Universitat de Barcelona

INSA UB

FACULTAT DE FARMÀCIA

Suplements de plasma animal en l'alleugeriment de malalties inflamatòries

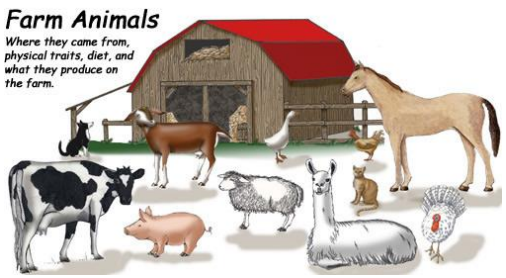
Anna Pérez-Bosque & Miquel Moretó

Grup de fisiologia digestiva i adaptacions nutricionals

Institut de Nutrició i Seguretat Alimentaria

28 d'octubre de 2014

Outline



Weaning and the consequences of stress

Animal blood plasma → Spray-drying →  SDP

SDP in a model of mild intestinal inflammation

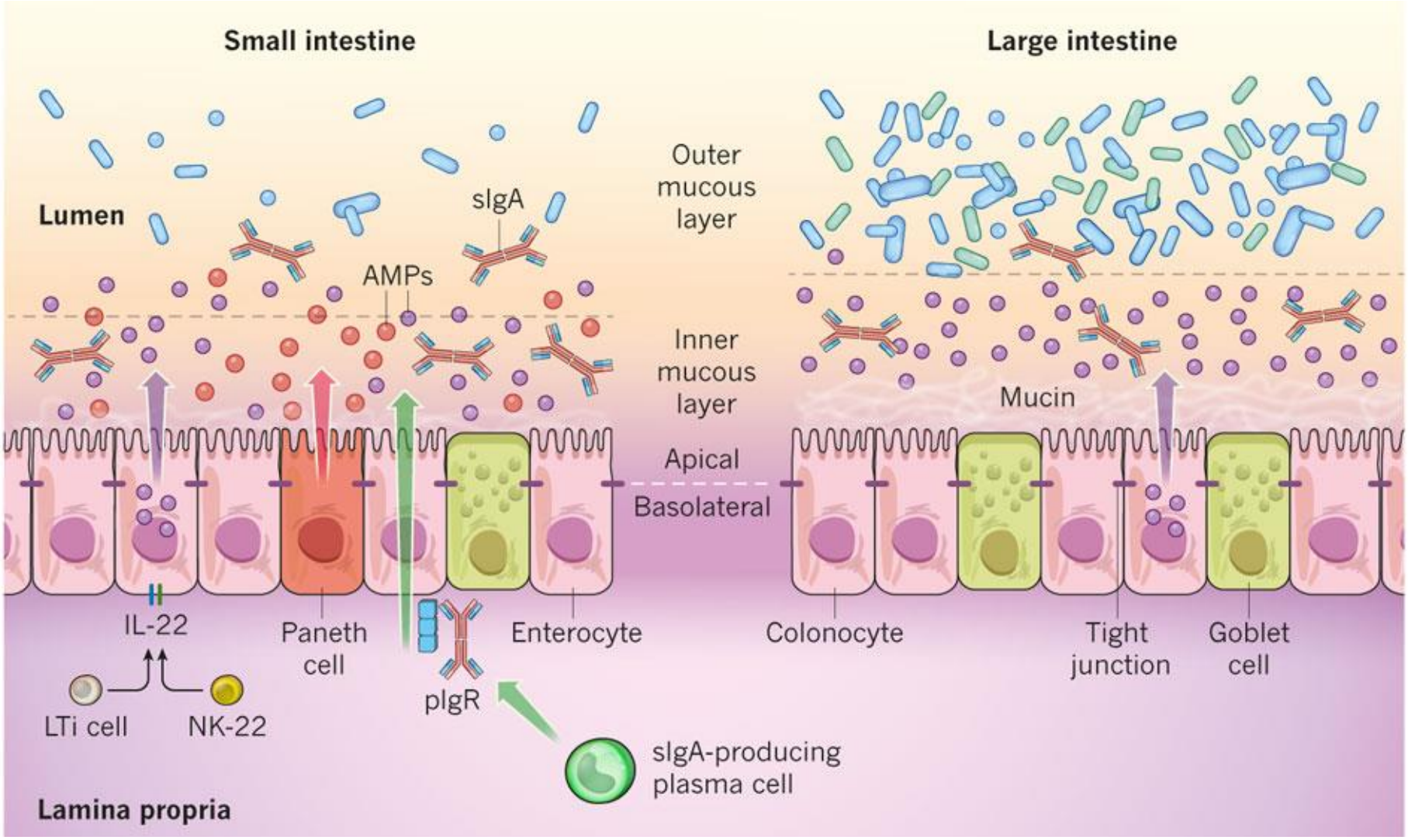
SDP in a model of acute lung inflammation

SDP in a model of colitis

The mechanism(s) of action of SDP

Background

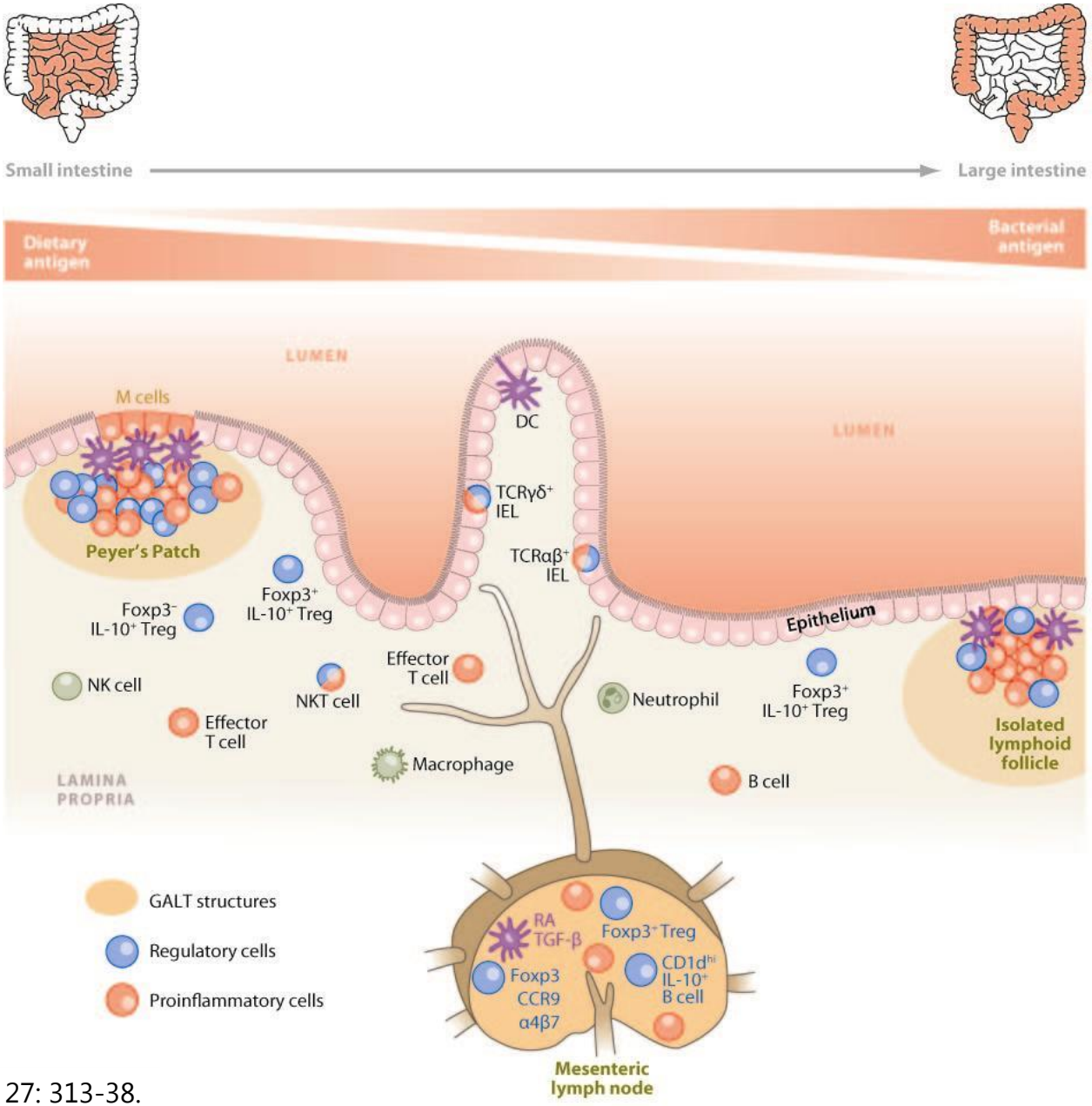
Intestinal mucosa



Craig et al (2012) Nature 489: 231-41.

Background

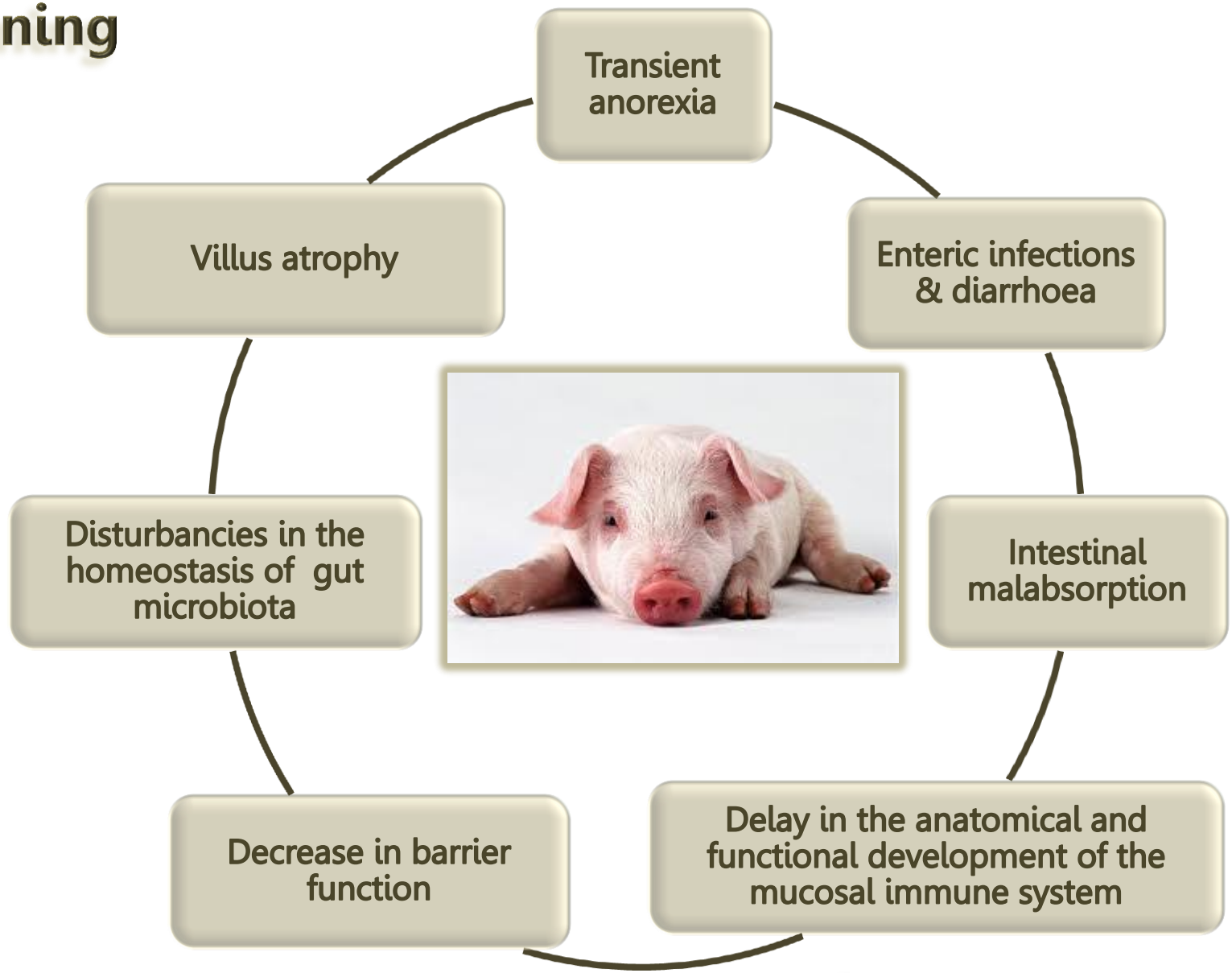
Gut associated lymphoid tissue



Izcue et al (2009) Annu Rev Immunol 27: 313-38.

