Successive infection: a model for how metagenomic communities shift to become more pathogenic over time

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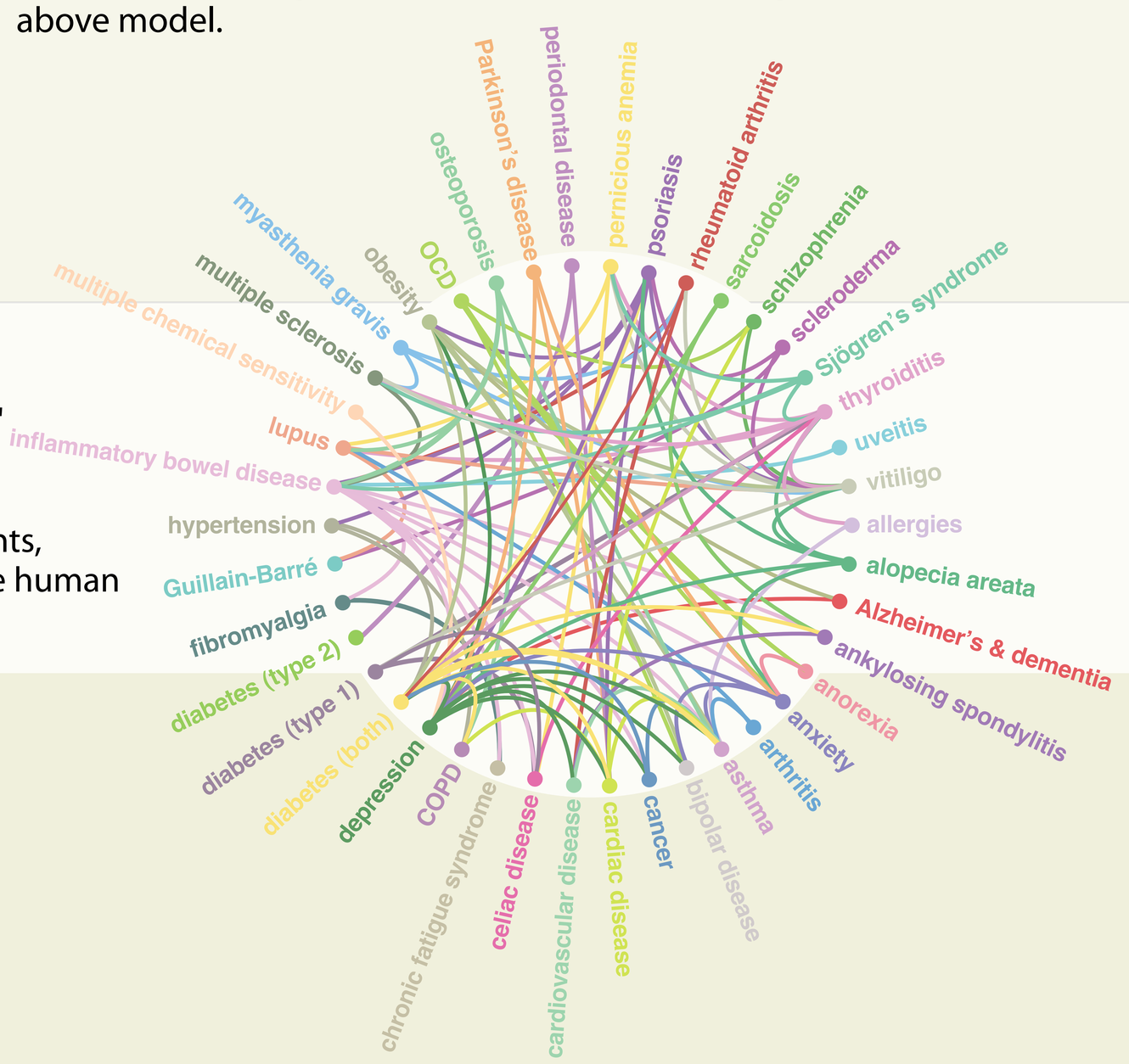
Recent studies have demonstrated that persistent microbial species such as Mtb, Borrelia, CMV, HIV, and EBV are able to suppress expression of TACO, TLR-2, and key endogenous antimicrobials such as cathelicidin and the beta-Defensins by dysregulating the VDR nuclear receptor. This marks such a logical survival mechanism that other less studied microbes have also likely evolved to slow VDR activity or the activity of other receptors involved in controlling the immune response. Each pathogen that decreases immune activity makes it easier for the host to pick up other pathogens, which themselves may further slow immune activity, creating a snowball effect. Thus, an inflammatory disease state may result from the combined pathogenicity of the sum of microbes, both bacterial and viral, that any one person accumulates over the course of a lifetime. As human genes are upregulated or downregulated by acquired components of the microbiota, the body shifts farther away from its natural state of homeostasis. Infected cells increasingly struggle to correctly produce human metabolites in the presence of numerous proteins and enzymes being created by pathogenic genomes. The process offers a framework for understanding how certain microbial populations may shift over time so that eventually people start to develop an inflammatory diagnosis, or gradually begin to present with symptoms of what is often deemed "normal" aging. We have developed a therapy for inflammatory disease that uses the VDR agonist Olmesartan to re-active the innate immune response. Many patients have reported significant improvement and/or objective markers indicating disease resolution, providing support for the above model.

