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Nutrition – Microbiome – Immune System

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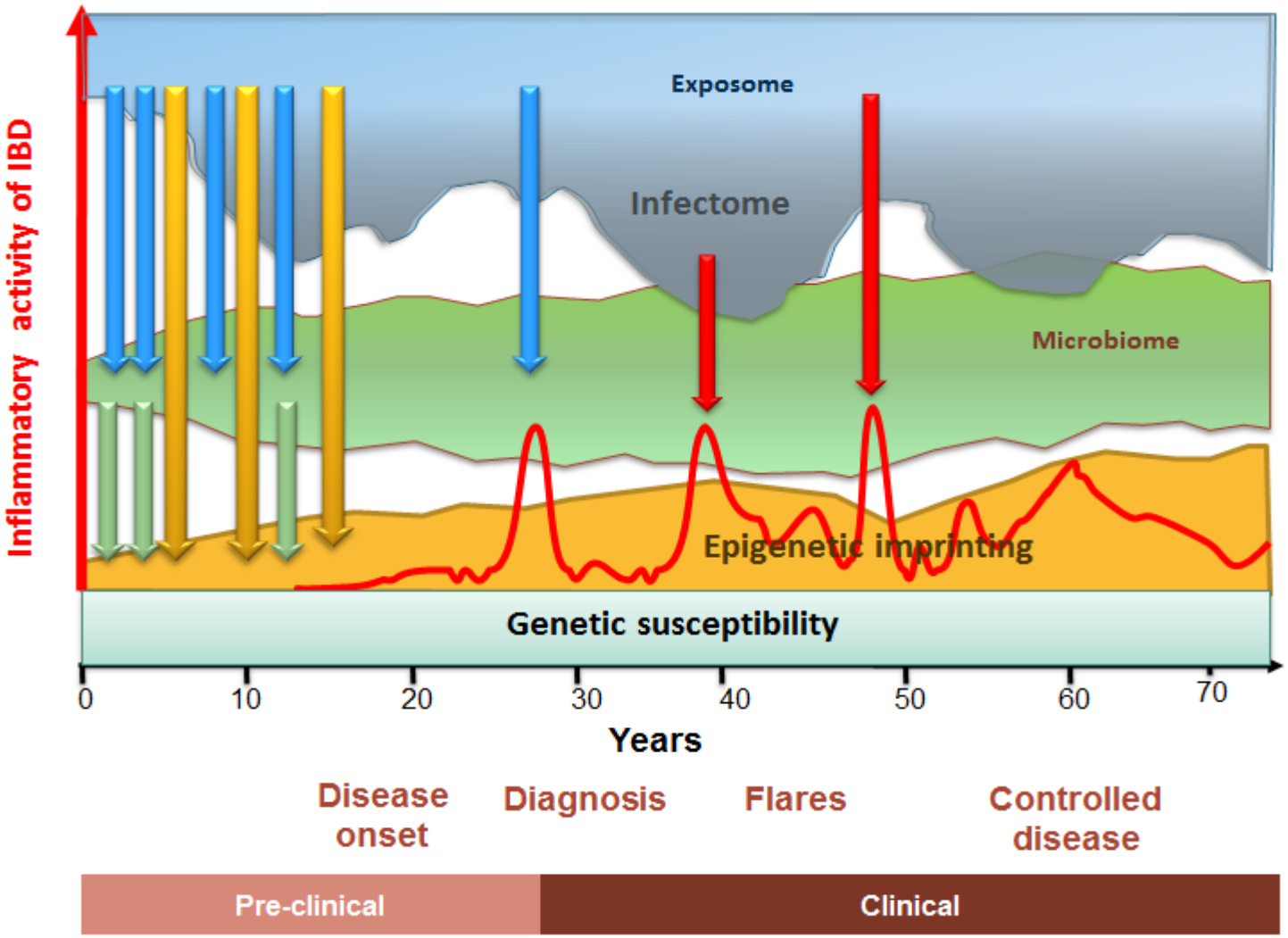
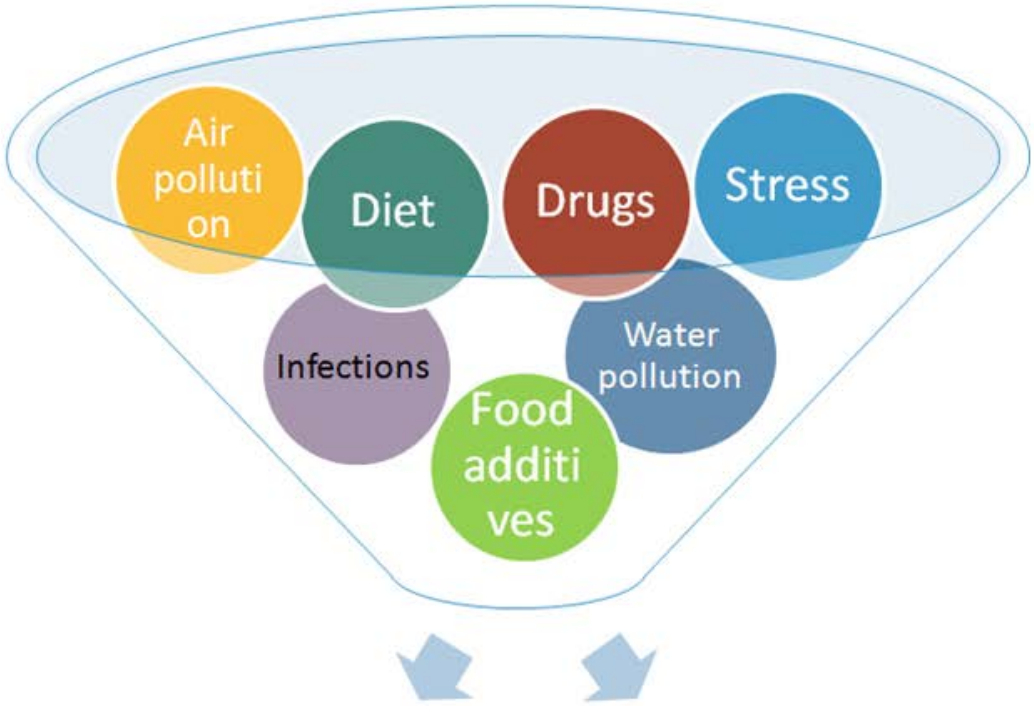
The exposome in IBD