Background

Weaning



Lallès et al (2009) Animal 3: 1625-42.

Background

SDP supplementation

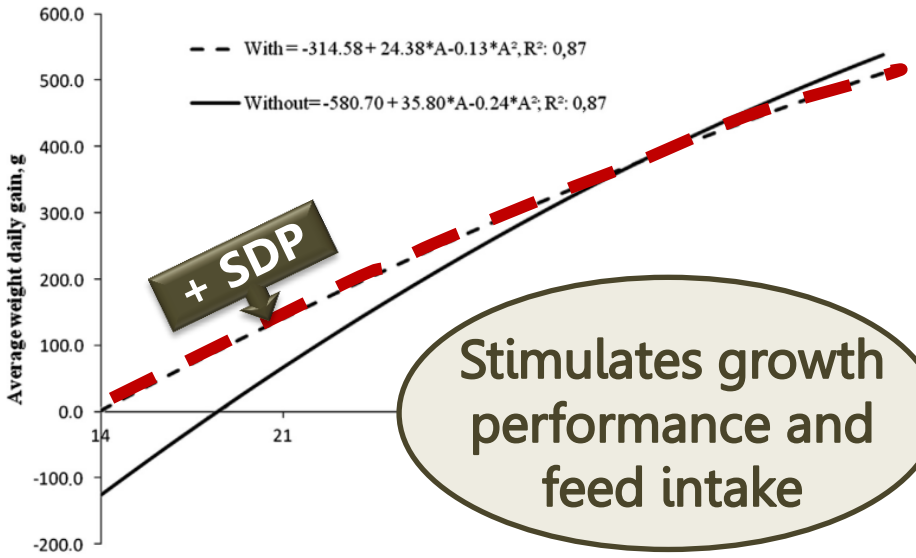
Animal blood plasma

Typical SDP composition

Nutrient	SDPP
Crude protein (%)	69.1 (lg 20.9)
Ash (%)	13.1
Fat (%)	1.9
Crude fibre (%)	–
Starch (%)	–
Moisture (%)	10.6
Phosphorus (%)	0.13
Calcium (%)	0.11
Sodium (%)	4.43
Potassium (%)	0.35
Magnesium (%)	0.03
Copper (mg/kg)	17
Iron (mg/kg)	101
Manganese (mg/kg)	5
Zinc (mg/kg)	9

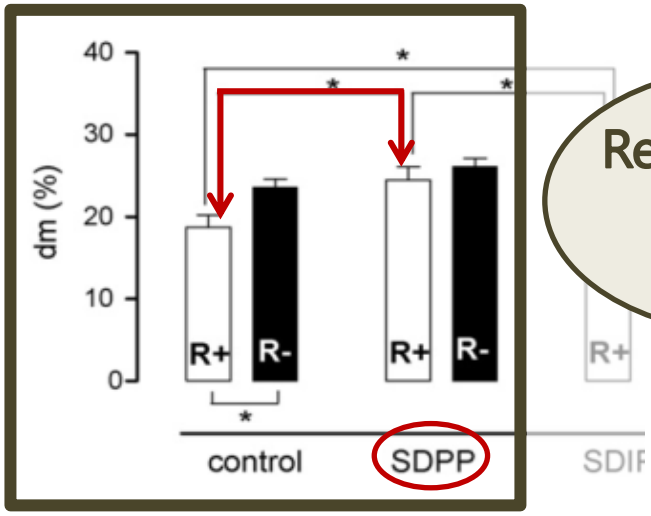
Van Dijk et al 2002, J Anim Sci 86:17-25

Piglets post-weaning



Stimulates growth performance and feed intake

Remus et al 2013, Livestock Sci 155: 294-300



Reduces post-weaning diarrhoea

Niewold et al 2007, Vet. Microbiol. 124: 3629

SEB model: EXPERIMENTAL DESIGN

Inflammatory agent: Entorotoxin B from *Staphyloccus aureus* (SEB)

C57/BL6 mice

Wistar-Lewis rats

SEB challenge
0.5 mg/kg (i.p.)

On diet (14 days)

24 h

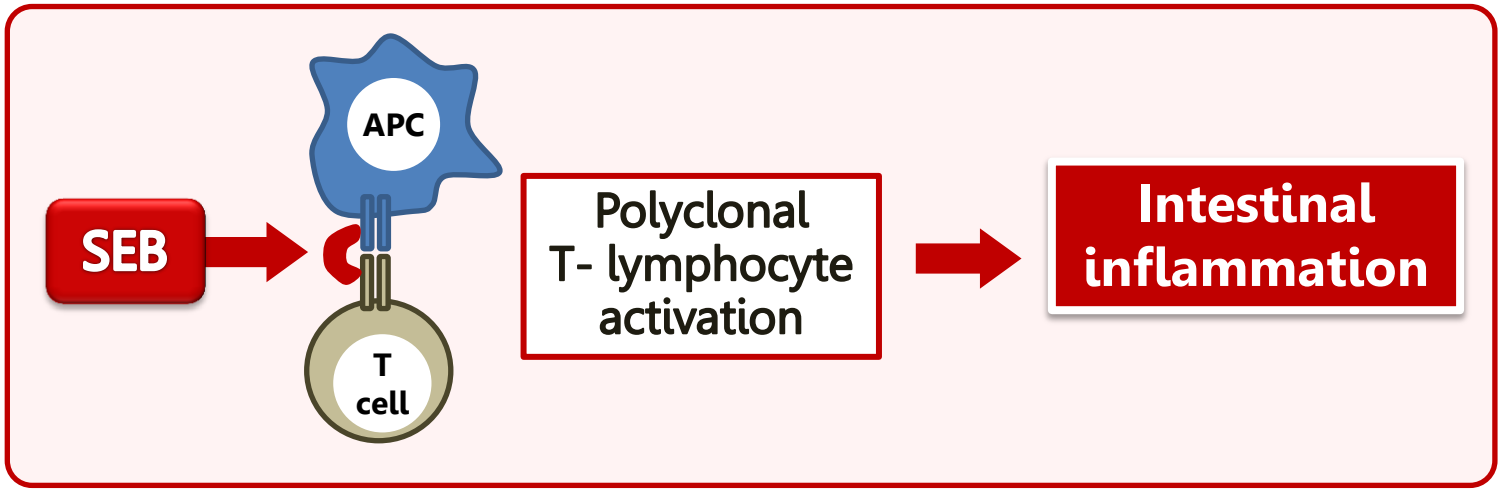
Weaning

CTL: Control diet
SEB: Control diet + SEB
SEB-SDP: SDP* suppl. (8%) + SEB

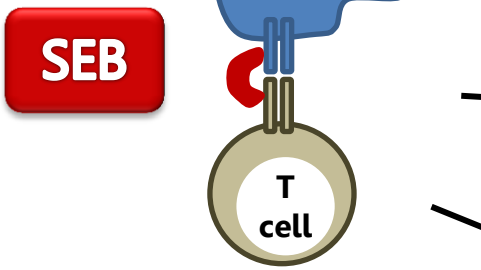
Sacrifice

Mice	(Day 19)	(Day 33)
Rats	(Day 21)	(Day 35)

*Supplied by APC An LGI Company



SEB model: SUMMARY



Luminal water contents

Epithelial permeability

- Flux of dextran and HRP and tight junction proteins

Mucosal defensins

- Cryptdin 4 and β-defensin 1 expression

Organized GALT (PP, MLN)

- Recruitment of cytotoxic populations

Diffuse GALT (LPL, IEL)

