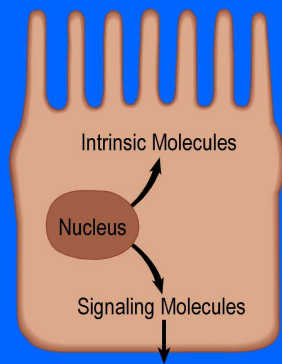
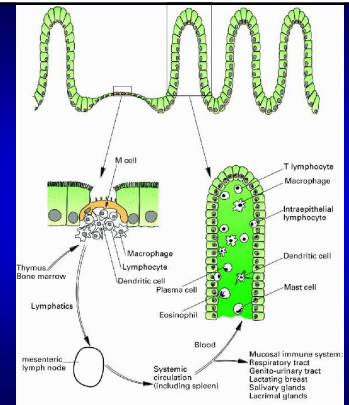


Food and intestinal gene expression

Ian R. Sanderson
Centre for Digestive Diseases

NSKE, Oslo, 14. Januar 2010

Gut-Associated Lymphoid Tissue



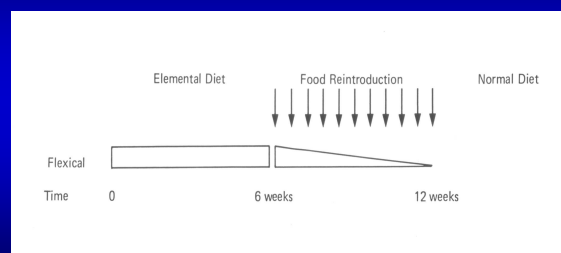
Synopsis

- Clinical relevance
- Evidence for enterocyte signaling *in vivo*
- Developmental regulation of MHC class II
- Developmental changes in lumen (SCFA)
- SCFA and signaling genes

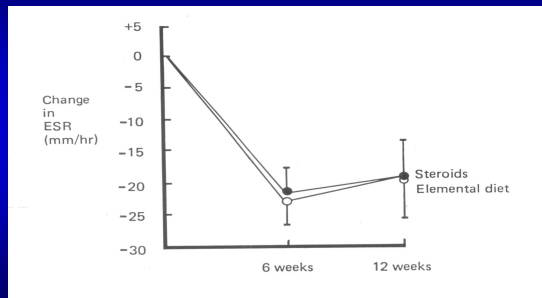
Diet and gastrointestinal disease

Crohn's disease
Necrotising enterocolitis

Enteral feeding

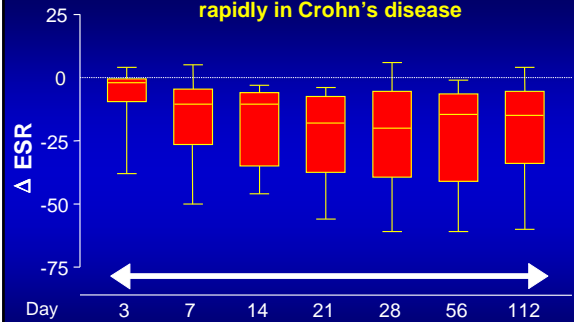


Changes in ESR



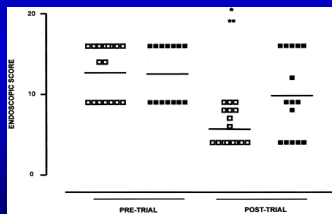
Sanderson et al., 1987

Enteral feeds reduce inflammation rapidly in Crohn's disease



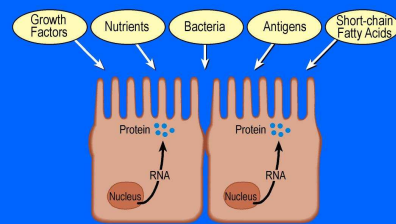
Bannerjee et al., 2004

Endoscopic score was significantly better after treatment in the diet group



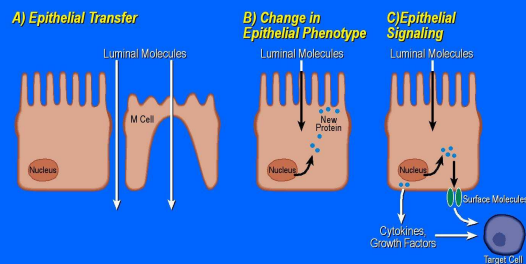
Borrelli et al., 2006

DIFFERENT LUMINAL FACTORS INFLUENCE GENE EXPRESSION IN THE ENTEROCYTE

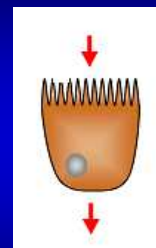


From: Sanderson, IR (1996)