Rogler G, Vavricka S. Exposome in IBD: Recent Insights in Environmental Factors that Influence the Onset and Course of IBD.Inflamm Bowel Dis. 2014

The role of the exposome (environment) in IBD



Rogler G, Vavricka S. Exposome in IBD: Recent Insights in Environmental Factors that Influence the Onset and Course of IBD.Inflamm Bowel Dis. 2014

“Environmental” factors known to play a role

“risk factor”	Disease	Effect Size
Vitamin D[1]	Crohn’s disease	0.55 (0.30 – 1.00) (Q4 vs. Q1)
NSAR ≥ 15d/mo[2]	Crohn’s disease	1.59 (0.99 – 2.56) (vs. non-users)
NSAR ≥ 15d/mo[2]	Ulcerative colitis	1.87 (1.16 – 2.99) (vs. non-users)
Depressive Symptoms [3]	Crohn’s disease	2.36 (1.40 – 3.98) (vs. MHI-5 86-100)
Fibers[4]	Crohn’s disease	0.62 (0.40 – 0.95) (Q5 vs. Q1)
Oral Contraceptives[5]	Crohn’s disease	2.66 (1.52 – 4.64) (current vs. non-users)
Hormon-substitution-therapy [6]	Ulcerative colitis	1.74 (1.09 – 2.77) (current vs. non-users)

1. Ananthakrishnan AN. Gastroenterology. 2012;142(3):482.
2. Ananthakrishnan AN. Ann Intern Med. 2012;156(5):350.
3. Ananthakrishnan AN, et al. Presented at DDW; May 20, 2012. Abstract 398.
4. Ananthakrishnan AN, et al. Presented at DDW; May 21, 2012. Abstract 863.
5. Khalili H, et al. Presented at DDW; May 20, 2012. Abstract 402.
6. Khalili H, et al. Presented at DDW; May 20, 2012. Abstract 401.

The evidence that diet may play a role

Observational studies

- IBD becomes more prevalent after Westernisation
- Meat and fats increase risk
- High fibre, fruits, vegetable lower risk

Animal models

- Numerous nutrients studied in rodent models
- High fat diets increase colitis severity
- PUFAs prevent / reduce colitis severity
- Amino acids eg glutamine, arginine, and tryptophan
- Plant polysaccharides and fibres

Reviewed in Richman E et al APT 2013;38:1156-1171

EEN probably affects the microbiome

Small studies

- Paediatric -11 children[1]
- Paediatric - 1 child[2]
- Paediatric 6 CD, 6 healthy[3]
- Adult 33 CD, 17 healthy[4]

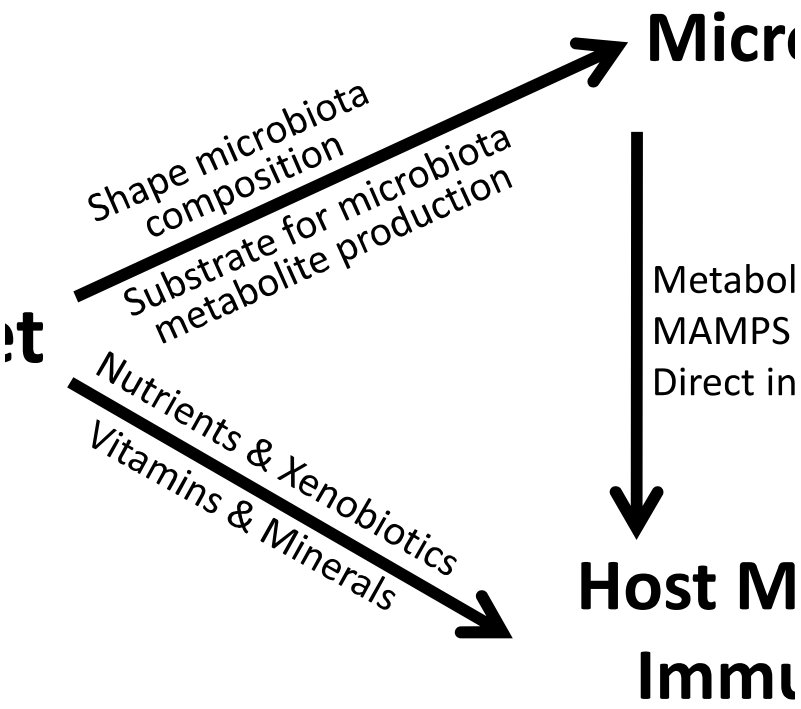
All confounded by inflammation

1. *Tjellstrom BA et al Scand J Gastro 2012;47:1454-1459*
2. *D'Argenio V et al Am J Gastroenterol 2013;108:851-852*
3. *Leach ST et al Aliment Pharmacol Ther 2008;28:724-33*
4. *Shiga H et al Dig Liver Dis 2012;44:736-42*

