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Diverticular Disease: Looking beyond fiber

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- “The last speaker of a long afternoon program should not expect a great response, again because folks are too worn out.
- Keep your presentation short and crisp **and acknowledge the lateness so that the audience knows you care about them**”.

And the advantage of being the last speaker is….

- Everyone introduced the topic already!

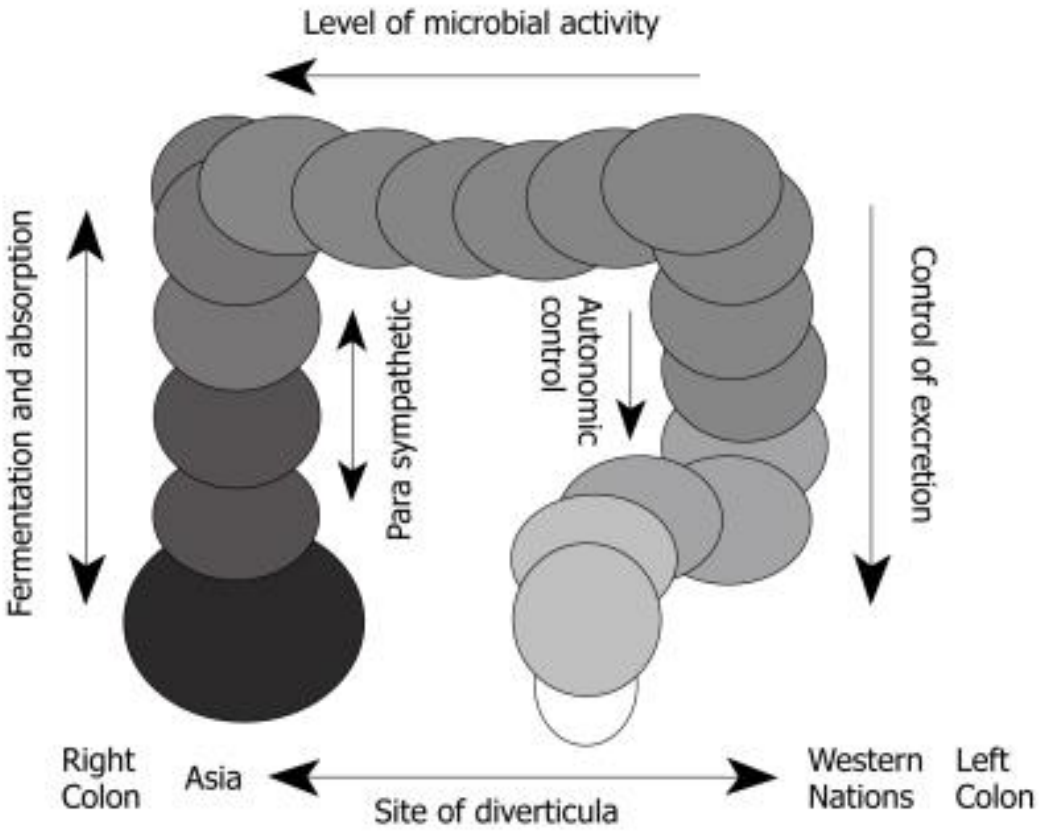
Epidemiology

- Common GI condition in the Western world
  - highest rates in the United States and Europe
  - “left sided” (descending and sigmoid colon)

- Asian Countries and Africa
  - “Right sided” (cecum and ascending colon)
  - Less common

At the functional level

- Cecum and ascending colon :primary sites of bacterial fermentation
  - Composition of the undigested material
  - Bacterial strains
- Descending colon serves primarily as a holding reservoir for fecal matter prior to excretion
  - Constipation (low fiber, dehydration)



World J Gastroenterol. 2009 May 28; 15(20): 2479–2488.