INTERACTIONS OF MOLECULES IN THE INTESTINAL LUMEN WITH THE EPITHELIUM



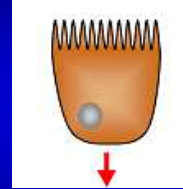
From: Sanderson, IR (1996)



The epithelium transduces afferent stimuli to efferent signals

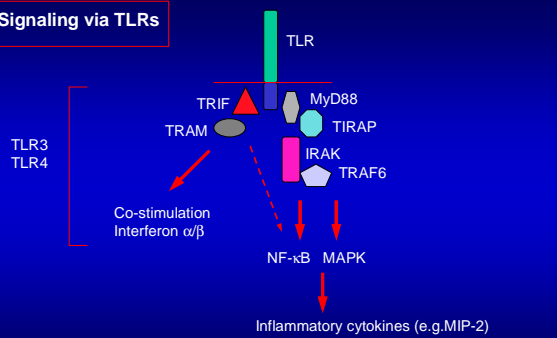
Afferent limb: Effect of the lumen on the epithelial cell

Efferent limb: Effect of the epithelial cell on the immune system



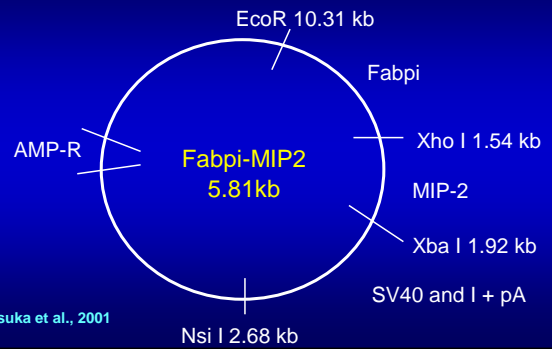
Epithelial cell signaling

Signaling via TLRs



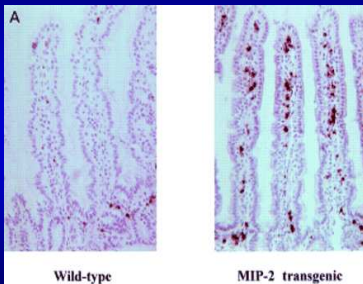
Based on *Nat. Rev. Immunol.*, 2001; 1: 135

Plasmid with Fabpi promoter and MIP-2



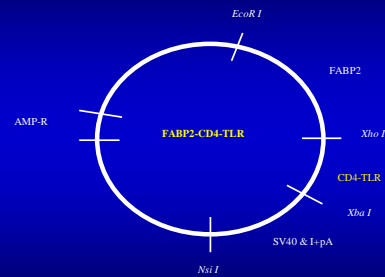
Ohtsuka et al., 2001

Epithelial cell chemokine (MIP-2) increases neutrophil recruitment



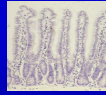
Ohtsuka et al., 2001

Construct used to generate transgenic mice



Phenotype of TLR transgenic mice

No difference in growth or weight
Equivalent stool production
No difference on intestinal histology

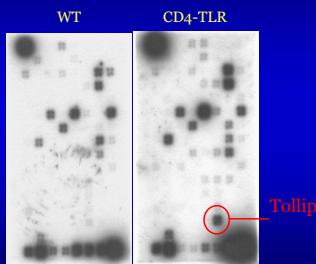


Intestinal morphometry: similar numbers of neutrophils, LP lymphocytes and IELs

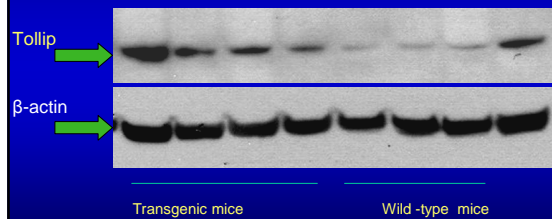
Superarray of intestinal epithelial cell RNA

