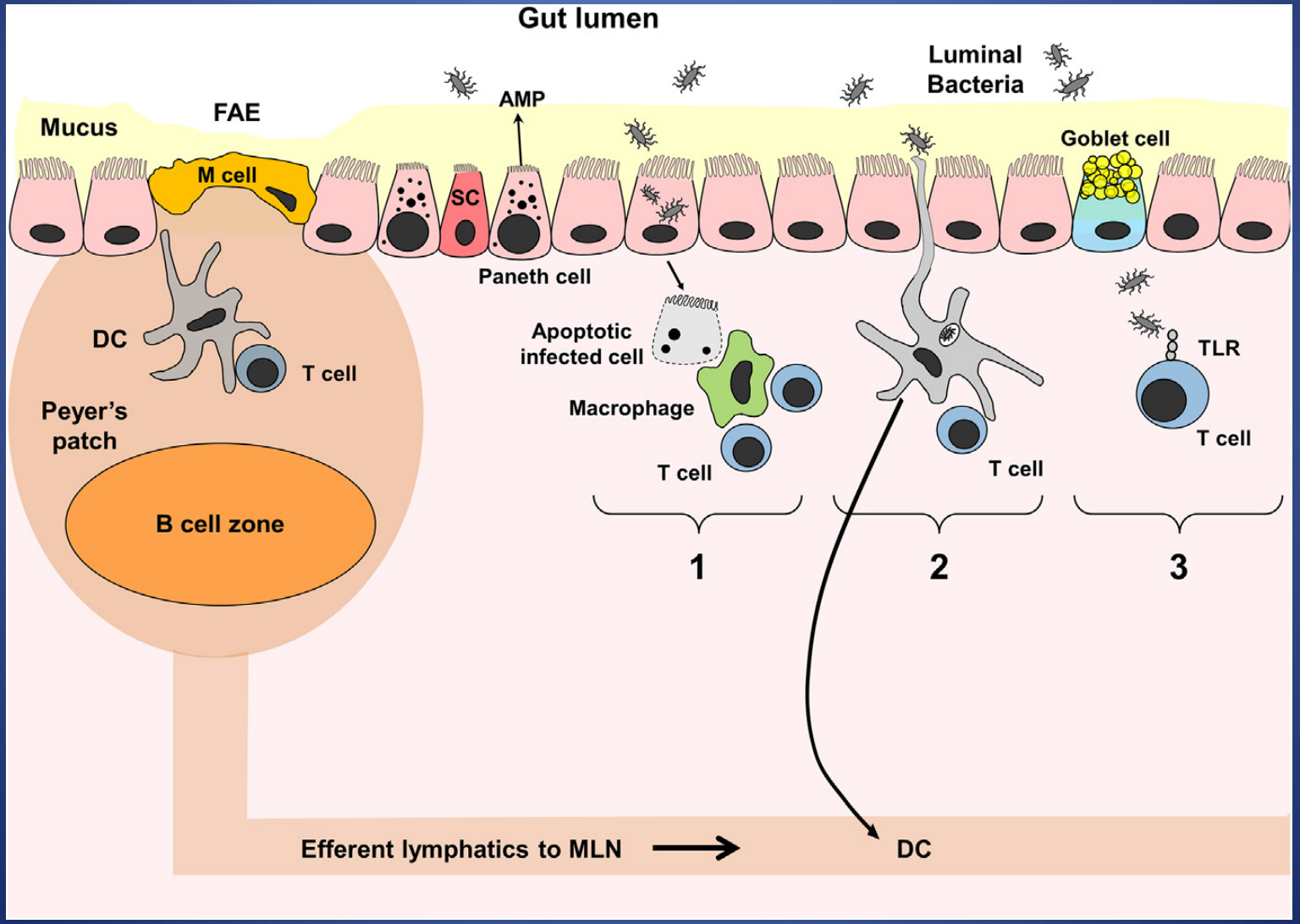
EPITHELIAL PERMIABILITY



INNATE IMMUNITY

- Rapid and less specific response to invading microorganisms or toxic macromolecules
- Innate immune cells
  - Macrophages
  - Dendritic cells
  - Atypical lymphocytes and NKT
- Pathogen recognition receptors (PRR) and pathogen-associated molecular patterns (PAMPs)
- Autophagy pathway

INTESTINAL MUCOSAL IMMUNE SYSTEM



PRR and PAMPs

- PRR
  - Membrane bound (ie, Toll-like receptors [TLRs], C-type lectin receptor) or
  - Cytoplasmic (ie, nucleotide-binding oligomerization domain family members [NODs], retinoic acid–inducible gene 1–like receptor)
- PAMPs (eg, lipopolysaccharide and peptidoglycan)
  - highly conserved molecules on microbes as they are central to survival