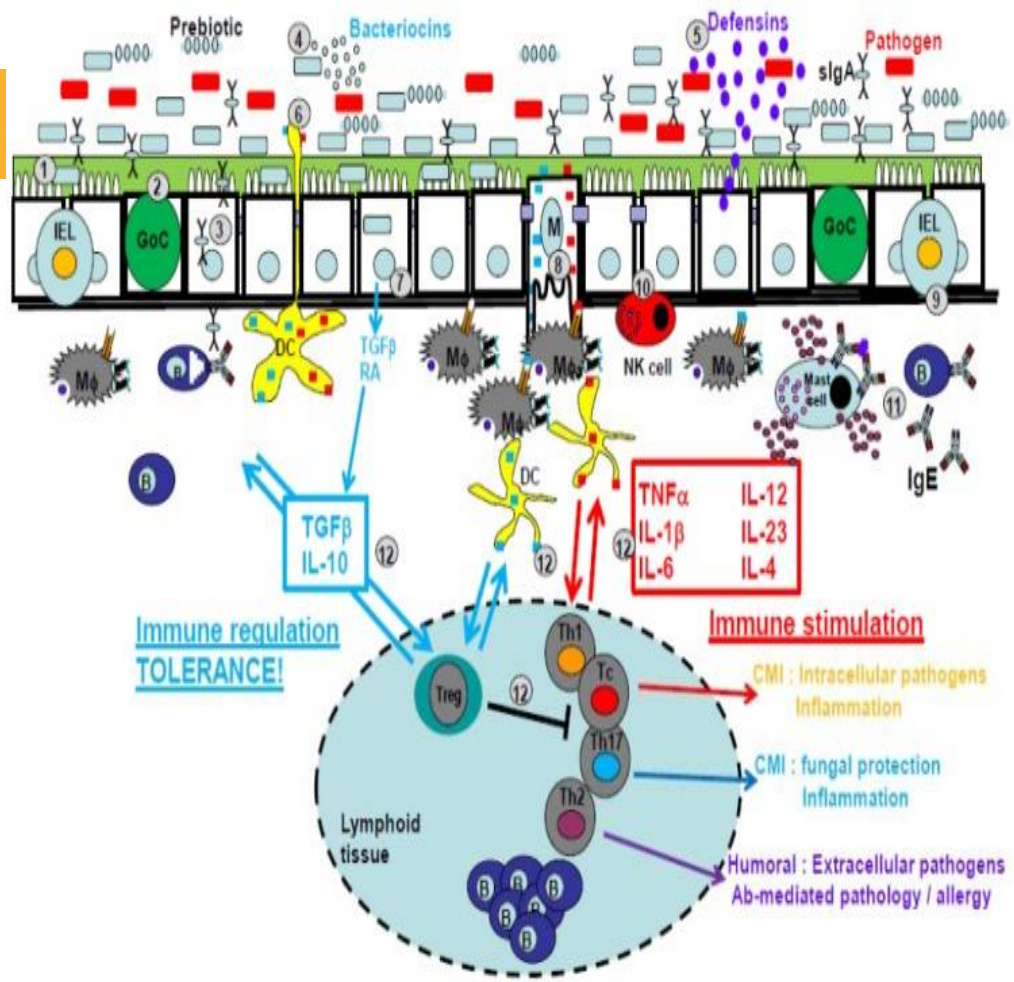
Inflammation in diverticular disease

- Low grade chronic inflammation is present in the colon in patients with diverticulosis without overt diverticulitis
- Chronic inflammation in diverticular disease is similar to that in inflammatory bowel disease (IBD)
  - Microbiota?
  - Vitamin D/VDR?
  - Dietary composition?
  - Omega 6/3 fats?