Diet – possible mechanisms

it D
n-3 PUFA

Unfavorable
Whole food
Red meat and fat
Iron
n-6 PUFA



Lee D et al Gastroenterology Jan 2015

The evidence: EEN as induction therapy

- Cochrane[1] review of 7 studies of EEN vs steroids for remission induction
- 352 patients (37 children)
- CDAI or PCDAI

- ITT analysis remission rates vs steroids were:

	EEN	Steroids
Remission rate	49%	75%

1. Zachos M et al Cochrane Database Syst Rev 2007;3:CD000542

Available induction medicines are better

Steroids

- Induction of remission between 60-80%[1,2,3]
- Well tolerated in short courses – side-effects are reversible if they occur

Anti-TNF

- Response rates 80-90%[4,5], remission 40-50%[5]
- Well tolerated – only 10% stop therapy due to AE[6]
- Safe over the longterm[7]
- Can be continued as maintenance therapy

1. Rutgeerts P et al NEJM 1994;331:842-5
2. Gross V et al Eur J Gastroenterol Hepatol 1996;8:905-9
3. Summers RW et al Gastroenterology 1979;77:847-69
4. Targan SR et al NEJM 1997;337:1029-35
5. Hanauer SB et al Lancet 2002;359:1541-1549
6, Siegel CA Gut 2012;61:459-65
7. D'Haens G et al Lancet 2008;371:660-667

Effect of EEN is transient

High relapse rate on returning to normal diet

Approximately 50% within 6 months[1]

Contrast this with azathioprine withdrawal – can expect 75% to remain well for at least 18 months[2]

1. *Raouf et al Gut 1991;32:702-7*
2. *Leman M et al Gastroenterology 2005;128:1812-1818*

The evidence for other diets

Exclusion diet[1]

- 136 patients – 1/3rd did not tolerate elemental diet
- The remaining 93 achieved were randomised to tapering 12 weeks steroids or an exclusion diet

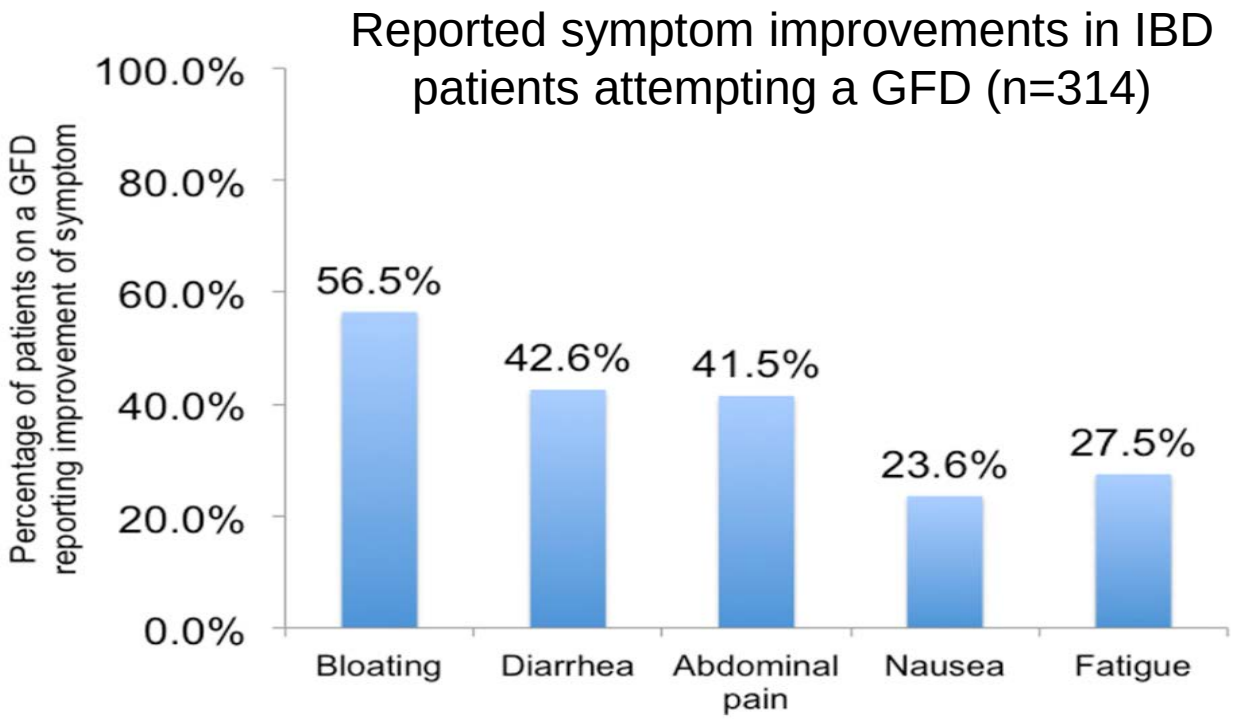
	Exclusion diet	Steroids
Median remission	7.5 months	3.8 months
Relapse rates at 2 years	79%	62%