- Recruitment of cytotoxic populations

Mucosal cytokines

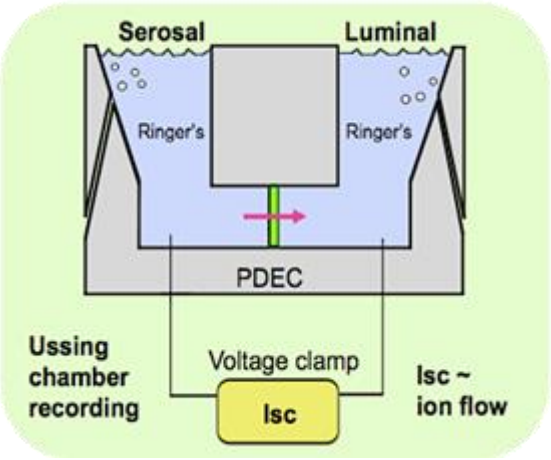
- Pro-inflammatory cytokine release

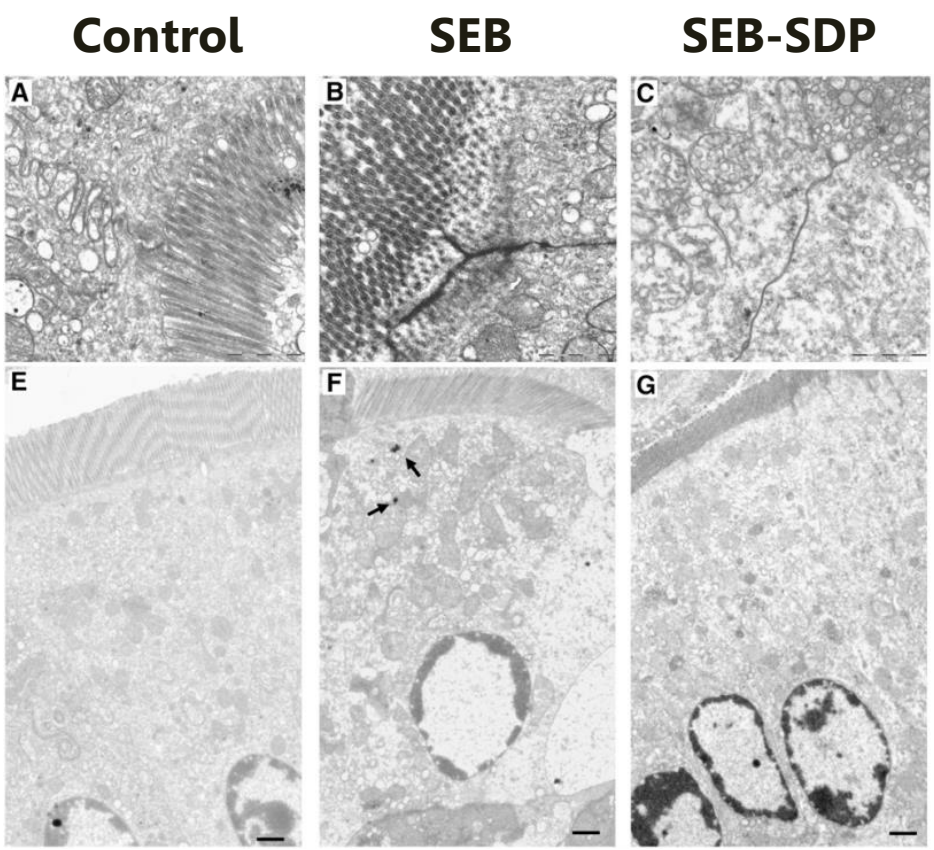
SEB model: RESULTS

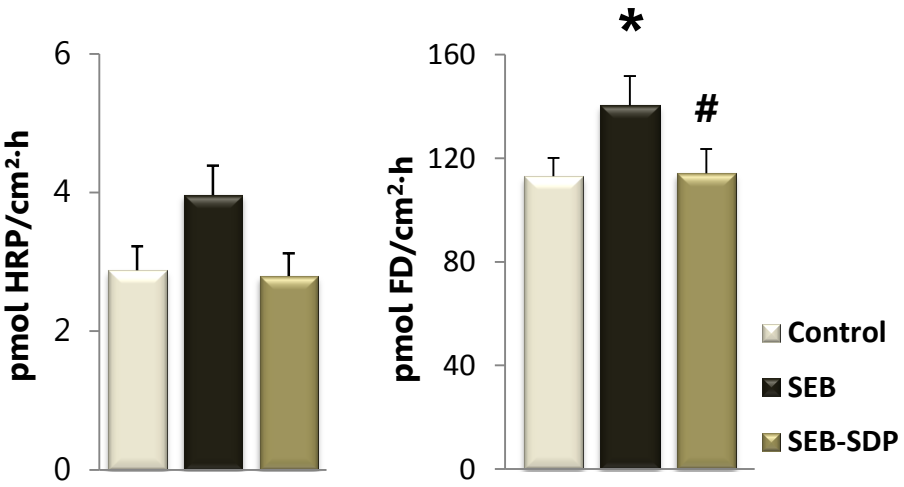
Intestinal permeability

Spray-Dried Animal Plasma Prevents the Effects of *Staphylococcus aureus* Enterotoxin B on Intestinal Barrier Function in Weaned Rats[1]

Anna Pérez-Bosque,[2] Concepció Amat,[2] Javier Polo,[3] Joy M. Campbell,[4] Joe Crenshaw,[4] Louis Russell,[4] and Miquel Moretó[2]*



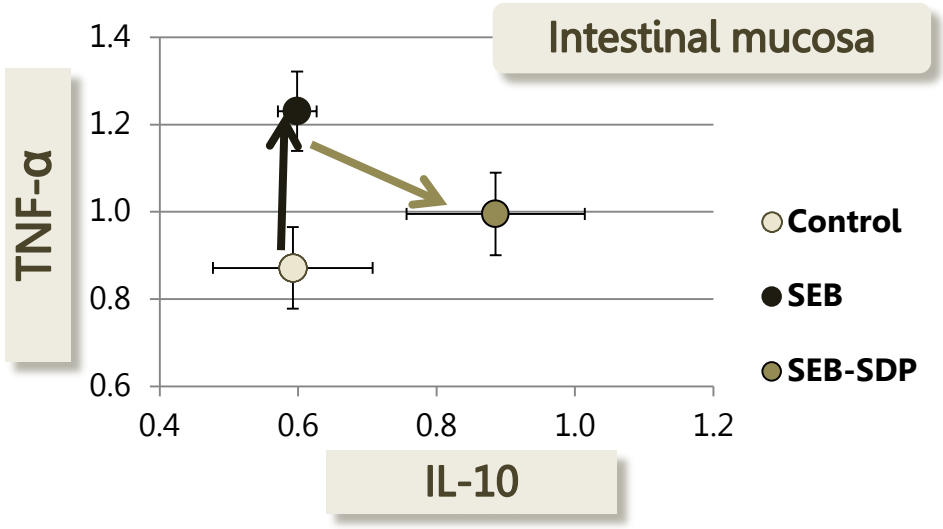




Pérez-Bosque et al (2006) J Nutr 136:2838-43

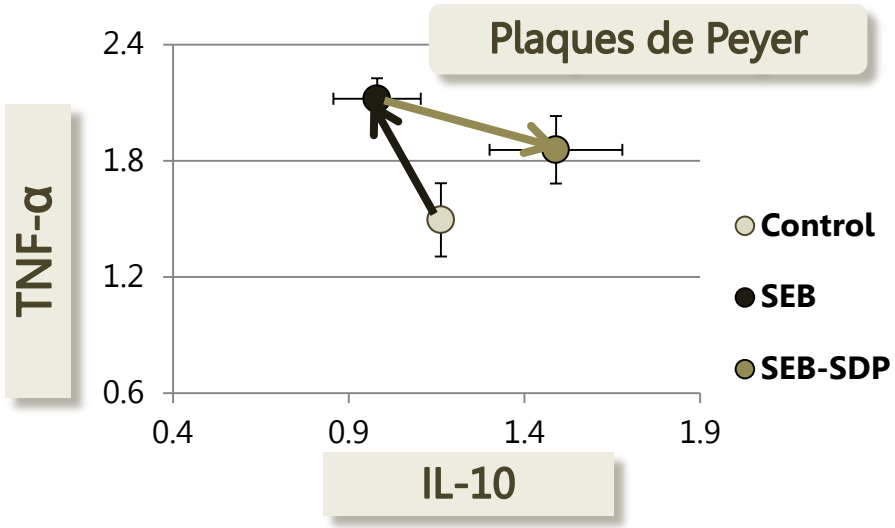
SEB model: RESULTS

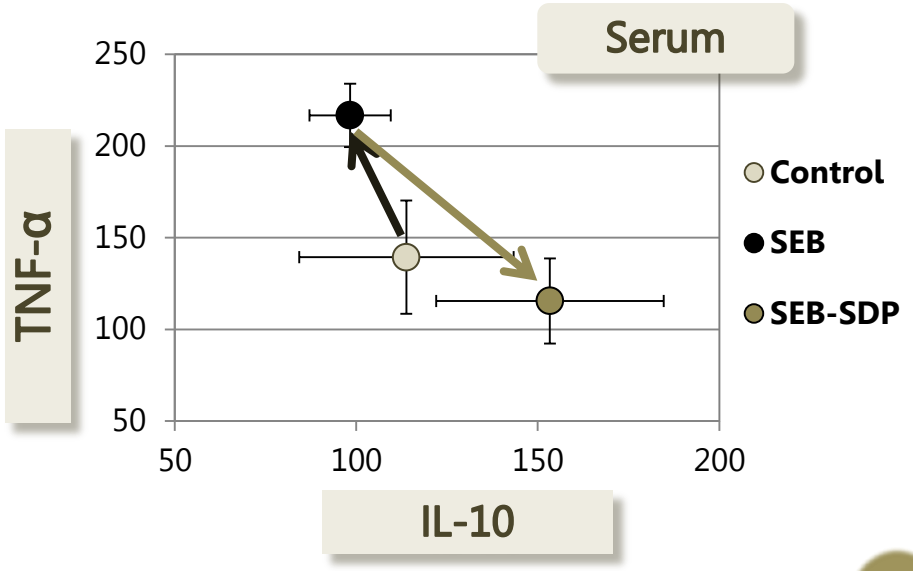
Cytokines



Effects of SEB

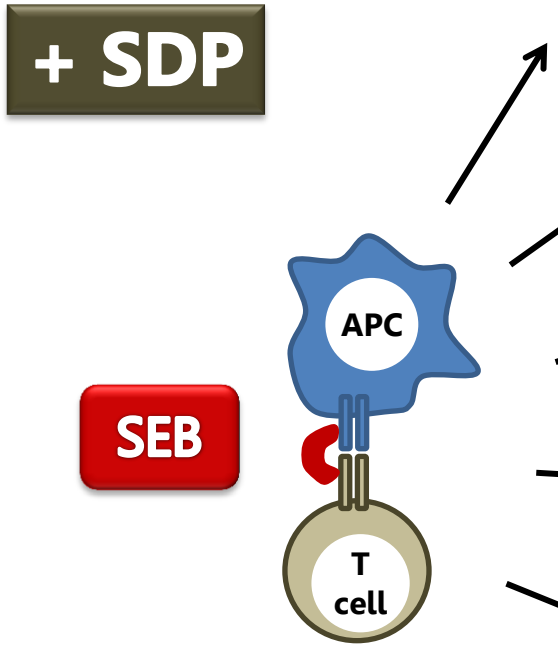
SEB + SDP supplementation





Pérez-Bosque & Moretó (2010) Proc Nutr Soc 69: 447-53.

SEB model: SUMMARY



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Organized GALT (PP, MLN)

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Diffuse GALT (LPL, IEL)