The role of bacterial flora

1. Modulation of immune function
2. Mucosal epithelial integrity
3. Anti-microbial agents: Bacterocin, microsin

4. ➔Variation in strains: environmental conditions, change in nutrient availability



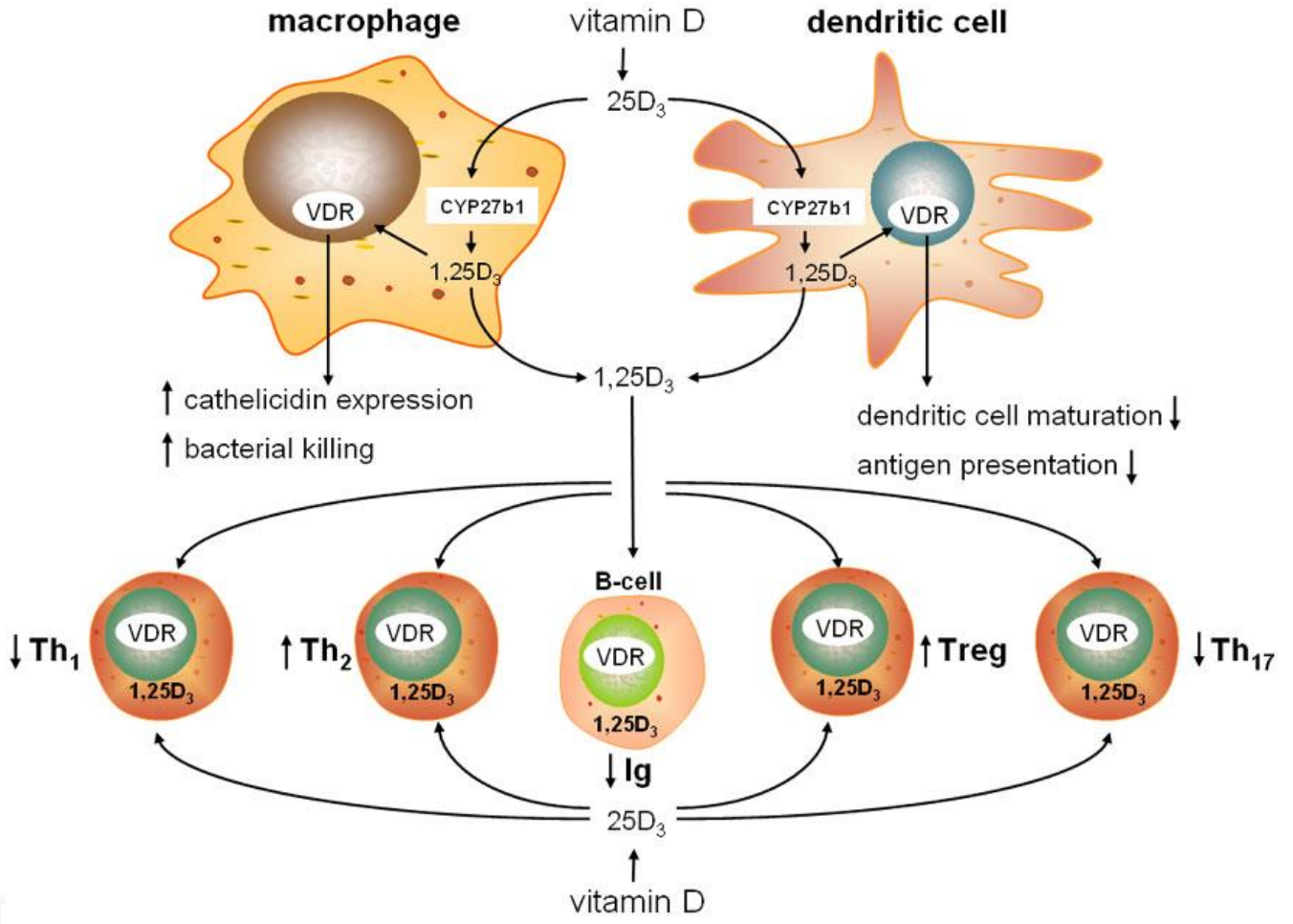
- Probiotics
- 1) compete with pathogenic bacteria for mucosal binding and for food.
- 2) Increase mucin production from goblet cells. Mucus contains IgA.
- 3) Produce anti-microbial peptides: bacteriocins
- 4) Stimulate epithelial cells to produce defensins
- 5) Produce Tranforming GFB (cytokine)and IL 10 to potentiate IgA
- 6) enforce tight junction
- 7) upregulate heat shock protein