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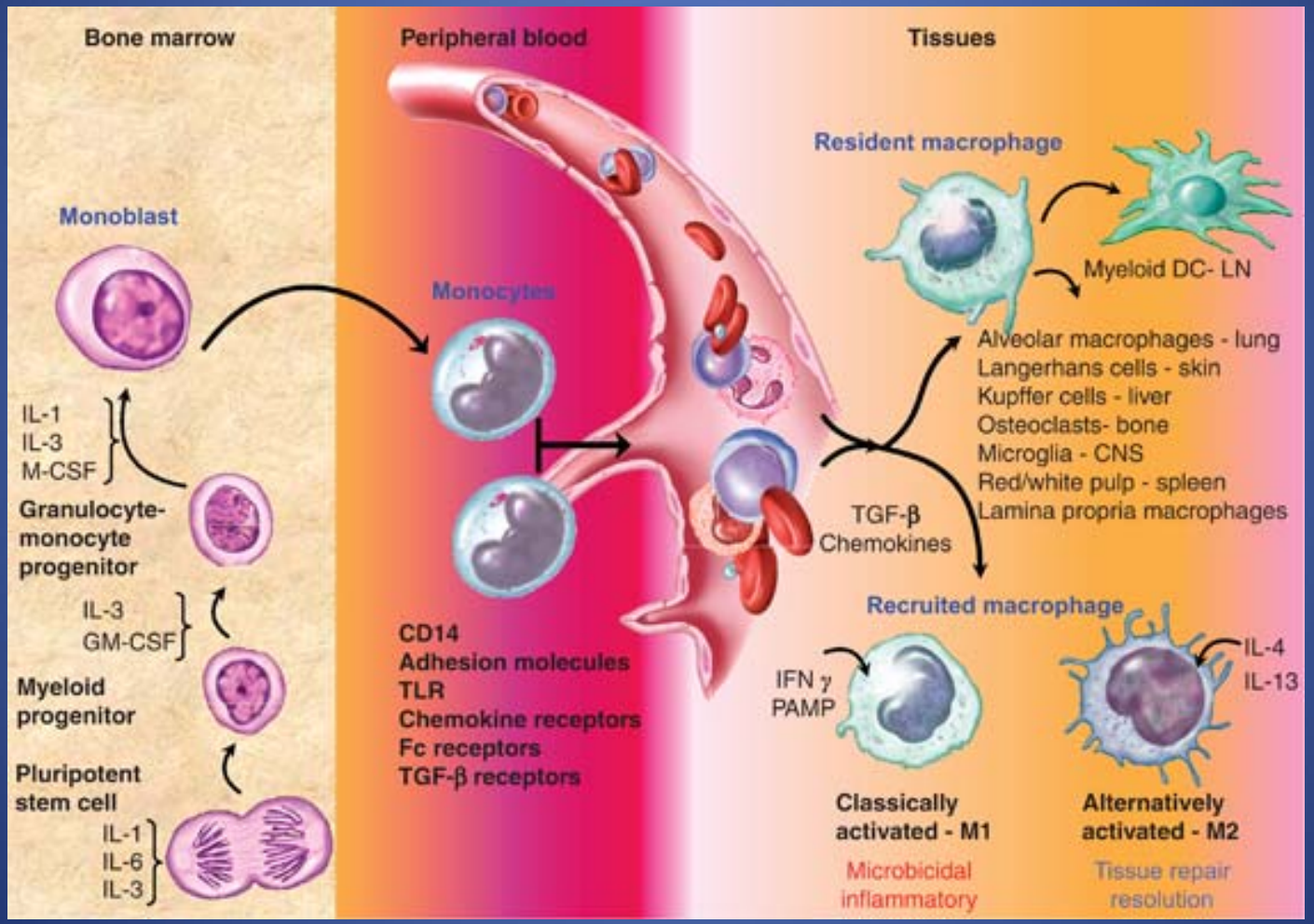
MACROPHAGES



Mucosal immunology 2011

MACROPHAGES

Setting of pathogen invasion/inflammation

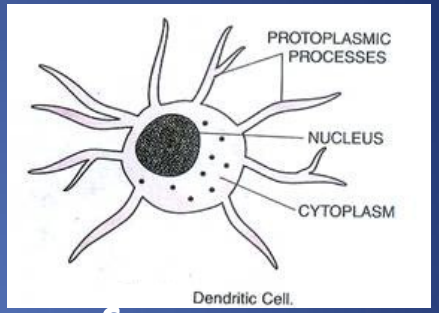
Convert to a proinflammatory phenotype (ligation of their PRR)