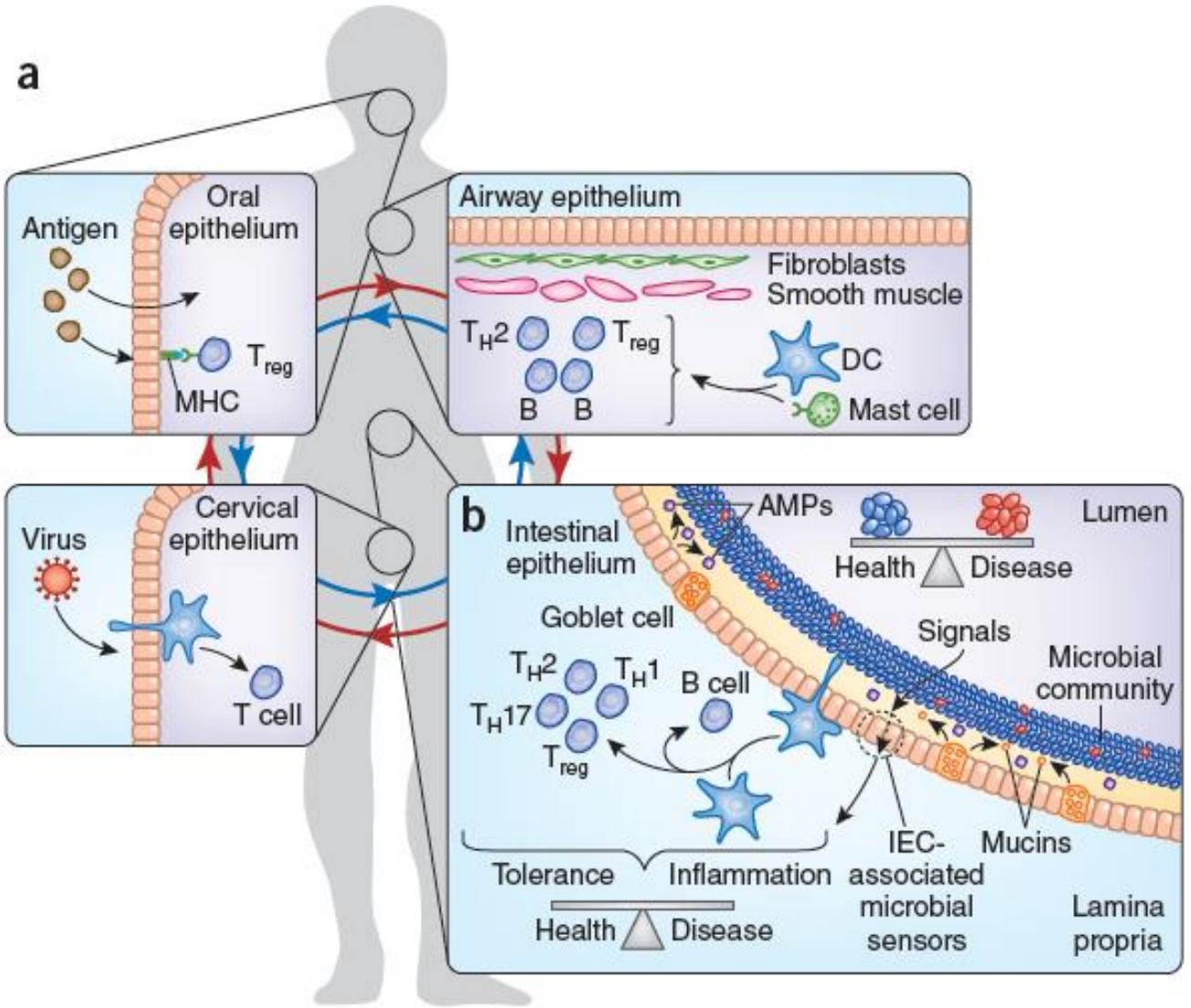
- Recruitment of cytotoxic populations

Mucosal cytokines

- Pro-inflammatory cytokine release

Plasma proteins can modulate the degree of GALT activation, restoring the barrier functions of the intestinal mucosa

Mucosal interconnection

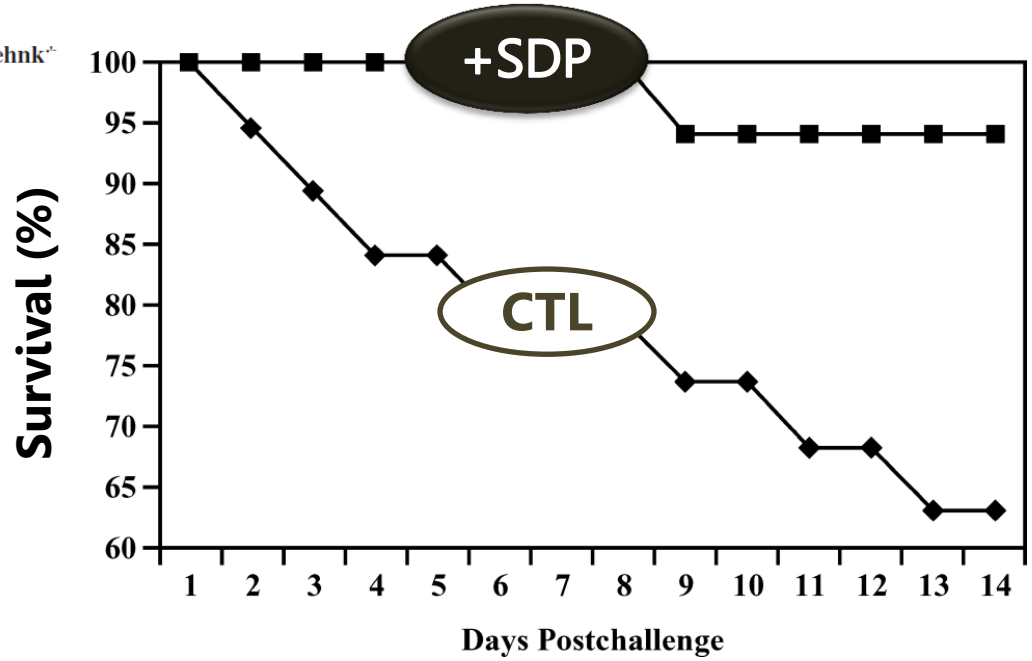


Gill et al (2010) Nat Immunol 11: 558-60.

Mucosal interconnection

Efficacy of Spray-Dried Bovine Serum on Health and Performance of Turkeys Challenged with *Pasteurella multocida*

J. M. Campbell,*[,1] J. D. Quigley, III,* L. E. Russell,* and L. D. Koehnk*



Oral SDP supplements:

- Increase performance of poults the first week after placement.
- Reduced mortality in turkeys exposed to *P. multocida.*

Campbell et al (2004) J Appl Poult Res 13:388–93.

LPS model: EXPERIMENTAL DESIGN

Inflammatory agent: Lipopolysaccharide from *E. coli*

C57BL/6 mice

LPS challenge
12.5 µg i.n. (day 33)

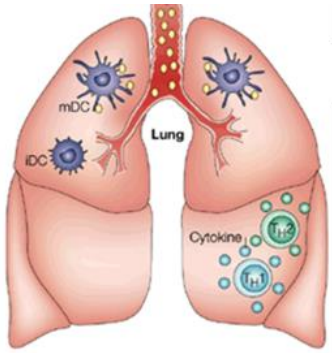
ON DIET (14 days)

Weaning
(day 19)

CTL: Control diet
LPS: Control diet + LPS
LPS-SDP: SDP* suppl. (8%) + LPS

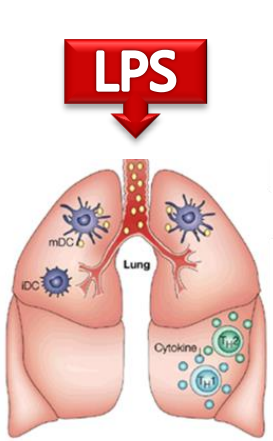
Sacrifice
(6 h / 24 h after the challenge)

*Supplied by APC An LGI Company



- Brochoalveolar lavage fluid (BALF)
- Lung tissue
- Blood

Colitis model: SUMMARY



Innate immunity

- Activated monocytes and neutrophiles, pro-inflammatory cytokines & chemokines.

Adaptive immunity

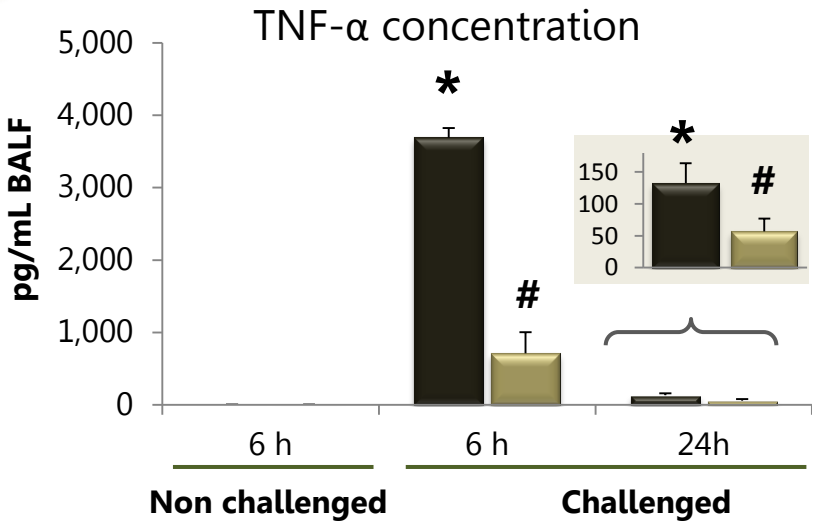
- Activated Th lymphocytes, pro-inflammatory cytokines.

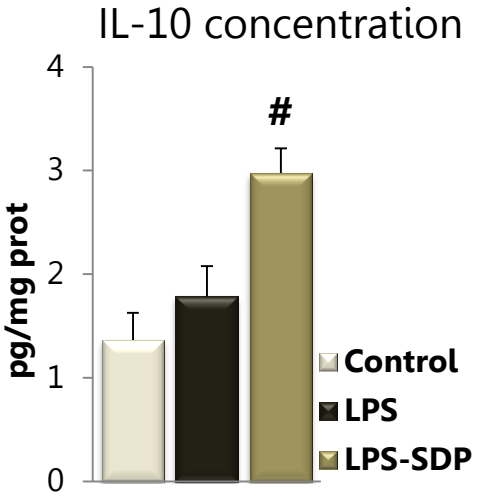
Regulatory immunity

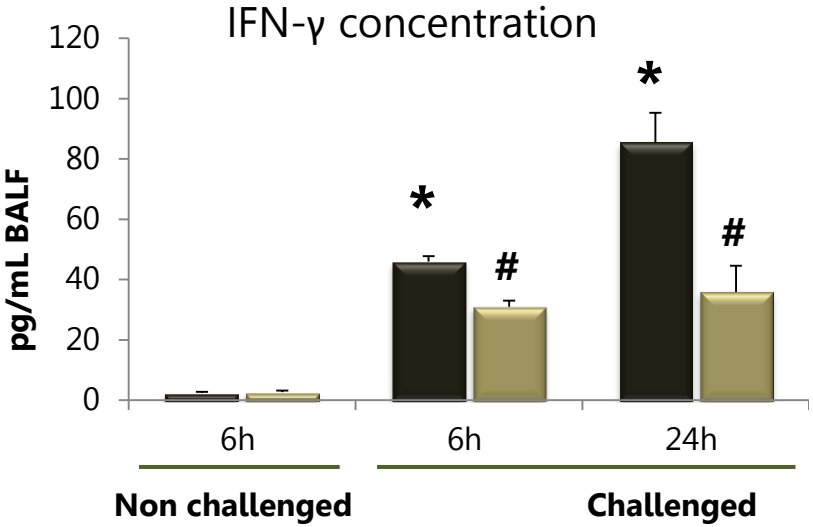
- Treg lymphocytes, anti-inflammatory cytokines.