Hardy et al., Nutrients. 2013

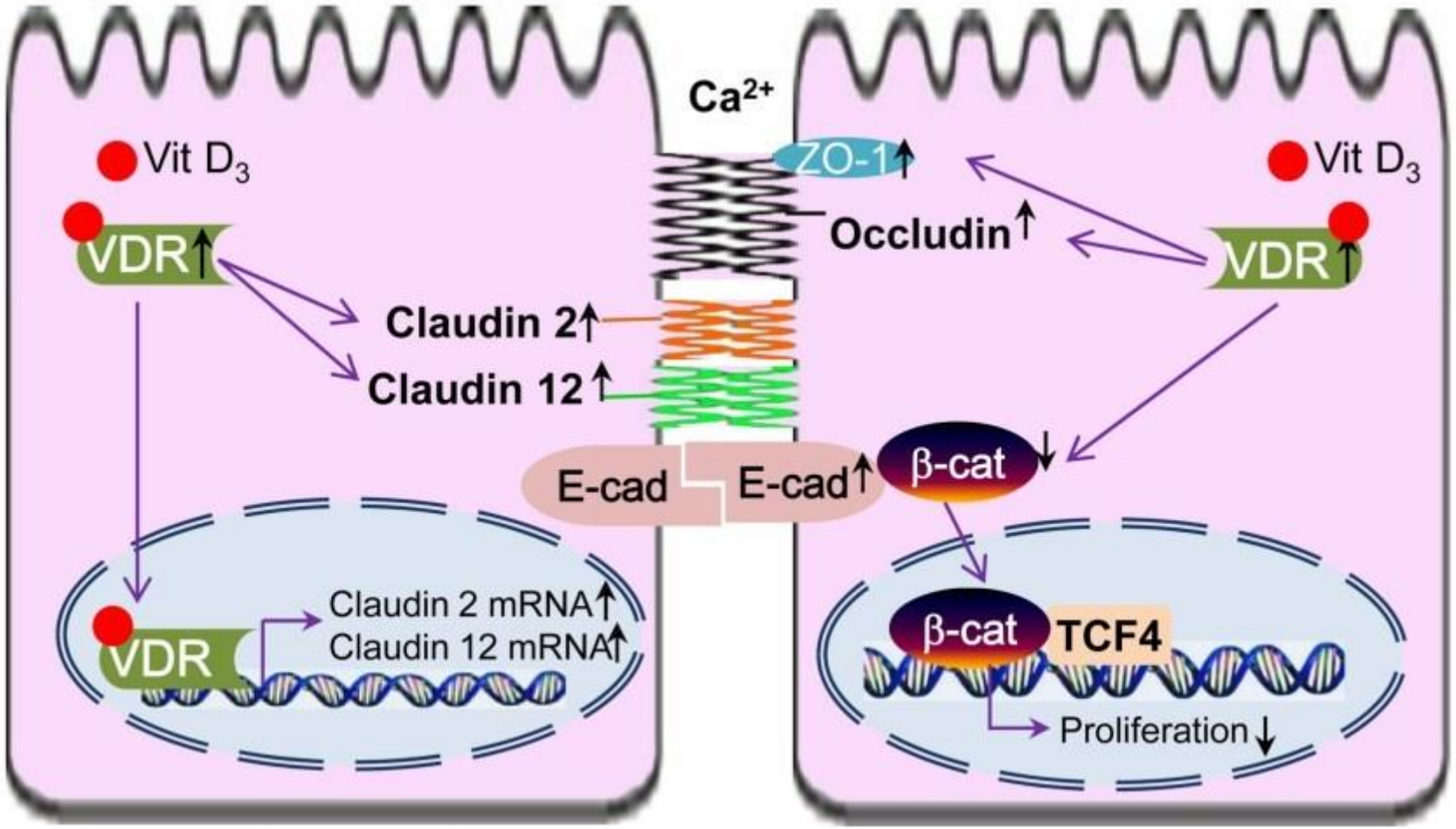
The composition of the diet dictates variation in strains