Phagocytosis + secretion of cytokines

IL-1, IL-6, IL-8, TNF-α and TGF-β and recruits cells

Critical link between innate and adaptive immunity

DENDITIC CELLS



- Phagocytic and APCs
- MHC class II molecules
- Normal physiologic state – low levels of costimulatory molecules –
  - T regulatory cells (Tregs)
  - Anti-inflammatory cytokines – IL-4, IL-10 and TGF-β
- Proinflammatory microenvironment -migrate to T cell areas of the GALT
  - induce effector responses
  - Induce mucosal homing receptor α4β7 and chemokine receptor CCR9 on T cells

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ATYPICAL LYMPHOCYTES

- $\gamma\delta$ TCR chains
- >10% of SI intraepithelial lymphocytes
- Do not depend on thymus for development
- Do not recognize antigen in association with MHC class I or II
- Effectors against pathogens and tumors and also act as APCs

Natural Killer T cells (NKT cells)

- Mature in the thymus and recognize lipid antigen (presumably bacterial)
- On activation, they secrete large quantities of proinflammatory cytokines and
- readily kill infected cells or tumor cells
- Produce large amounts of proinflammatory cytokine IL-13 have been found in the intestine of patients with UC

INNATE IMMUNE CELLULAR DYSFUNCTION

- The most recent metaanalysis GWAS in IBD
  - susceptibility genes involved in innate mucosal defense (NOD2, CARD9, REL,SLC1A) and
  - antigen presentation (ERAP2, LNPEP)
- Small bowel CD is the loss-of-function polymorphisms in the bacterial sensing gene CARD15/NOD2

INNATE IMMUNE CELLULAR DYSFUNCTION

- In CD -defective inflammatory response to injury and bacterial products
- Failure of clearance of bacteria and inflammatory debris
  - Disruption in the autophagy pathway
  - GWAS - ATG16L1 risk allele contributes to Paneth cell dysfunction
- Multiple ER stress-related genes like XBP1 have been associated with IBD

NOD 2 GENE AND CD

- 2-fold risk for CD heterozygotes and an approximately 20-fold risk FOR homozygotes or complex heterozygotes
- Mutation- reduced NFkB expression
- But NFkB elevated in CD
- Multiple theories to explain this

Nature 2001, Biochem Biophys Res Commun 2013

TARGETS FOR THERAPY

- TNF α inhibitors – Infliximab etc
- IL-12/23 - Ustekinumab
- IL-13 –
  - QAX576 IL-13,
  - Anrukinzumab,
  - Tralokinumab
- TLR- DIMS0150 and BL-7040

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ADAPTIVE IMMUNITY

- Central role in human and experimental IBD models
- Adaptive immune cells
  - T cells
  - Tregs
  - B cells

T CELLS

- CD4+ AND CD8+ - equal proportions in LP
- CD4+ essential role in the pathogenesis
- Costimulation via CD28 (on T cells) and B7.1 or B7.2(on APC) -T-cell activation
- Costimulation mediated by cytotoxic T-lymphocyte antigen 4 (CTLA-4) (on T cells) by B7.1 or B7.2 results in T cell inhibition