Many transcripts of TLR signaling products examined simultaneously (against internal standards)

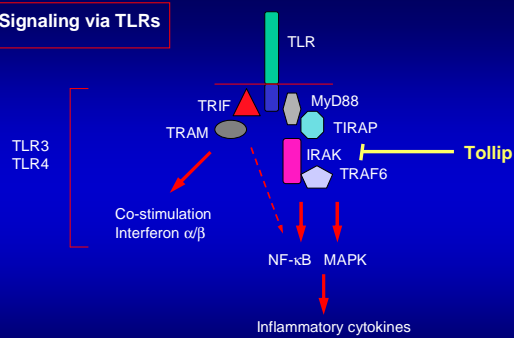
Tollip is up-regulated in TLR4 transgenic mice



Tollip (protein) is expressed in greater amounts in TLR transgenic mice

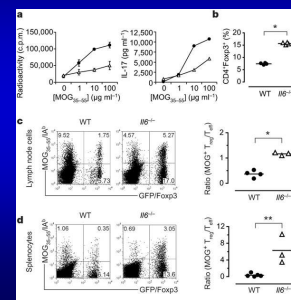


Signaling via TLRs

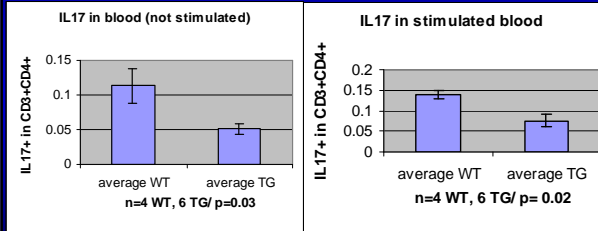


Based on *Nat. Rev. Immunol.* 2001; 1: 135

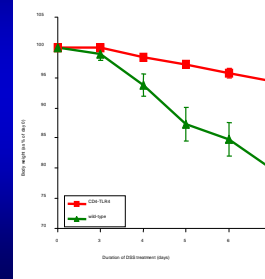
IL-6 increases IL17 cells and decreases Treg (Korn et al., 2007)



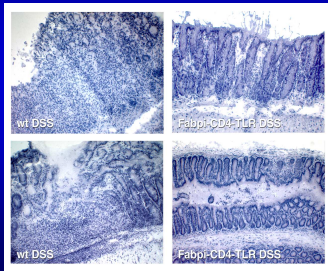
TLR transgenic mice have fewer circulating IL17 cells



TLR transgenic mice sustain greater body weight during DSS inflammation

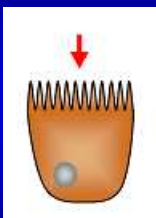


TLR transgenic mice have less inflammation after DSS



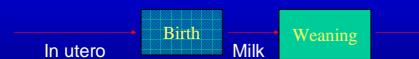
Persistent TLR activation:

- does not alter intestinal morphology
- decreases circulating T17
- protects against inflammation

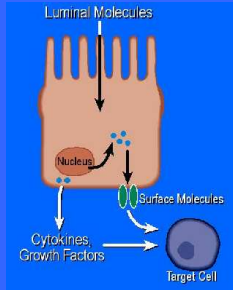


Luminal regulation of epithelial cell gene expression

Luminal changes in infancy

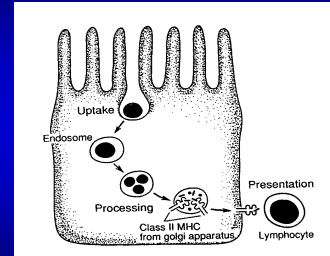


Signaling occurs through surface molecules or secreted proteins



Surface molecules include MHC class II

Antigen presentation: MHC class II and invariant chain

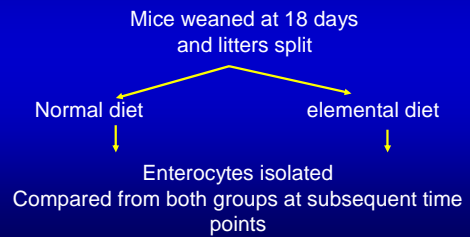


Sanderson & Walker, 1993

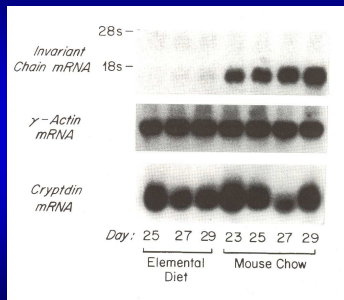
Elemental diet on enterocyte MHC Class II expression

