Clinical Applications: The Gut Microbiome in Advanced Endocrinology

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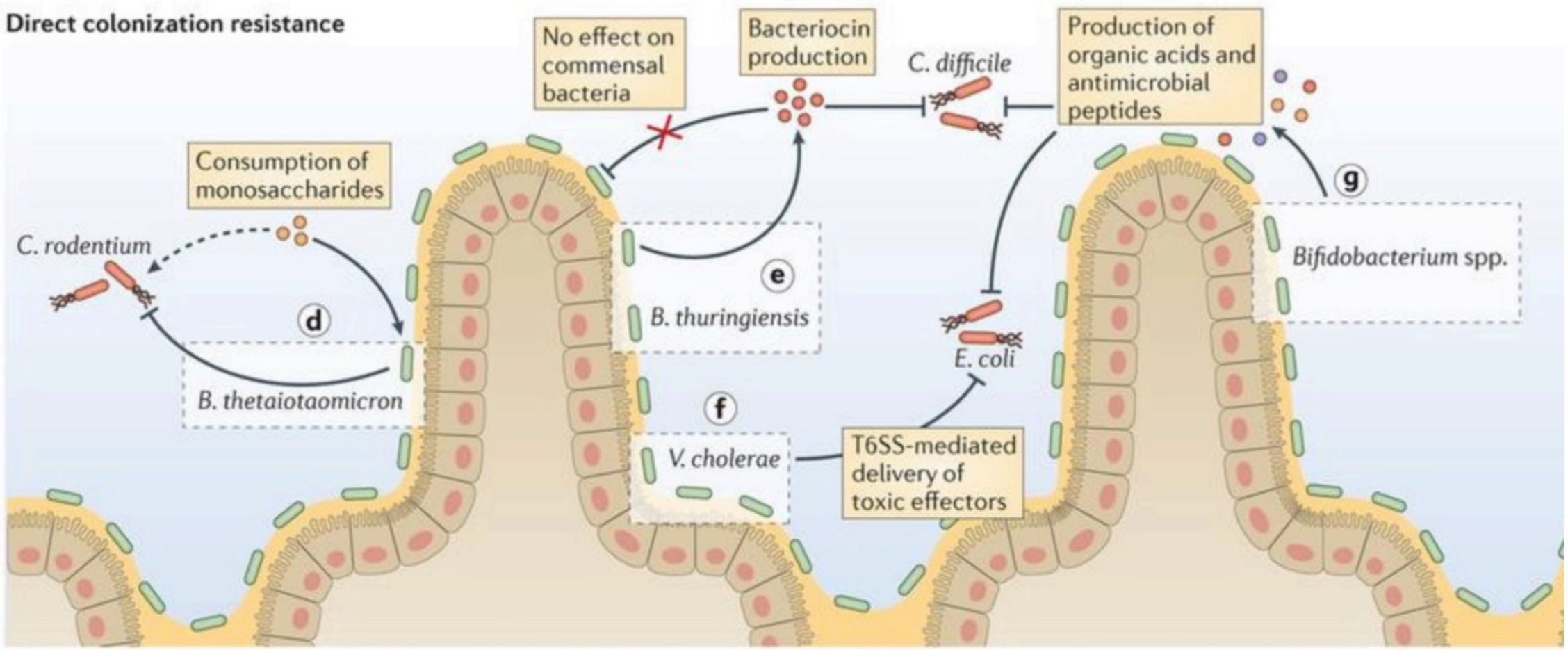
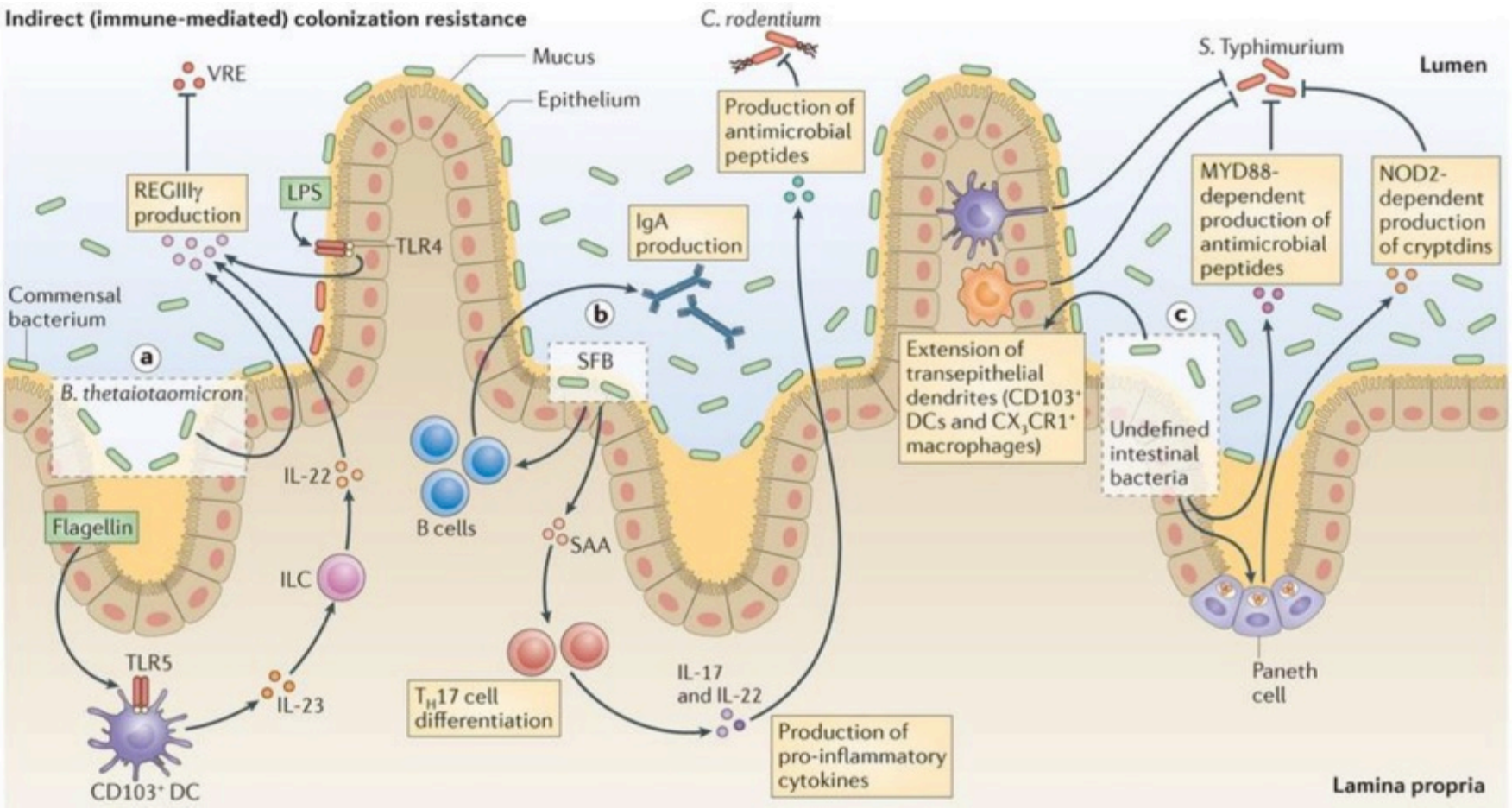
The Healthy Microbiome