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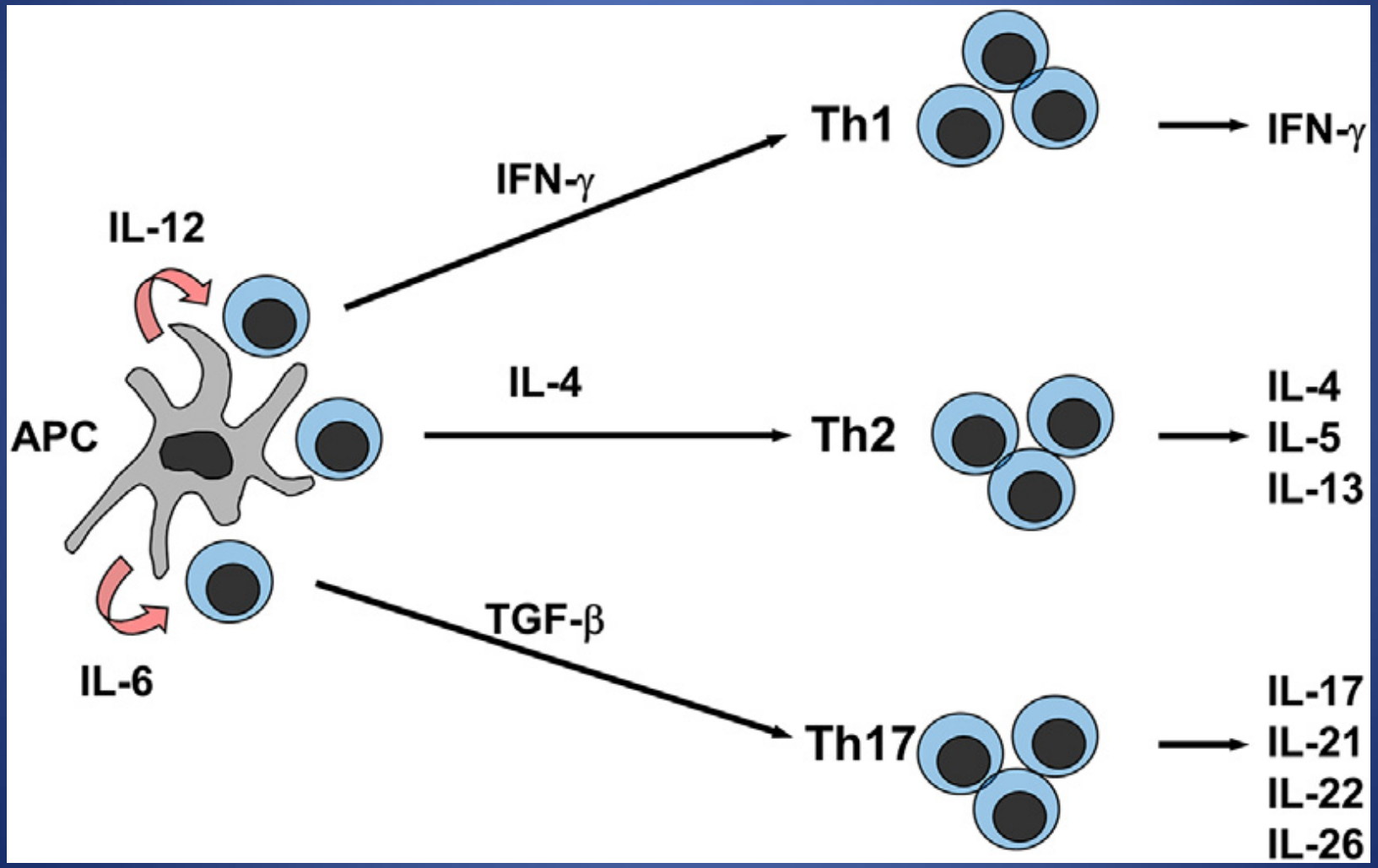
T HELPER CELLS



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ACTIVATED T CELLS

Cognate antigen+T cell – proinflammatory cytokines – TNF α

Upregulate adhesion molecules, alter the blood flow, endothelial cell shape, and vascular permeability to enhance the migration of inflammatory cells

Structural alterations in the inflamed tissue, including ulceration

Tregs

- Subpopulation of CD4+ T cells
- Restrain not only effector T cells but also innate inflammatory leukocytes
- suppress mucosal inflammation and murine colitis
- Evidence that effector T cells obtained from patients with IBD are refractory to suppression by Tregs

Gastroenterology 2009

ADAPTIVE IMMUNE CELLULAR DYSFUNCTION

- T cell–driven animal models of colitis mimic human IBD
- IL-23 receptor variant associated with CD impairs the IL-23–induced Th17 effector function and is a protective genetic variant
- Established and emerging therapies – destruction of activated effector T cells or the blockade of T cell–derived proinflammatory cytokines

J Clin Invest 2004, PLoS One 2011, Gut 2012

ADAPTIVE IMMUNE CELLULAR DYSFUNCTION

- Clonal populations of T cells (ie, expansion of T cells in response to persistent and specific antigens) – CD
- Animal model of IBD, similar T-cell clones
- Patients with IBD have antibodies directed against particular microbial antigens