- Mediterrean diet style: source of indigestible CHO
  - Increase in saccharolytic bacteria: SCFA
  - Decrease in “bile tolerant” bacteria : AA

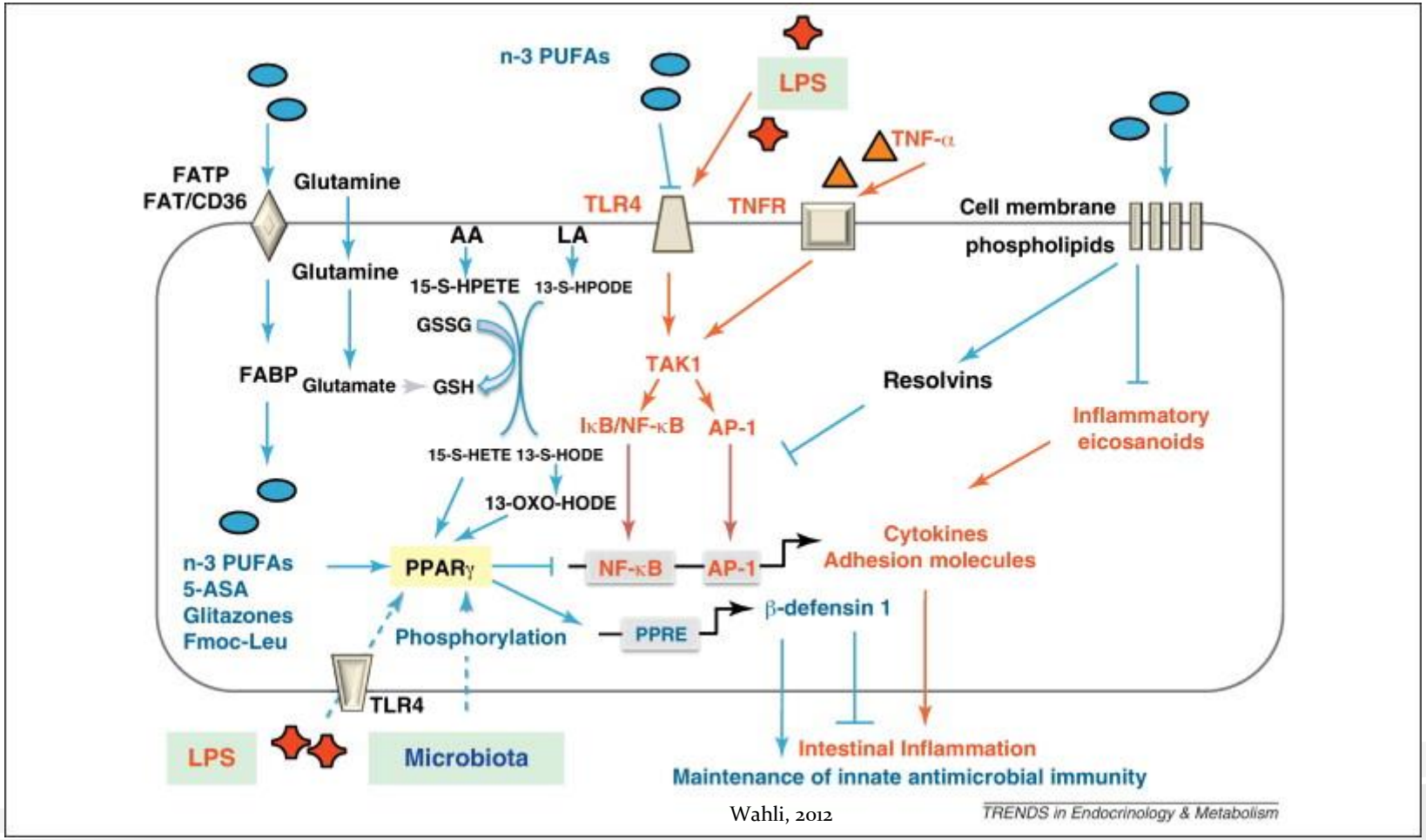
Vitamin D: anti-microbial, anti-inflammatory