BUT

- Remission based on clinical score
- No CRP or faecal calprotectin
- Omitted foods typically wheat, dairy

Riordan JO et al Lancet 1993;342:1131-4

Improvement of clinical symptoms in patients with IBD upon gluten free diet



"Testing a GFD in clinical practice in patients with significant intestinal symptoms, which are not solely explained by the degree of intestinal inflammation, has the potential to be a safe and highly efficient therapeutic approach"

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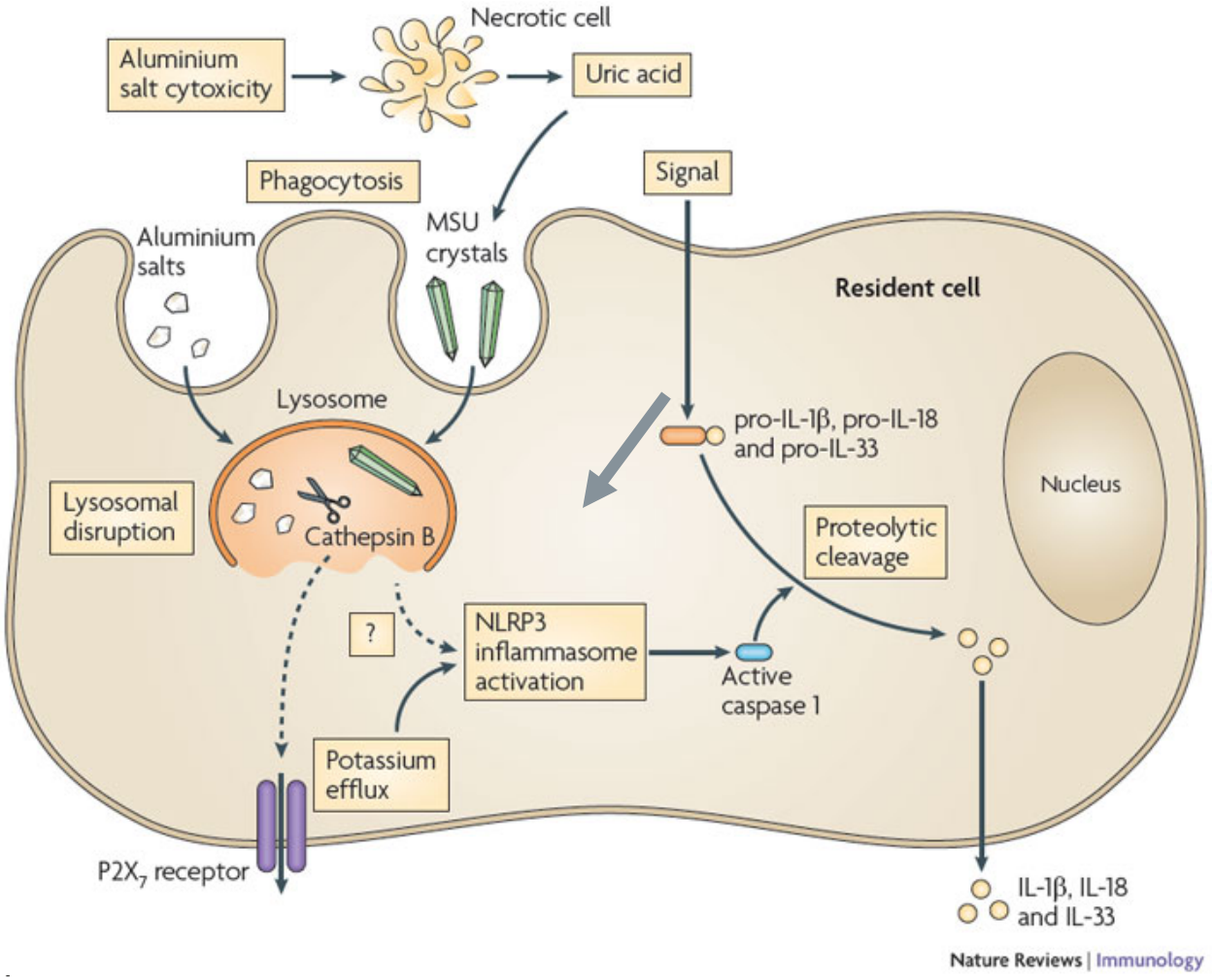
Herfarth H et al. Inflamm Bowel Dis. 2014 Jul; 20(7): 1194–1197.