Common inflammatory disease co-morbidities

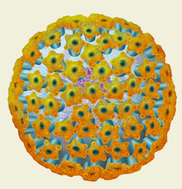
It may not be by accident that the uniqueness with which patients' autoimmune disease symptoms develop parallels the incredible variability of the human microbiome. If the spectrum of autoimmune disease were driven by a person's microbial inhabitants, variability in disease could be explained by accounting for how the human microbiota accumulates and develops in any one person.



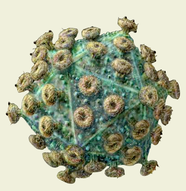
Microbes downregulate expression of the VDR nuclear receptor

Mycobacterium tuberculosis
Downregulates the VDR 3.3-fold
Source: Chin Med J (Engl). 2003;116:1070-3.

Borrelia burgdorferi
Live Bb downregulates the VDR 50-fold
Lysed Bb downregulates the VDR 8-fold
Source: PLoS Pathog. 2009 May;5(5):e1000444



Epstein Barr Virus (EBV)
Downregulates the VDR 32-fold in some B cells
Source: Experimental Oncology. 2009; 31(2): 92-96.

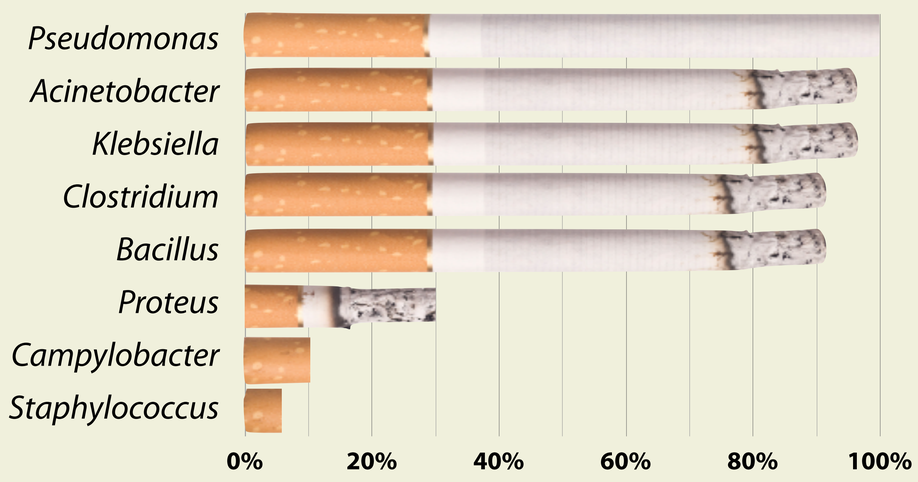


Human Immunodeficiency Virus (HIV)
Completely takes over the VDR
Source: J Mol Endocrinol. 2007;38(6):587-601

Early infections predispose a person to later disease

- *E. coli* food poisoning predisposes to hemolytic uremic syndrome.
- GI/respiratory infection predisposes to Guillain-Barré syndrome.
- Prenatal infection predisposes to schizophrenia.
- Infection with enteric pathogens predisposes to reactive arthritis.
- Infection with enteric pathogens predisposes to IBS.
- Common infections predisposes to stroke & other vascular events.
- SARS predisposes to mental health problems.
- Airborne infectious disease at birth predisposes to early mortality.
- Infant diarrhea predisposes to cardiovascular disease.
- Early childhood infections predispose to MS and Type I Diabetes.
- Perinatal herpes virus predisposes to chronic liver disease.
- *Streptococcus* and *Haemophillus* predisposes to asthma.
- Measles predisposes to secondary bacterial infections.