Vitamin D and mucosal integrity



The anti-inflammatory effect of Ω3 fatty acids



Wahli, 2012

Low fiber hypothesis revisited

- Painter and Burkitt: excessive luminal pressures as a consequence of dietary fiber deficiency

1. increase in DD incidence in Western countries throughout the twentieth century
2. decrease in dietary crude fiber consumption in Western countries over the same period
3. an observed low prevalence of DD in Africa where crude fiber intakes were assumed to be higher. (comparable prevalence of DD amongst African Americans with the white American population)

Recent publications

- Peery et al (2012). A high Fiber diet does not protect against asymptomatic diverticulosis
  - NC
- Peery et al (2013) Constipation and low fiber diet not associated with diverticulosis
  - Vitamin D/Calcium
- Crowe et al (2011) Vegetarians had a significantly lower incidences DD
  - Europe

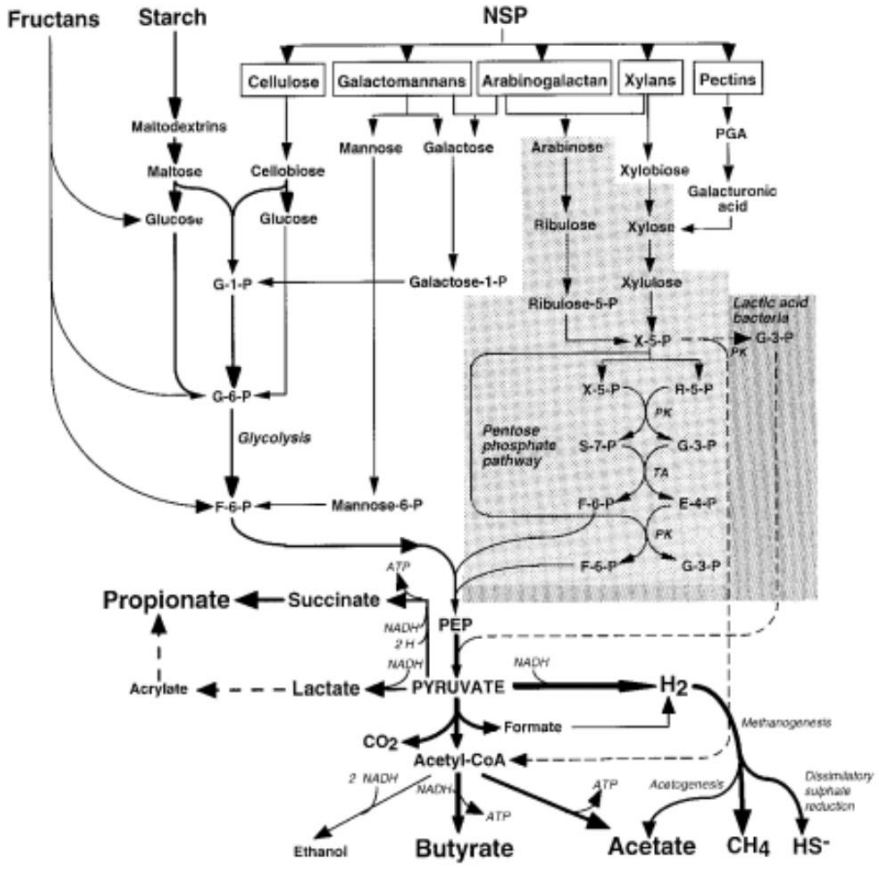


Fig. 1. Pathways of polysaccharide breakdown, and the major routes of fermentation of dietary carbohydrate in the gut microbiota, showing the principal end products of metabolism. NSP, non-starch polysaccharides; PK, phosphoketolase; TA, transaldolase.