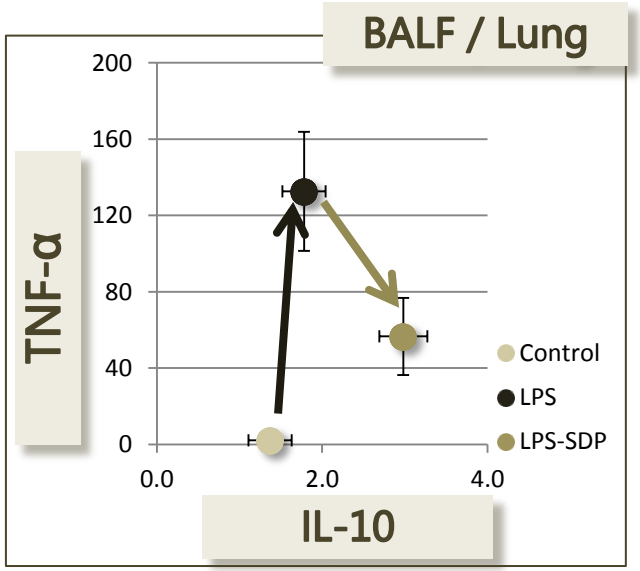
LPS model: RESULTS

Cytokines







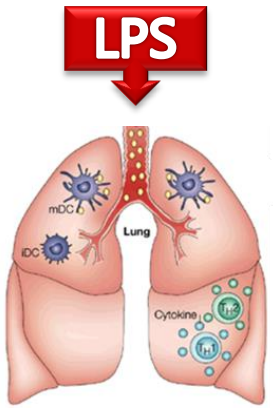


Maijó et al (2012) Br J Nutr 107:867-75

Maijó et al (2012) J Nutr 142:264-70

Colitis model: SUMMARY

+ SDP



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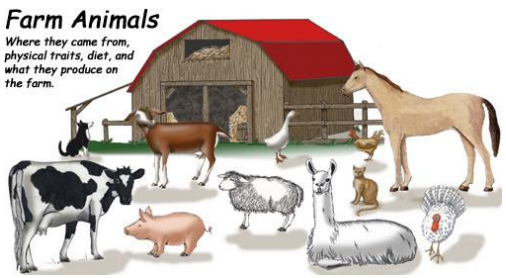
Regulatory immunity

- Treg lymphocytes, anti-inflammatory cytokines.

Dietary plasma proteins reduce the immune response that characterizes the acute lung inflammation syndrome

Outline



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SDP in a model of acute lung inflammation

SDP in a model of colitis

The mechanism(s) of action of SDP

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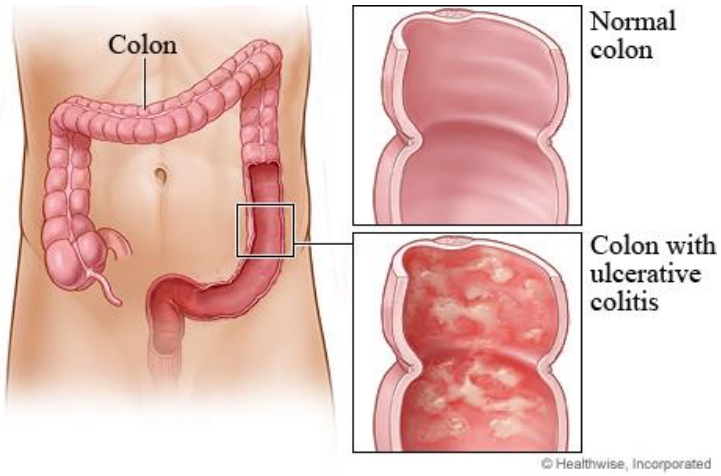
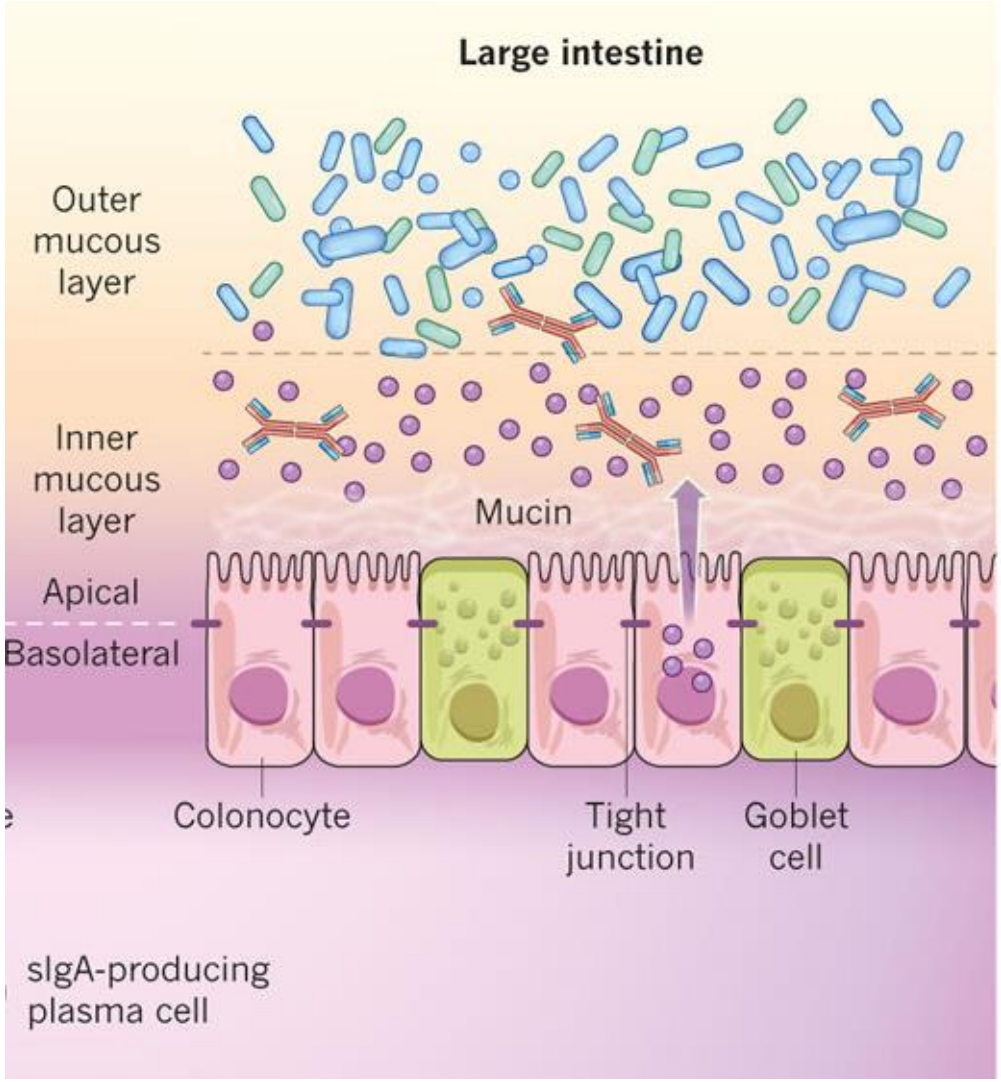
Colon mucosa

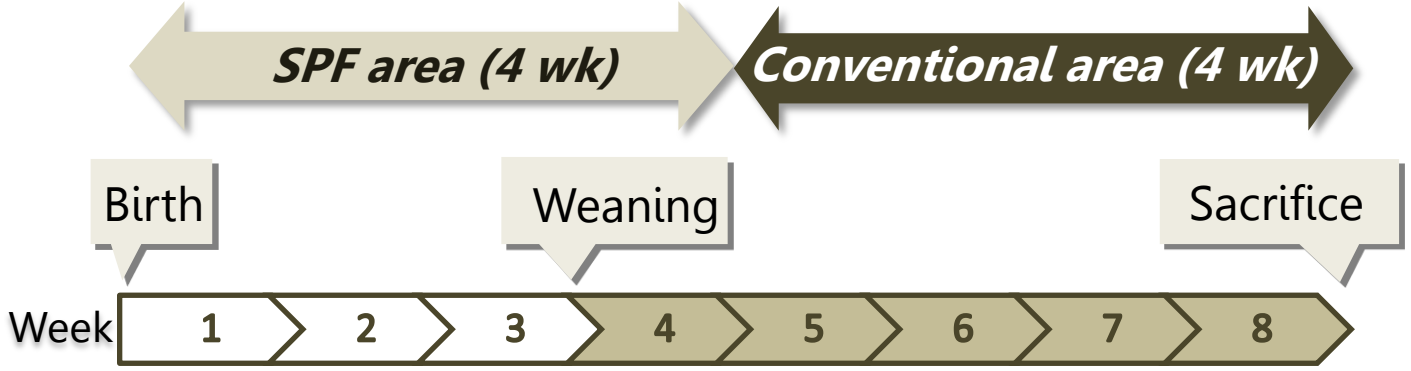




Craig et al (2012) Nature 489: 231-41.

Colitis model: EXPERIMENTAL DESIGN

mdr1a -/- **mouse**

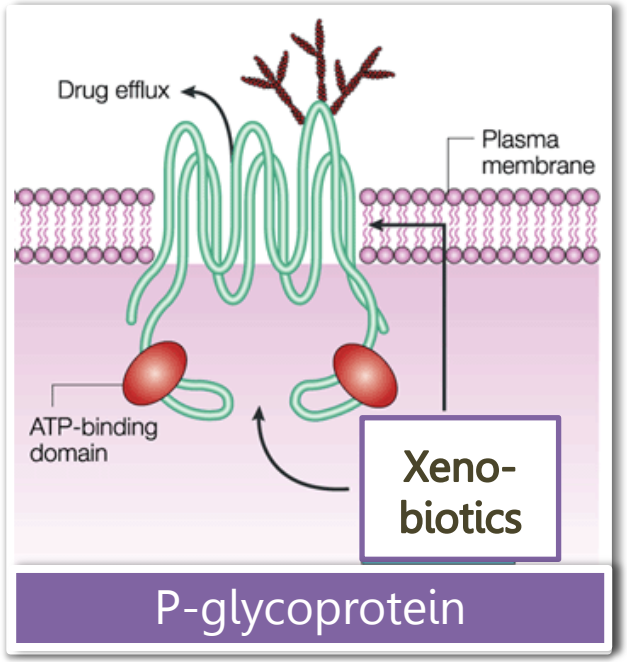


On diet (5 wk)

- **WT-CTL**: Control diet
- **KO-CTL**: Control diet
- **KO-SDP**: SDP suppl. diet (8%)*

*Supplied by APC An LGI Company

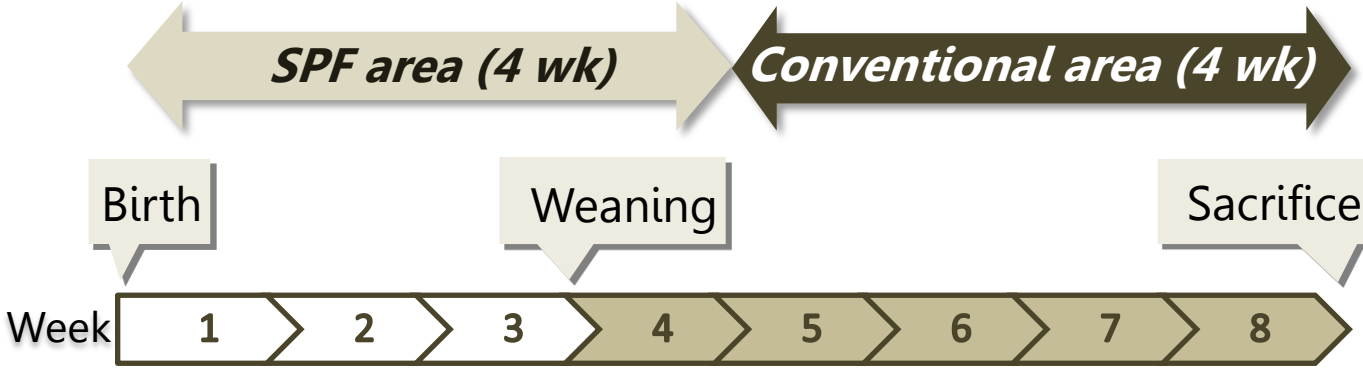
The model



- P-glycoprotein is expressed in the apical membrane of enterocytes.
- It pumps xenobiotics back into the intestinal lumen.
- In the absence of P-glycoprotein, bacterial products and toxins can cause damage to the intestinal barrier and subsequently initiating the inflammatory process.