Potential mechanisms of diet: Inflammasome-activation via nanoparticles (not just microbiota)



Adair-Kirk L. et al.(2008)

How much titaniumdioxide (TiO2) do we eat?

source	mg / person / day
Coffee whitener	0.52
Pastry	0.32
Tooth paste	0.30
Chewing gum	0.28
Ibuprofen	0.27
Marshmallows	0.27
others	0.54
Total (Median)	**2.5**

Lomer et al. (2004)

Summary

- **Environmental (lifestyle) factors such as diet** most likely contribute to **onset** and **disease course** of IBD (and are more important than genetic factors)
- **EEN** may be an **alternative to steroids in children**
- Results on **other diets** are conflicting
- Effects may be mediated via the **intestinal microbiota** or directly via **innate immune mechanisms** in epithelial cells.
- **Further studies are most urgently needed**

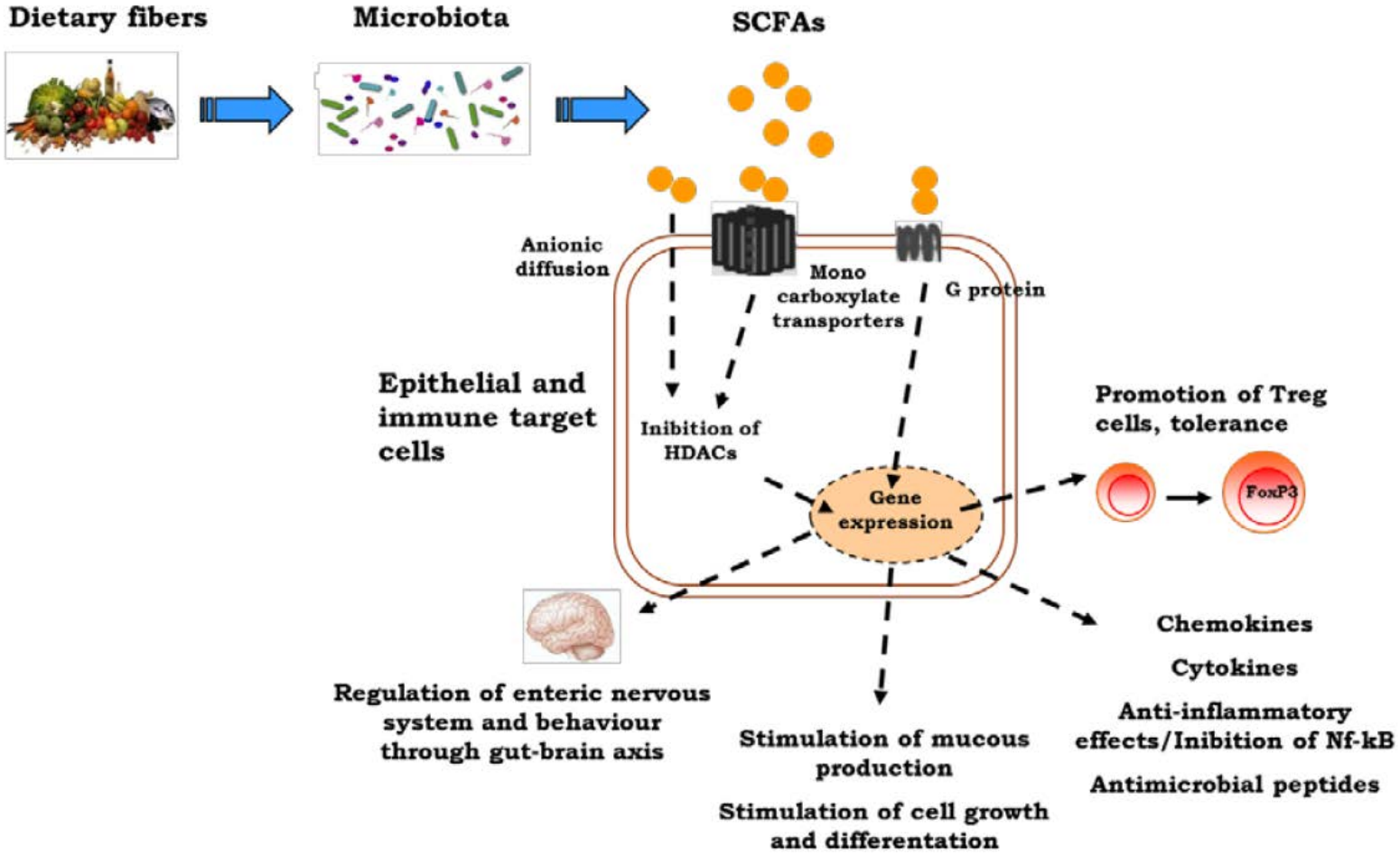
General recommendations

- **During flares:**
  - More and lighter meals
  - Avoid fruit juices (orange juice, lemon juice)
  - Avoid fibres, uncooked vegetables, food additives
  - Avoid coffee, avoid nicotine

- **During remission**
  - **Don’t care about any special diet restrictions and have fun with your food!!!**
  - Avoid food additives, «convenience products»
  - Eat fibres and vitamins