MHC class II is expressed on the normal mouse intestinal epithelium after weaning

Elemental vs complex diet on enterocyte MHC class II ontogeny

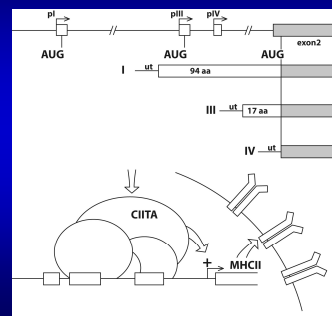


Invariant chain and MHC class II induced on weaning with a complex (normal) diet

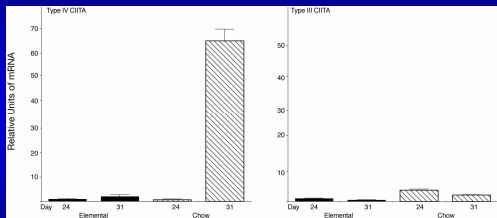


Sanderson et al, 1993

Class II MHC is regulated by three isoforms of the class II transactivator



Weaning mice onto normal diet induces type IV



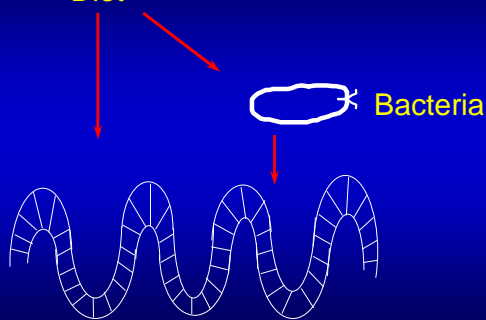
Sanderson et al, 2004

Class II MHC ontogeny

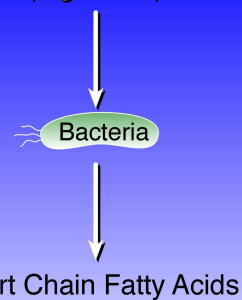
Type III regulated by time (independent of diet)

Type IV regulated by diet (independent of time)

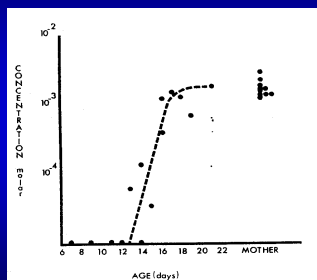
Diet



Unabsorbed Carbohydrate
(e.g. Fiber)

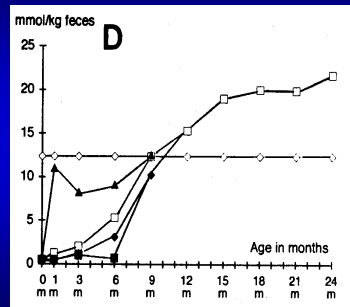


Appearance of butyrate in the large intestine of weaning mice



Lee & Gemmell, 1972

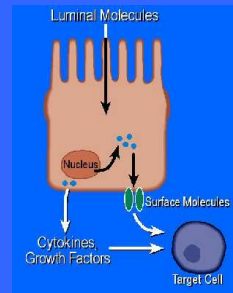
Appearance of butyrate in the large intestine of children



Midtvedt & Midtvedt, 1992

Butyrate regulation of signaling molecules

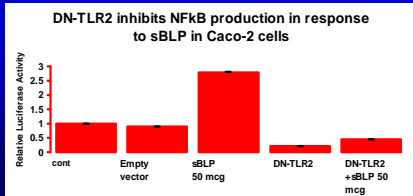
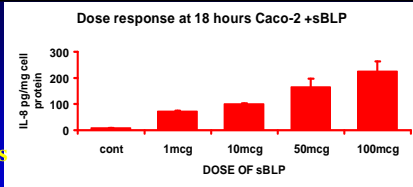
Signaling occurs through surface molecules or secreted proteins