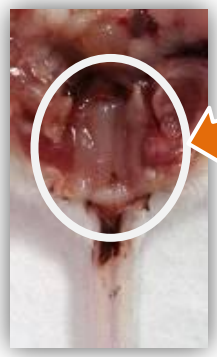
Colitis model: EXPERIMENTAL DESIGN

mdr1a -/- **mouse**

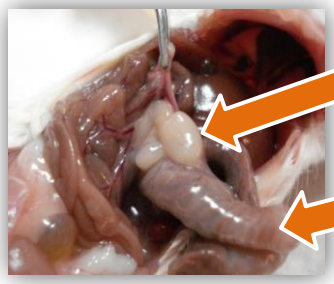


The model

Bloody rectal discharge



Rectum ulcers



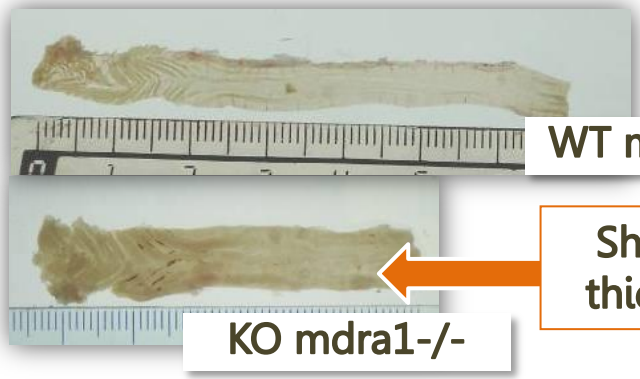
MLN hyperplasia

Colon distension

On diet (5 wk)

- **WT-CTL**: Control diet
- **KO-CTL**: Control diet
- **KO-SDP**: SDP suppl. diet (8%)*

*Supplied by APC An LGI Company



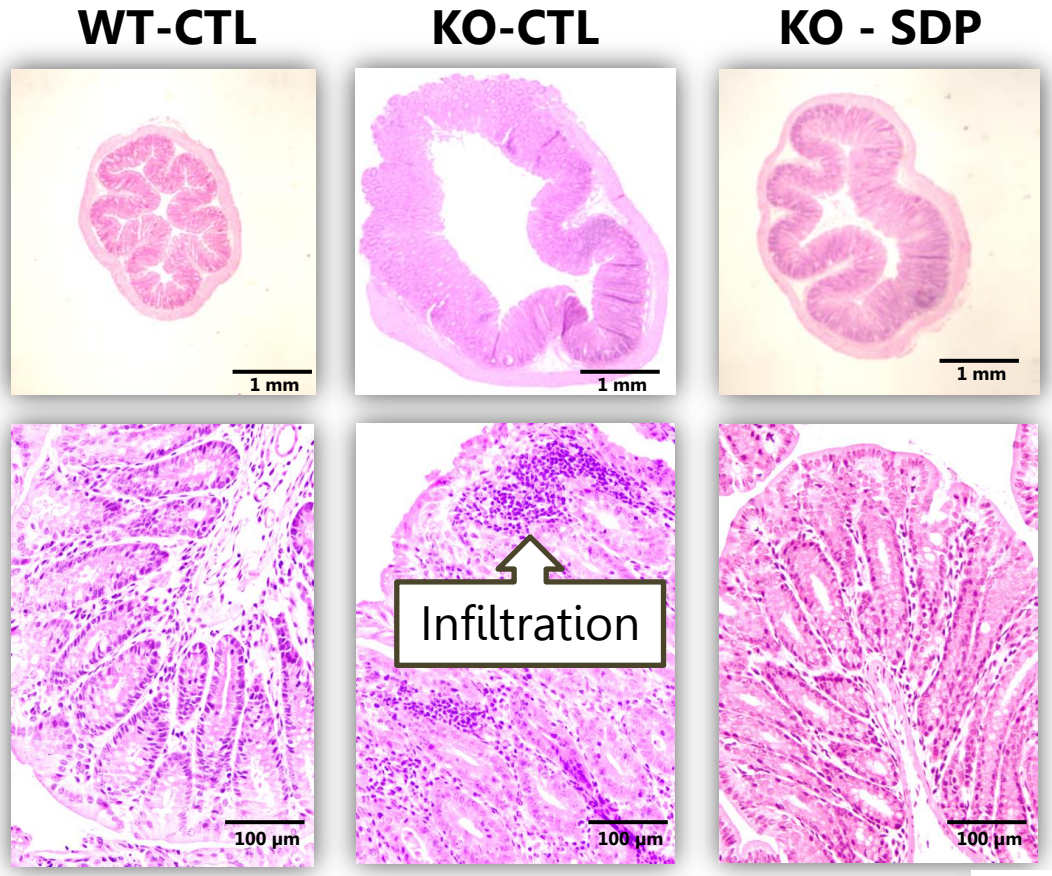
Shorter and thicker colon

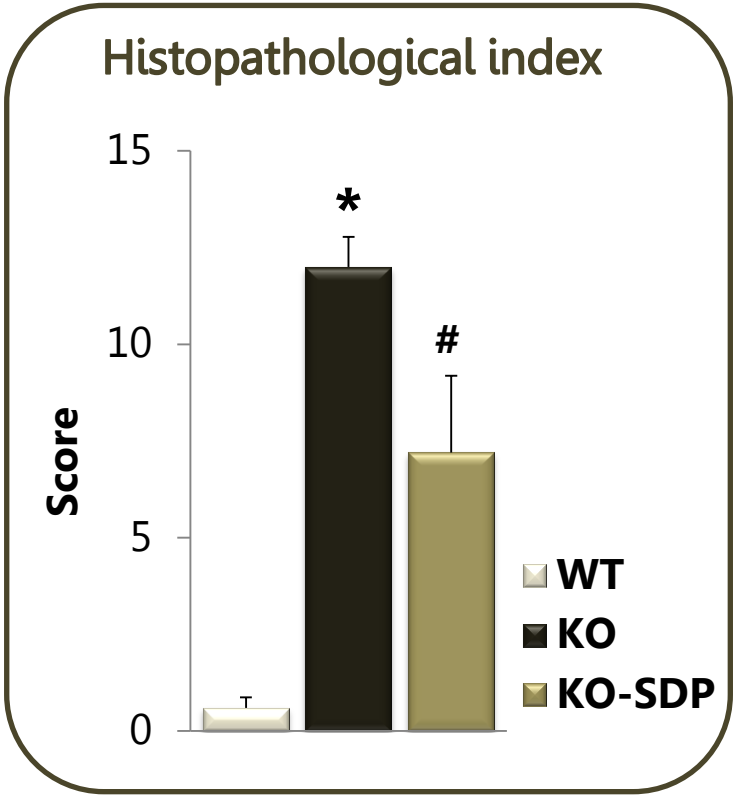
Colitis model: RESULTS

Histopathological index

Variables considered

- *Lamina propria cell* infiltration
- Transmural cell infiltration
- Cryptitis
- Mucosal ulceration
- Crypt abscess formation
- Goblet cell depletion



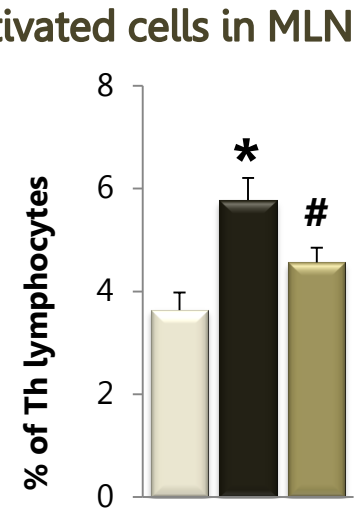


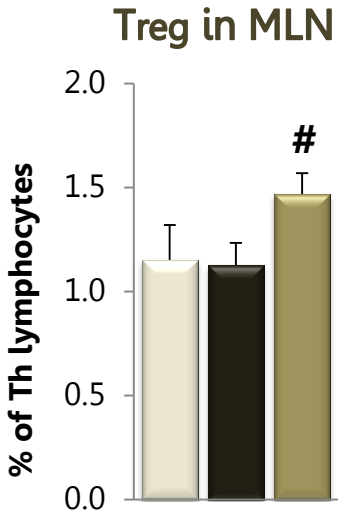
Pérez-Bosque et al (2010) Proc Nutr Soc 69:E262.

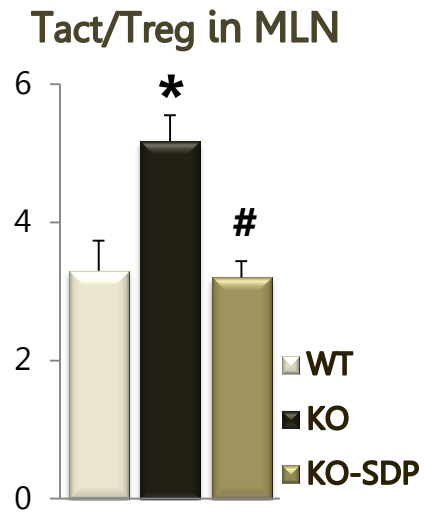
Colitis model: RESULTS

Cell populations

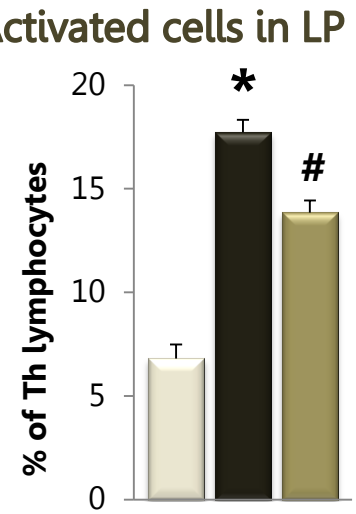
ORGANIZED GALT

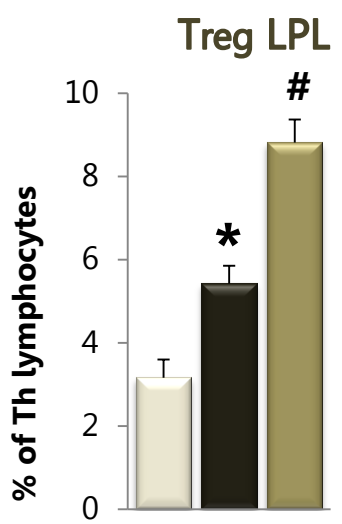


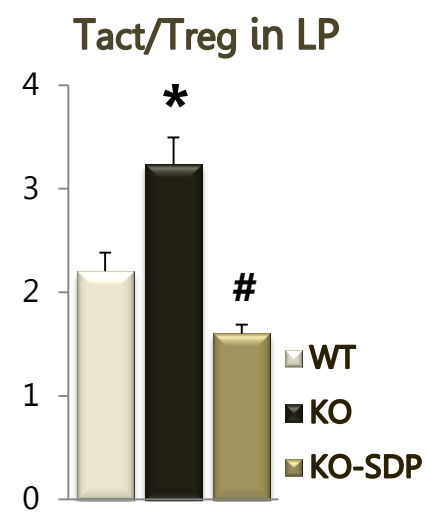




DIFFUSE GALT





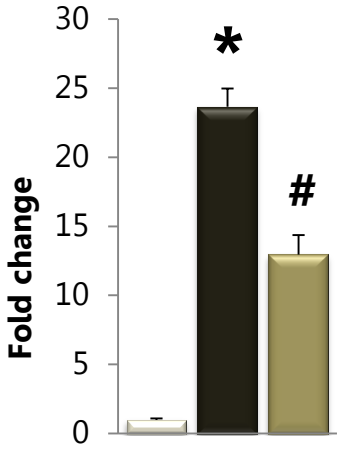


Moretó et al 2010 Dig Dis Week Meeting, New Orleans, LA.