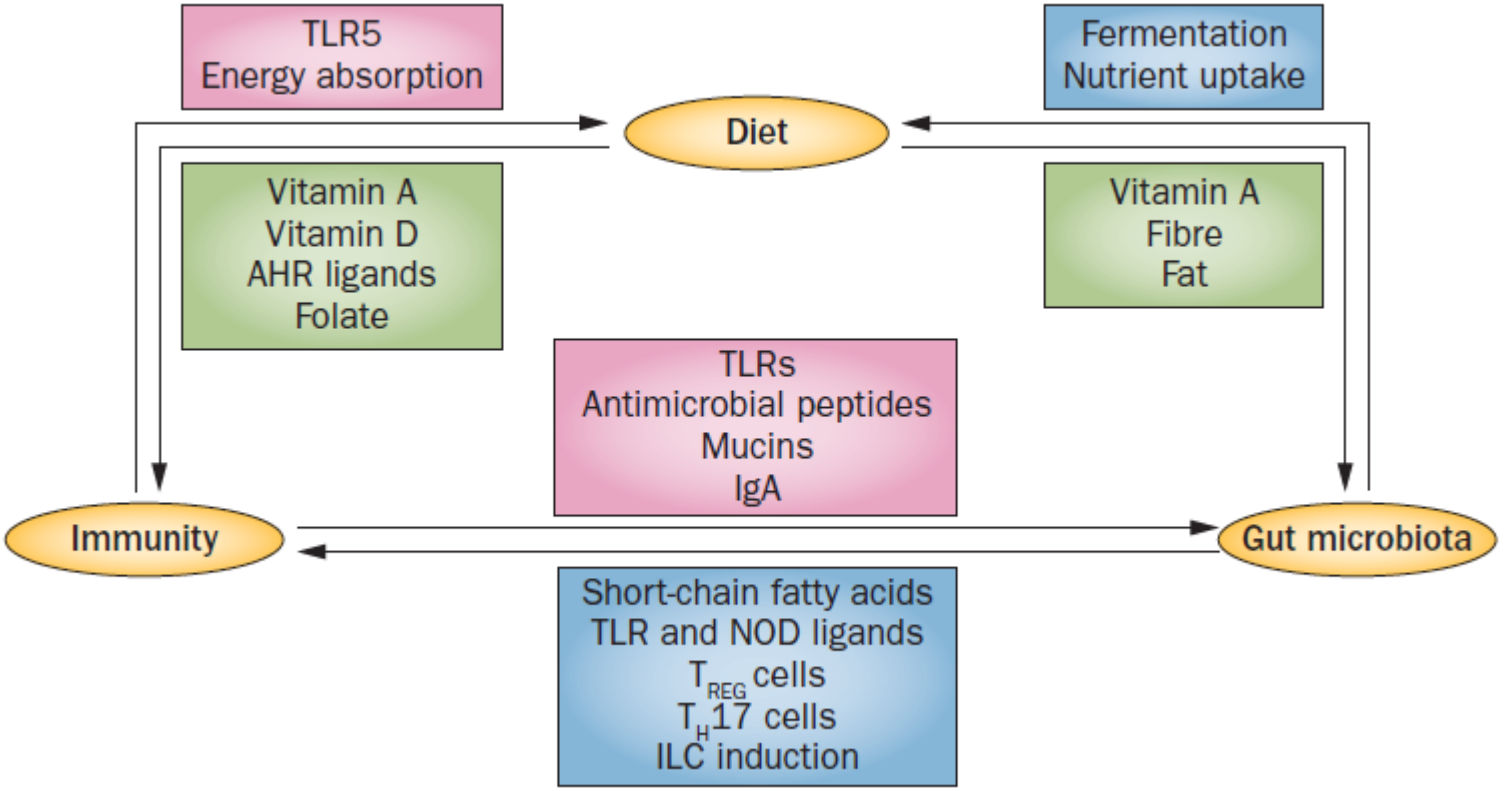
Thank you for your attention!