http://www.microbecolhealthdis.net/index.php/mehd/article/viewFile/8103/9458

Closer look at fiber

- Soluble vs insoluble
- Soluble:
  - Viscous
  - Fermented: Butyric acid, propionic acid, acetic acid
- Insoluble:
  - Bulk
  - Poorly fermented

Butyrate

- 70-80% colonocyte energy
- Absorbed in proximal colon, more important in distal
  - Processed food, void of butyrate in distal

Fiber and diverticulitis: Is it actually butyric acid?

- Effects of dietary microencapsulated sodium butyrate improves:
  - intestinal mucosal morphology and immune response (Liu et al., 2014)
- Microencapsulated sodium butyrate administered to patients with diverticulosis
  - decreases incidence of diverticulitis (Krokowicz et al., 2014)

Check this out

http://www.nature.com/ejcn/journal/v63/n11/full/ejcn200964a.html

The effect of probiotics

- Use of probiotics restores the altered intestinal flora due to stasis and reduced colonic transit time.
- In one prospective open trial by Fric and Zarovral (2003), *Escherichia coli* strain Nissle 1917 was administered to 15 patients with uncomplicated diverticular disease
  - longer periods of remission and improved abdominal symptoms after receiving probiotic compared to before treatment.

Probiotics and anti-inflammatory agents

- A multicenter prospective randomized controlled study (2006):
  - 90 patients with symptomatic diverticular disease randomized to three groups
    - mesalazine alone, *Lactobacillus casei* alone or both
    - The combination group was 100% symptom free at 12-month follow up
    - 76.7% of the mesalazine group or *Lactobacillus* group.
    - Mesalazine and *L. casei* together were superior to either treatment alone in preventing symptom recurrence.

Higher Serum Levels of Vitamin D are Associated with Reduced Risk of Diverticulitis

- Recent analysis of a national database of hospital admissions observed a seasonal variation in hospitalizations for diverticulitis. (Maguire et al., 2013)
  - May reflects variation in ultraviolet (UV) light exposure

Vitamin D levels and Diverticulitis

	Group				
	Uncomplicated Diverticulosis	Acute Diverticulitis	Complicated Diverticulitis	Surgical Diverticulitis	Recurrent Diverticulitis
	N = 9,116	N = 594	N = 124	N = 65	N = 139
First vitamin D level, mean (SD), ng/mL	29.1 (14.0)	25.9 (13.4)	25.8 (12.8)	22.7 (14.9)	23.5 (14.0)
p-value[a]		<0.0001	0.0095	0.002	<0.0001

p-value compares each group to the uncomplicated diverticulosis group

Vitamin D in inflammation and gut homeostasis

- $1,25(OH)_2D_3$ and its receptor VDR have been
  - inversely correlated with NF-κB upregulation
  - Correlated with expression of antimicrobial peptides, such as cathelicidin
    - Paneth cells secrete antimicrobial peptides regulated by VDR

Western diet

- Simple sugars➔ No leftovers for gut bacteria
- Lots protein➔ Amino acid metabolites (ammonia, sulphide,..)
- ➔ Change in strain variability: shift gram negative bacteria
- Mucin: 90 % CHO
- ➔ digested
- ➔ immunity and mucosal integrity affected

Western Diet

- High omega 6/omega 3 fats➔ promotes inflammation
- Low in Vitamin D

Conclusion

- Diverticular disease progression might be due to a gene-dietary interaction
- Fiber role needs to be further specified : soluble vs insoluble fiber