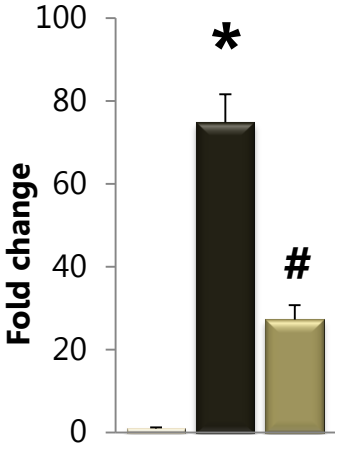
Colitis model: RESULTS

Cytokines

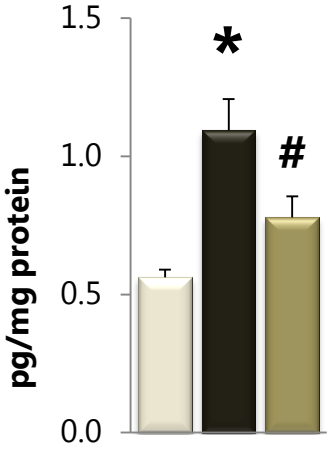
TNF-α expression



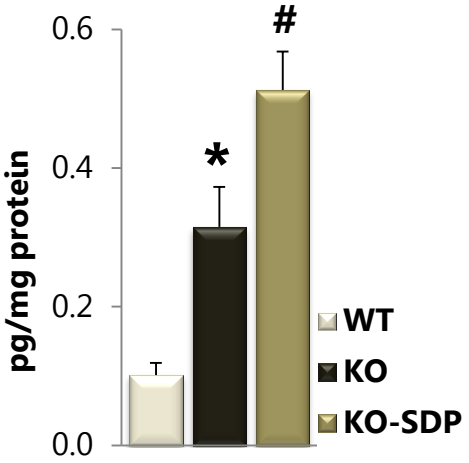
IFN-γ expression



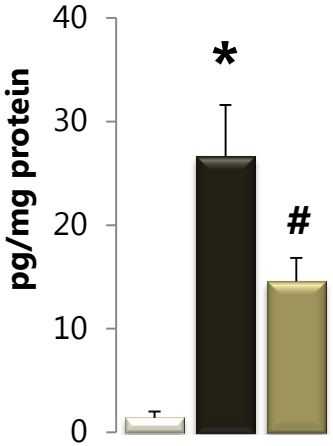
IL-2 in colon



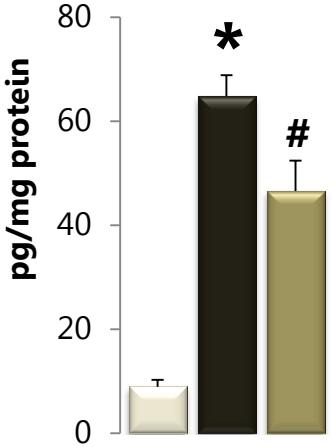
IL-10 concentration



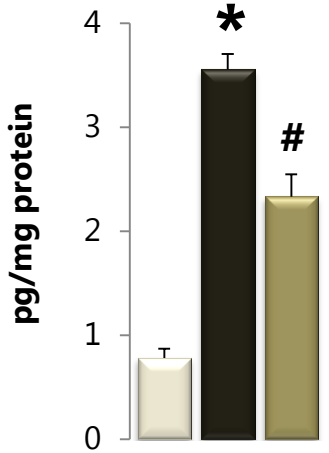
IL-17 in colon

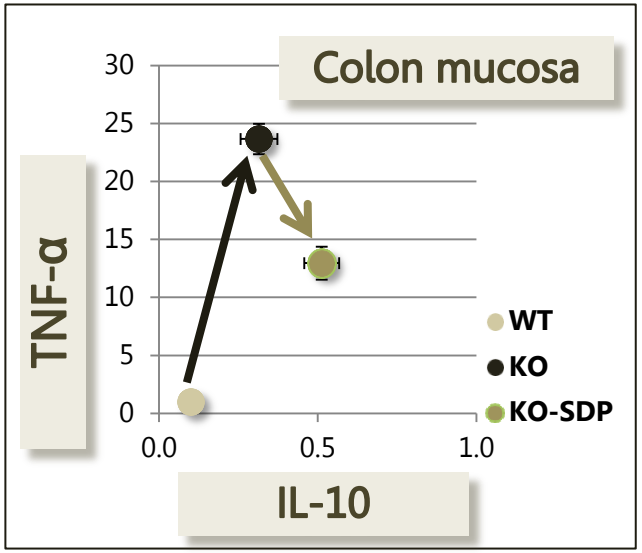


MCP-1 in colon



MIP-1b in colon

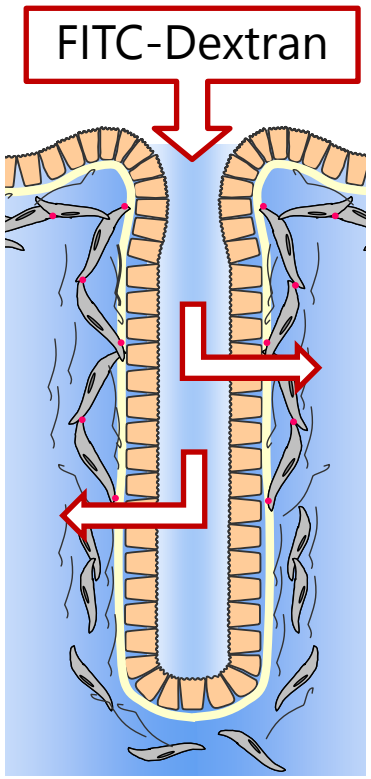


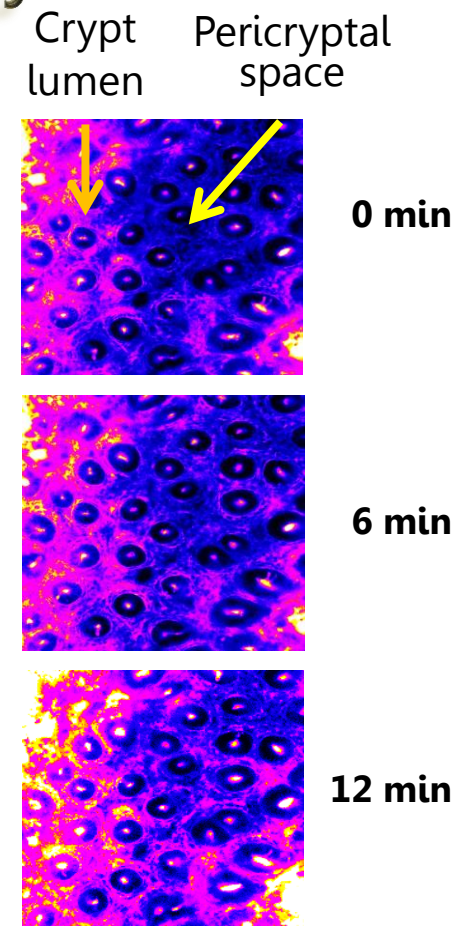


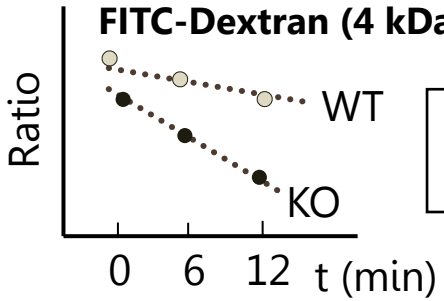
Moretó et al 2010 Dig Dis Week Meeting, New Orleans, LA.

Colitis model: RESULTS

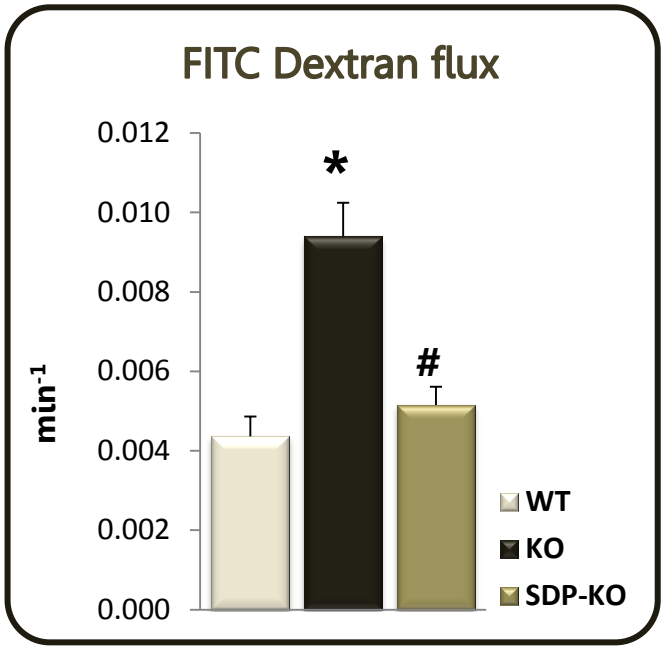
Crypt permeability

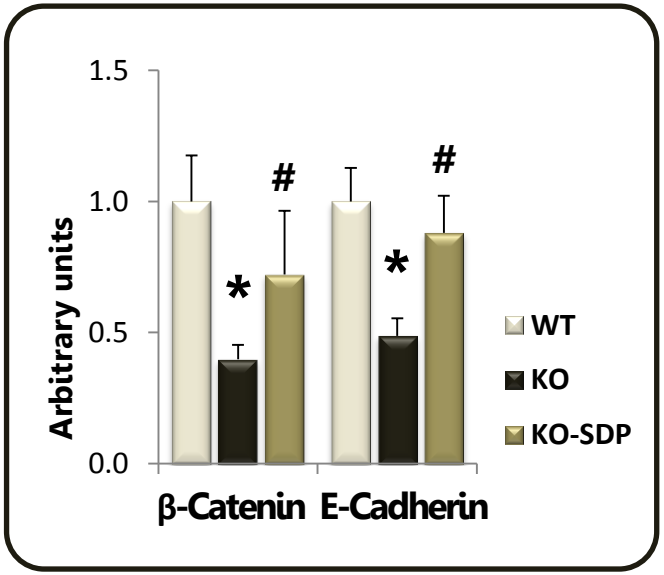






Slope = Permeability index (min^{-1})