J Exp Med 1998, J Clin Invest 2004

TARGETS FOR THERAPY

Biologic Target	Antibody/Drug	Mechanism of Action	CD, UC, or Both
CCR9	CCX282-B	Inhibition of CCR9	CD
	CCX 025	Inhibition of CCR9	CD
IL-21	PF 05230900	IL-21 receptor antagonist	CD
IL-13	QAX576	IL-13 antagonist	CD
	Anrukinzumab	IL-13 antagonist	UC
	Tralokinumab	IL-13 antagonist	UC
IL-17	Vidofludimus	Inhibitor of IL-17 A and IL-17F	Both
IL-12/23	Ustekinumab	Blockade of IL-12/23	CD
IL-18	GSK1070806	Blockade of soluble IL-18	CD
IL-6 and IL-6R	Tocilizumab	Inhibitor of IL -6	CD
	PF04236921	Inhibitor of IL -6	CD
IP-10	MDX 1100	Blockade of interferon-γ inducible protein (IP-10 or CXCL10)	UC
IRAK4/TRAF6/ MyD88	RDP58	Disrupts IRAK4/TRAF6/MyD88 signaling and reduces production of proinflammatory cytokines	Both
JAK3	Tofacitinib	Inhibition of JAK3	Both

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TARGETS FOR THERAPY

MAdCAM-1	PF-547659	Blocks MAdCAM-1	Both
NF-κB	HE3286	Synthetic steroid that modulates NF-κB activity	UC
NKG2D	NN8555	Anti-NKG2D receptor monoclonal antibody	CD
PKC	AEB071/Sotrastaurin	PKC inhibitor	UC
T Cell	Laquinimod	Reduces IL-17 level and interferes with migration of T cells	CD
TLR	DIMS0150	Blockade of Toll-like receptor	UC
	BL-7040	Blockade of Toll-like receptor	UC
TNF-α	Infliximab	Neutralization of TNF-α	Both
	Adalimumab	Neutralization of TNF-α	Both
	Certolizumab pegol	Neutralization of TNF-α	CD
	Golimumab	Neutralization of TNF-α	UC
	Debiaerse	Vaccine against TNF-α consisting of a TNF-α derivative TNF-α kinoid	CD
Effector T cells, B cells	Antigen specific Type 1 regulatory cells (OvaSave)	Autologous ova expanded regulatory T cells injected	CD
α4 integrin	AJM-300	Blockade of α4 integrin	CD
α4 integrin	Natalizumab	Blockade of α4 integrin	Both
α4β7 integrin	Vedolizumab	Blockade of α4β7 integrin	Both
β7 integrin	Etrolizumab (aka rHuMab β7)	Anti-β7 integrin	UC

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GUT MICROBIOTA

- Pivotal role
- No germs: No IBD (No IBD in germ free rats)
- The flora in IBD:
  - More often has pathogens
  - More adherent bacteria
  - Reduced diversity : ecology disturbed
  - Increased Enterobacteriace; Decreased Firmicutes
  - ? Role of fungus (ASCA +vitiy)

MICROBES AND IBD

- Change of flora effective in Rx
  - Antibiotics
  - Probiotics
  - Elemental diet
- Infection precipitates flares

PATHOGENIC OR ALTERED COMMENSAL BACTERIA

- Enhanced epithelial adherence
- Epithelial invasion
- Resistance to killing
- Acquisition of virulence factors
- Stimulation of innate and adaptive immunity
- production of butyrate causes poor epithelial integrity
- Increased production of toxic metabolites like H_2S

MICROBIAL PATHOGENS

- *Mycobacterium avium paratuberculosis (MAP)*
  - May infect genetically susceptible CD patients with intracellular bacterial killing defects due to ATG16L1, NOD2, or NCF4 polymorphism
- Adherant invasive *E.coli*
  - Identified from inflamed ileal mucosa of CD
  - E coli DNA in 80% of granulomas
  - High titres of Anti-Ecoli Ab in 55% of Crohns disease
- Enterotoxigenic *Bacteroides fragilis* in 19% of IBD
- *Enterococcus faecalis*

DYSBIOSIS

- Alteration of indigenous microbiota alters
  - Dominant antigens
  - Metabolic function of the gut
- Intestinal mucosal bacteria found at concentration greater than 10^9/ml in
  - 95% of IBD patients
  - 65% of IBS patients
  - 35% of healthy controls
- CD occurs in intestinal segments with the highest bacterial concentrations

J Clin Microbiology 2005

TARGETS FOR THERAPY

- Probiotics
- Antibiotics
- Limited success

TO SUMMARIZE

TARGET	THERAPY
Epithelial barrier	
Innate immunity	Biologicals
Adaptive immunity	Steroids, Immunosupressive medications, Biologicals, Immunotherapy
Gut microbiota	Probiotics, Antibiotics

CONCLUSION

- Studies of mucosal immunity have lead to recent advances in therapy
- GWAS data and studies on microbiome – unraveled the complex interaction between host and environment
- Many aspects of mucosal immunity remain unclear
- Clinical phenotype doesn’t correspond to the immunophenotype of patients