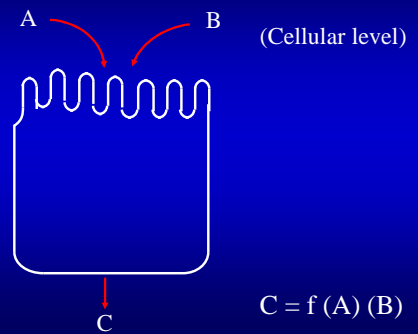
Secreted proteins include:

Chemokines and IGF binding proteins

1. Bacterial lipoprotein (BLP) [Pam3Cys SerLys4] acts through TLR2



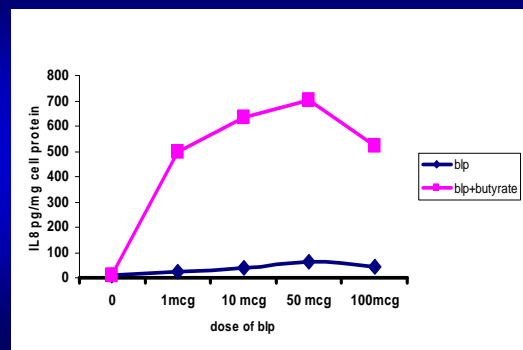
Signal integration



Short chain fatty acid modulation of signaling chemokine

1. Bacterial lipoproteins
2. IL-1

IL8 response to BLP + Butyrate in Caco2 cells

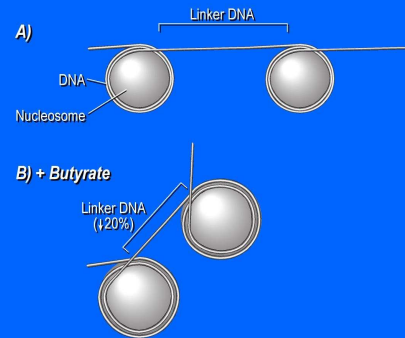


Hypothesis

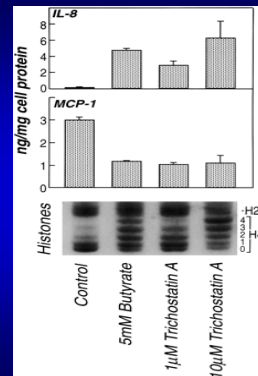
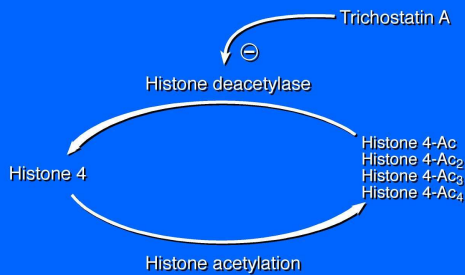
Butyrate up regulation of gene expression:
histone acetylation

Butyrate down regulation of gene expression:
transcription factor acetylation

DISRUPTION OF NUCLEOSOME-DNA PACKAGING BY HISTONE ACETYLATION



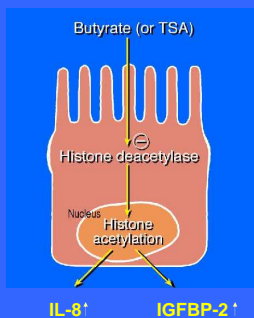
Trichostatin A Inhibits Histone Deacetylase



Butyrate and TSA increase histone acetylation and alter chemokine expression

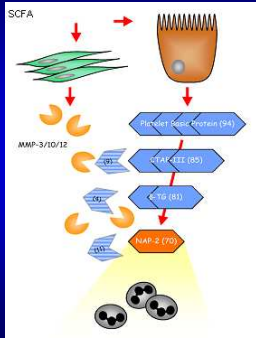
Fusunyan et al, 1999

Butyrate up-regulates through histone acetylation



Stromal cells enhance epithelial cell chemokines

Two sites for SCFA action

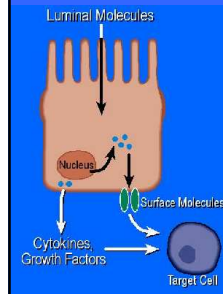


Conclusions

Diet plays a critical role in the developing intestine in health and disease

Luminal molecules regulate gene expression by promoter and epigenetic pathways

Epithelial signaling can orchestrate the mucosal immune system in vivo



ACKNOWLEDGEMENTS

Bob Fusunyan
Demetra Stamm
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