How fibers might influence epigenetics in the immune system



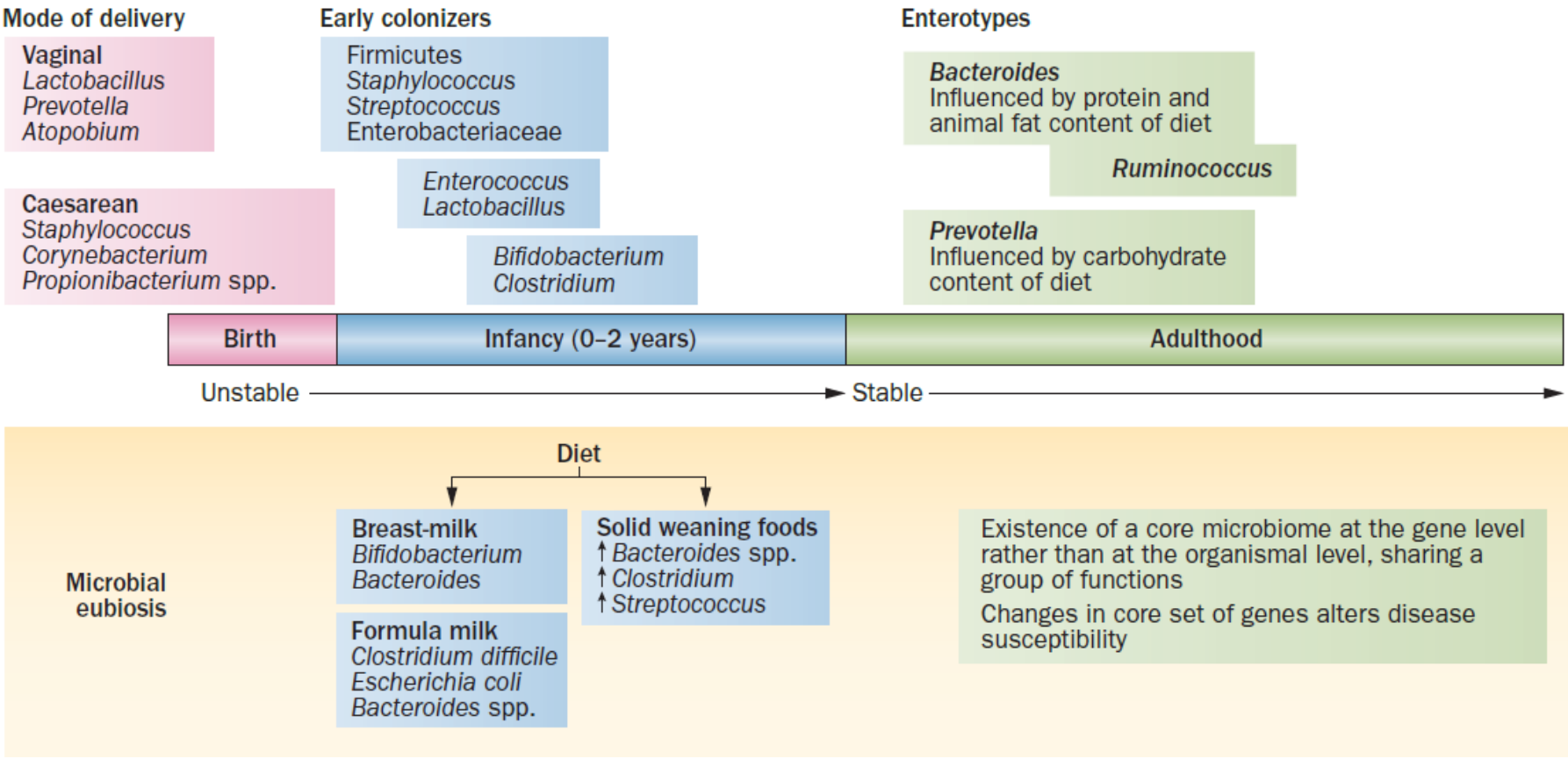
L. Paparo. Nutrients 2014, 6, 4706-4719;

The diet hypothesis



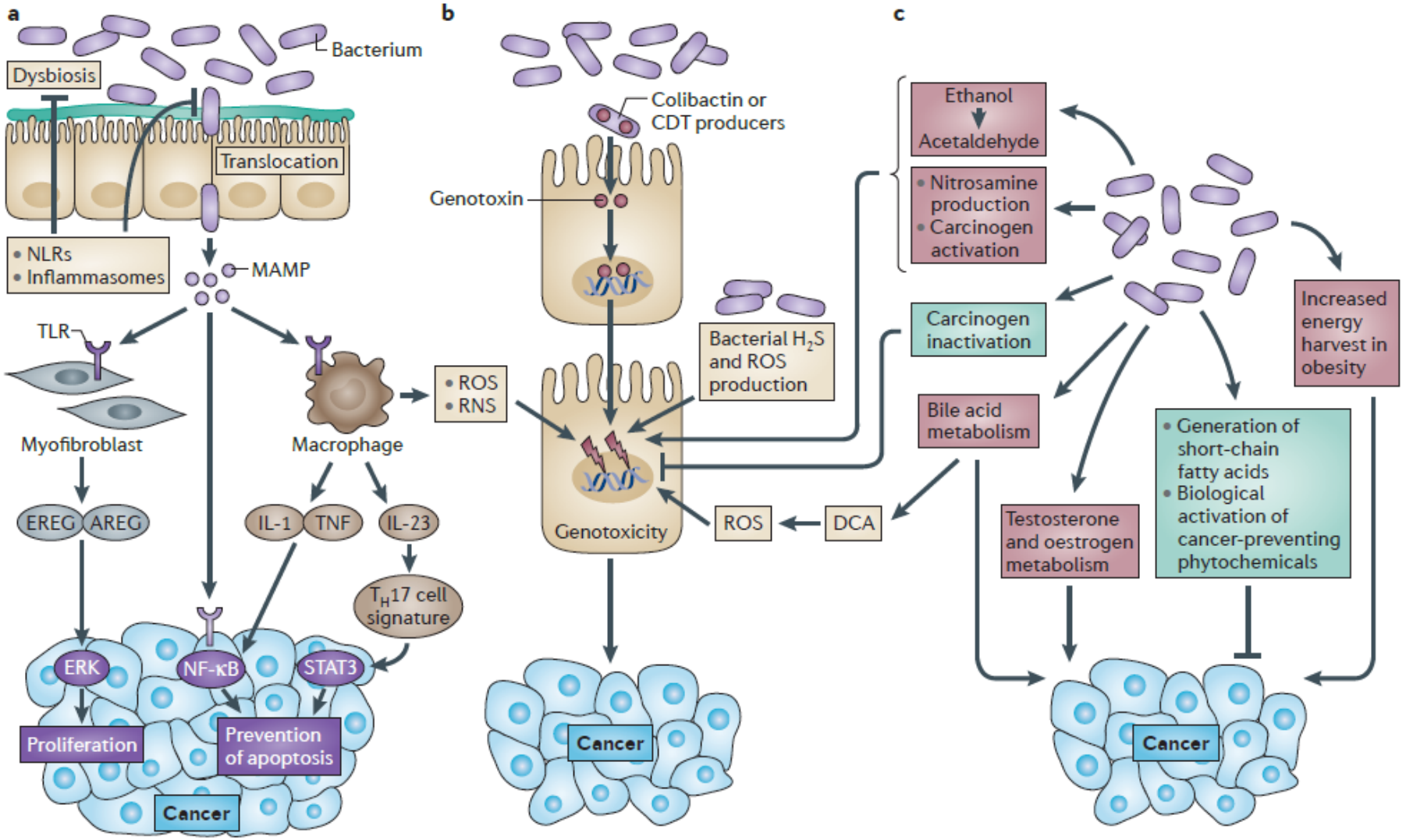
N. Jain and W. A. Walker; Nat. Rev. Gastroenterol. Hepatol. 12, 14–25 (2015);