Dysbiotic Gut Inflammation



Microbiome-induced inflammation

- Specific diseases have specific genetic & epigenetic (microbial and inflammatory) profiles

- EXAMPLE: Psoriasis is associated with low levels of Faecalibactrrium praunitzii and IL-17 mediated inflammation

Chronic illness etiology:
dysbiotic gut inflammation

- NEURO: Dementia, mood d/o: depression, anxiety, migraine
- METABOLIC: Sarcopenia / frailty, Obesity
- RENAL: CKD3
- MUSCULOSKELETAL: Degenerative arthritis
- ONCOLOGY: Cancer-breast, uterine, lymphoma, prostate
- CARDIAC: CHF, CAD
- GU: nephrolithiasis, BPH
- ENDOCRINE: T2DM, PCOS, hypothyroid
- GI: Cholelithiasis
- AUTOIMMUNE DISEASE
- NON-AUTOIMMUNE Functional pathologies: fibromyalgia, RSD, CFS, chronic Lyme
- OBGYN: Post partum syndromes, ovarian cyst, fibroid, PMS, endometriosis

Etiology of gut dysbiosis

- Medications
- Antibiotics
- Depression, chronic stress, insomnia, chronic pain
- Low fiber / synthetic feeds
- Other meds -> antidepressants, PPIs (high stomach pH)
- Herbicides (Glyphosate)
- Inadequate breast feeding
- Westernization