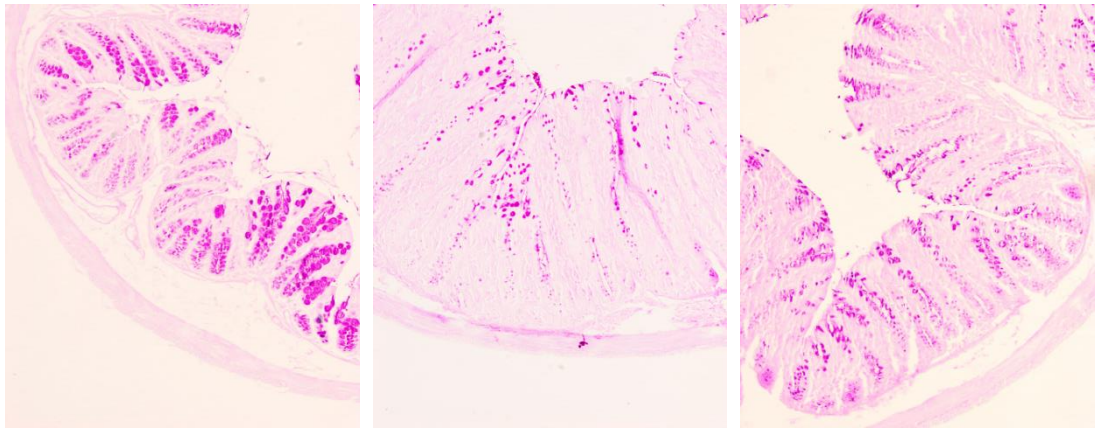


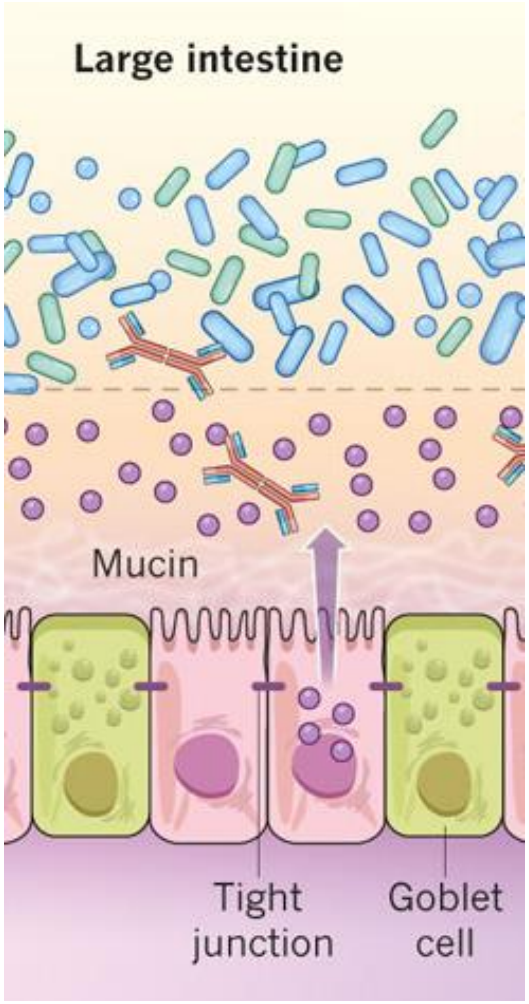


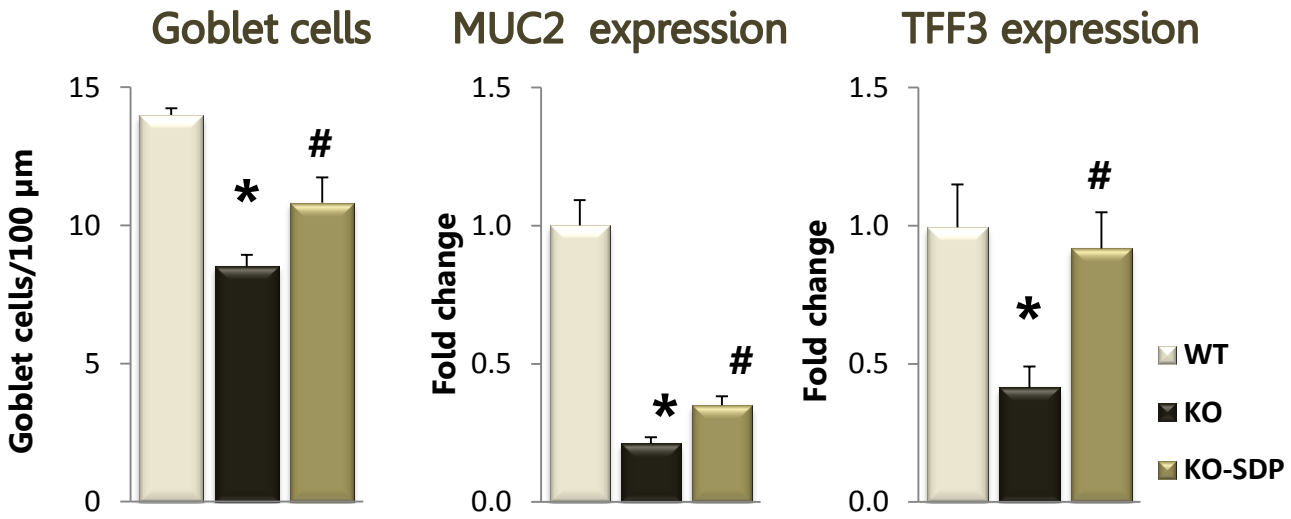
Moretó et al (2009) Dig Dis Week Meeting, Chicago, IL.

Colitis model: RESULTS

Mucin expression







Moretó et al (2013) IUPS Meeting, Birmingham, UK.

Colitis model: SUMMARY

Histopathological index

Organized GALT (MLN)
- Recruitment of cytotoxic populations

Diffuse GALT (LPL, IEL)
- Recruitment of cytotoxic populations

Mucosal cytokines
- Pro-inflammatory cytokine release

Apical junctional complex
- Expression of β-catenin and E-cadherin

Epithelial crypt permeability
- Flux of dextran

Mucosal mucins
- Expression of MUC2 & TFF3

Colitis model: SUMMARY

+ SDP

mdr1a -/- **mouse**

Histopathological index

Organized GALT (MLN)
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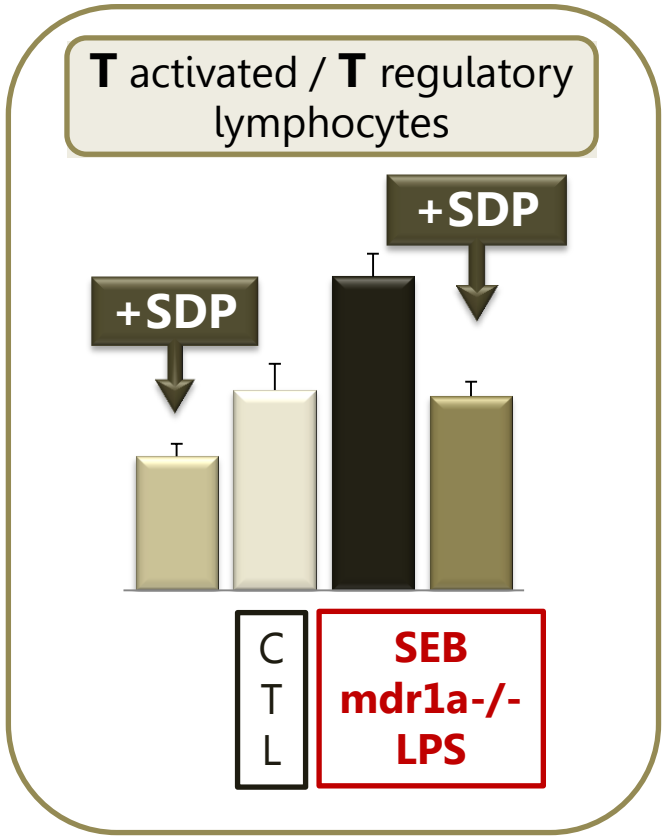
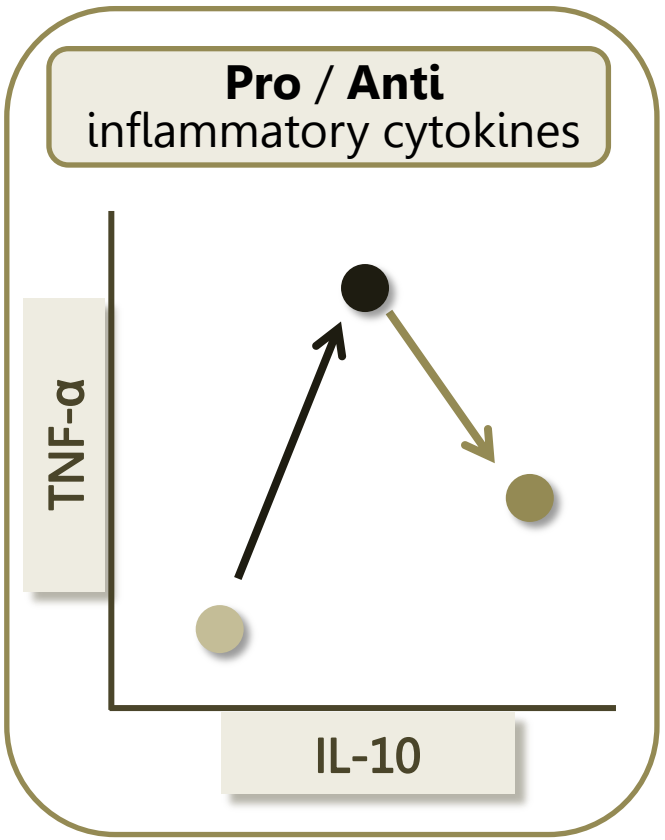
Mucosal mucins
- Expression of MUC2 & TFF3

Plasma proteins can modulate the degree of GALT activation, restoring the barrier functions of the colonic epithelium

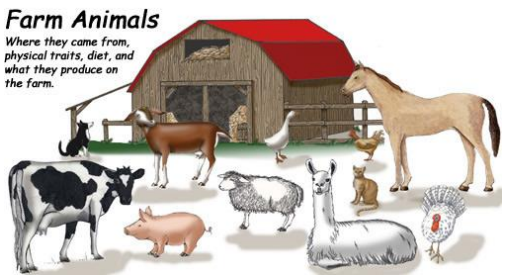
Take home message





In animal models of inflammatory diseases, dietary supplementation with animal Spray Dried Plasma, by mechanisms involving the luminal - mucosal crosstalk and the participation of GALT and CMIS, can induced changes in physiological variables that can alleviate disease.

Outline



Weaning and the consequences of stress

Animal blood plasma → Spray-drying →  SDP

SDP in a model of mild intestinal inflammation

SDP in a model of acute lung inflammation

SDP in a model of colitis

The mechanism(s) of action of SDP

Mecanism of action