Diet and gut microbiota during lifetime



N. Jain and W. A. Walker; Nat. Rev. Gastroenterol. Hepatol. 12, 14–25 (2015);

How the microbiome may modulate carcinogenesis



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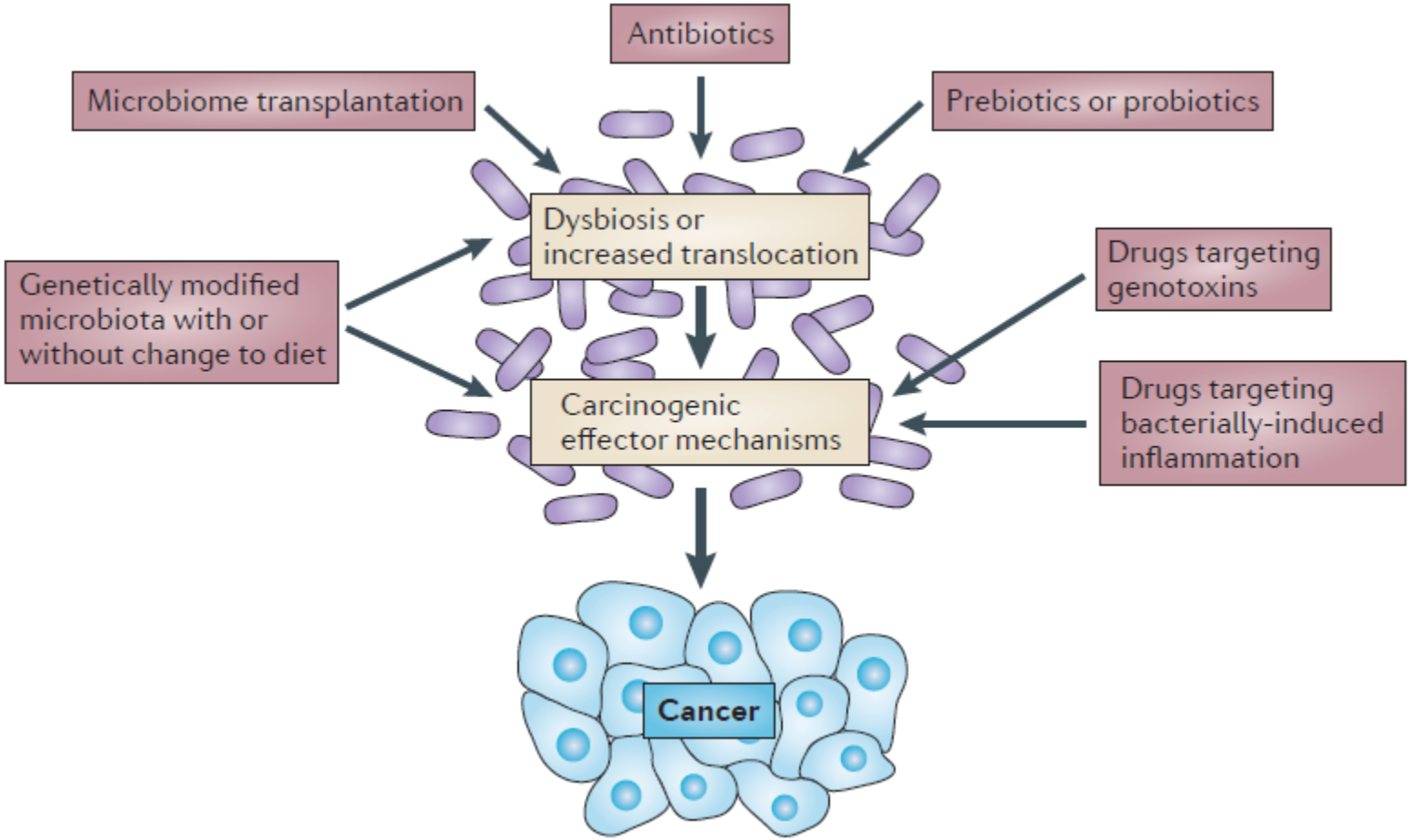
R. F. Schwabe and C. Jobin The microbiome and cancer Nat. Rev. 2013

Targeting the microbiome for cancer therapy



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