Microbial manipulation directly impacts endocrine concerns

- *Patients with drug resistant bacterial intestinal overgrowth often require antimicrobial treatments over a long period of time*
- Patient NR. 63 yo F. Weight loss plateaued off of anti-microbial therapy, due to persistent MDR intestinal overgrowth
- Patient AS. 35 yo F. Acne, fatigue, allergy Rx wean all dependent on anti-microbial therapy
- Patient VM. 72 yo M reversed Stage 1 Prostate CA using anti-microbials and increased RS intake
- Patient JS. 83 yo chronic venous insufficiency resolved with estrogen-lowering and anti-microbial therapy
- Patient AV. 85 yo man with chronic bilat- LE neuropathic pain syn resolved with conventional antibiotics

Microbiome- repair treatments improve end-organ function

- FMT for weight loss, autism, colitis, NASH
- Florastor study for CHF: (RCT pub Int J of Cardiology , Volume 179 , 348 – 350)
  - decreases lipids, uric acid, LA diameter, and increases EF in CHF patients
- Probiotics beneficial for cognition and depression
- Anti fungal Rx ->
  - decrease fungal intestinal overgrowth
    - decreases PGE2 meditated allergic pulm inflammation

- Higher fiber intake →
  - Decreased all cause mortality, decreased risk of breast cancer, and decrease risk of death in patients with colon cancer
- Fiber increases weight in underweight children
- Metformin decreases mortality in diabetics
- Resolution of SIBO / dysbiotic gut inflammation can increase fecal elastase levels (and resolve pancreatic exocrine insufficiency)

Enteroimmunology: Microbiome repair

Increase commensal diversity	Increase SCFA production	Improve immune tolerance	GPR109A receptor activation
Suppress pathogenic overgrowth	Increase levels of SCFA producing bacteria	Liver & Detoxification support	Reduction of toxic metabolite production
Increase bacterial diversity	Optimize digestion	Pancreas support	Enhance binding and excretion of dietary antigens and toxic metabolites
Increase nutritional prebiotic fiber intake	Eradication of food allergy	Glycocalyx support	Optimization of oral, sinopulmonary, and pelvic microbiomes
Reduction of viral / fungal / parasitic dysbiosis	Repair of intestinal lining	Reduction of Beta-Glucoronidase activity	
	Prokinetic Treatments	Immune modulation	
		Promotion of bacterial conjugation	

Endocrinopathy associated with organ-specific disease pathogenesis

- **Aldosterone** in excess promotes remodeling in cardiomyopathy
  - Kidney Int. 2000 Apr;57(4):1346-51
- Dementia is associated with **insulin** resistance
  - J Alzheimers Dis. 2011;25(1):29-41
- Most refractory obesity syndromes are associated with altered cortisol secretion impaired estrogen metabolism / insulin resistance
- Hypothyroidism is associated with hyper **estrogen** states
  - J Thyroid Res. 2011; 2011: 875125
- All diabetics demonstrate **hypercortisolism.**
  - Diabetes Care 2007 Jan; 30(1): 83-88

- Underweight states are associated with chronic catabolic and degenerative states
- CKD Is associated with multiple steroid hormone deficiencies
- Chronic fatigue is associated with excess CRF production
- Prostatopathy is associated with low Vit D, high estrogens, low progesterone/testosterone, insulin resistance

Endocrinology

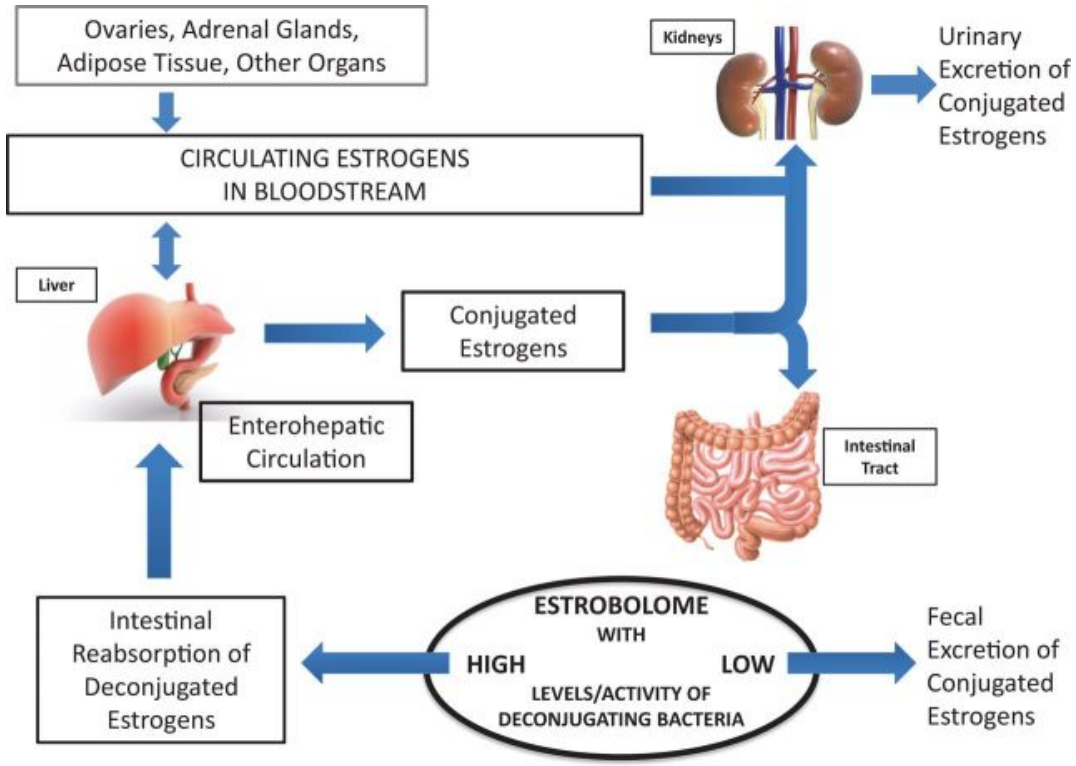
- Dysbiotic gut inflammation ->> leads to **immune modulating response -> IL1 & TNFa production -> stimulates cortisol production, directly affecting tissues with high** 11 β -HSD1 expression (liver, gonads, fat, brain)
  - Cortisol modulates the immune response, especially endogenous enteric & autoimmune inflammation and is associated with dysbiosis in animal models

- Altered cortisol secretion ASSOCIATED WITH **secondary endocrinopathy** attributable to hypothesized shunting of steroidogenic precursors to generation of cortisol rather than to generation of anabolic hormones.
  - → worsens dysbiotic gut inflammation, promotes autoimmunity
    - Insulin Resistance & Type 2 diabetes and impaired insulin secretion, eventually leading to pancreatic beta cell failure
    - Deficiency of steroid hormones DHEA, progesterone, testosterone, 25OH Vit D, estriol
    - Thyroidopathy: Elevated TSH / low free T3 / (which may be complicated by autoimmune thyroidopathy)
    - Hyperestrogenism (or deficiency of progesterone leading to loss of regulation of nuclear estradiol receptors)

Endocrinology Treatments

- BHRT: T3, T4, testosterone, P4, DHEA, hydrocortisone, pregnenolone, fludrocortisone, Vitamin D3, estradiol, estriol
- Estrogen lowering: aromatase inhibitors, CaD-Glucarate, Ketogenic/thermogenic
- 5aReductase inhibitors – finasteride
- Insulin sensitizers: Metformin, Berberine
- Micronutrients, amino acids
- Plant based treatments
  - hormone balancing herbs such as red raspberry and clarysage
  - essential oils such as lavender and cinnamon bark
- Seed cycling
- Microbiome manipulation

Gut Estrobolomics



- Underweight F > 70 -> higher risk for osteoporotic fractures & falls & frailty
- Hyperestrogenism associated with fluid retention syndromes (pre-eclampsia, venous insuff)
- Who is a candidate for estradiol Rx?
  - Consider those who have enhanced fecal excretion of estrogens who are concomitantly underweight and osteoporotic

Illness-specific success stories

- Prostate Cancer (PSA 12 ->4 over 6 months)
- Venous Insufficiency (40lb water weight resolved from chronic venous stasis)
- Diabetes (A1C downtrending in multiple patients)
- Obesity (lasting weight loss)
- Chronic degenerative joint disease
- Endometriosis / chronic pelvic pain syn
- Mood d/o: depression/anxiety
- Chronic fatigue, IBS, GI illnesses
- HTN, dyslipidemia
- Aging: patients in 60s returning to work full time, 70s keeping up with partners who are decade(s) younger, 70s pursuing new life ventures without the burden of chronic illness

Type 2 Diabetes clinical trial update

Patient	Oct 2016 (A1c)	Jan 2017 (A1c)	July 2017 (A1c)
KC	7.2	6.8	6.4
NR	5.9	6.0	5.6
BF	16.1	14.7	11.3
VM	6.0		5.6
SM	6.8		14.2

Fourfold Therapeutics

Microbiome • Sustain microbiome balance by Increasing fiber intake	**Lifestyle** • Exercise • Anti-sedentary • Sleep
Endocrinology • Hormone balance	**Belong & Connect** • Purpose • Meditation & Yoga • Connection – large and small scale • Where/with whom do I belong