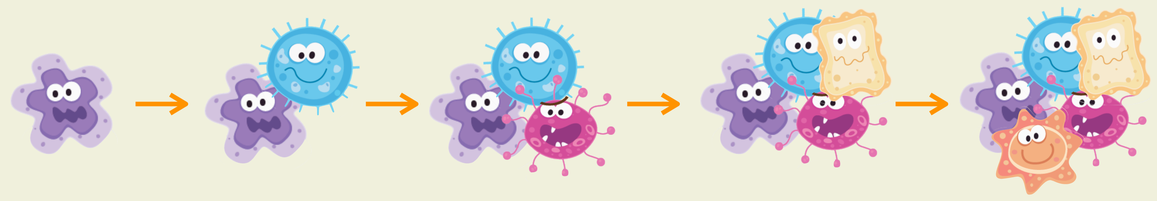
Microbes are everywhere – select bacterial genera detected in commonly smoked cigarettes



Source: Environ Health Perspect. 2010 Mar;118(3):351-6.

PMIDs: 8008534, 8498807, 16469941, 12787523, 19901154, 12787523, 20008700, 12714552, 11281409, 16604192, 15508102, 17928596, 3098977

Executive summary



Multiple reports of symptom exacerbation on immunostimulatory treatment for autoimmune disease

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Over the past seven years, we have been observing patients with autoimmune diagnoses use the VDR-agonist olmesartan to stimulate components of the innate immune response. Nearly all of the hundreds of patient reported outcomes describe an initial increase in symptoms specific to their autoimmune diagnoses. Additionally, patients consistently report fluctuations in objective markers of inflammation such as CRP, ACE, BUN, creatinine, and markers of liver function. After months of dealing with these fluctuations in disease state, symptomatic improvements begin to be reported, in some cases with objective markers indicating disease stabilization or remission. These symptomatic flares cannot easily be attributed to adverse events from olmesartan, as the drug is well known and unremarkable. Additionally, when healthy individuals have been administered the same medications, they suffer no similar symptoms. The most viable hypothesis for these symptomatic flares is that, by activating the innate immune system, olmesartan allows the body to mount an effective attack against pathogenic components of the microbiota. For a century, researchers have noted that death of acute and persistent pathogens is accompanied by a surge in inflammation, endotoxin, and cytokine release. Known as Jarisch-Herxheimer, or immunopathology, this phenomenon has been demonstrated in numerous diseases. Olmesartan seems to be generating immunopathology. These preliminary results also indicate immunopathology may be a necessary part of reducing the metagenomic load in patients with autoimmune diagnoses.

Changes in Antibodies

Female, 49, Hashimoto's Thyroiditis

Date	Peroxidase	
Sept. 2004	200 IU/ml	Begins Protocol
July 2005	217 IU/ml	
Oct. 2005	51 IU/ml	

Female, 55, Hashimoto's Thyroiditis

Date	Thyroglobulin	
Nov. 2004	>1,000	Diagnosis
Feb. 2006	2,000	Begins Protocol
Jan. 2009	232	

Female, 58, Rheumatoid Arthritis

Date	ANA titer	
Aug. 2004	1:160	Begins Protocol
Mar. 2005	1:320	
Aug. 2005	1:160	
Nov. 2006	negative	
8 subsequent tests also negative		

Changes in Other Markers of Inflammation

Male, 56, Sarcoidosis

Upon starting the treatment in December 2005, this patient's renal function began to decline and reach the upper limit of normal - BUN 20mg/dL, GFR >60ml/min/1.73m^2, CR 1.3mg/dL. As he managed immunopathology over the next two years, his kidney function continued to steadily decline. In October 2007, his kidney function had reached its lowest point - BUN 29mg/dL, GFR 42ml/min/1.73m^2, CR 1.8mg/dL. Yet the patient continued the Protocol, and since October 2007 has shown a steady improvement in renal function. In August 2008, BUN was 17mg/dL, GFR 52ml/min/1.73m^2, and CR 1.5mg/dL. He is now 95% free of his previous symptoms and no longer takes oral or inhaled steroids. We hypothesize his rise in BUN, etc. corresponded to a period of high bacterial death and increased inflammation that subsequently subsided as pathogens were killed. Indeed, doctors who have allowed patients to continue the Protocol despite fluctuations in blood work generally find that patients remain unharmed and that markers eventually fall back into a permanently healthy range.

Female, 46, CFS and Fibromyalgia

This patient experienced steady immunopathology from treatment start During her third year of the treatment, she experienced a rise in liver enzymes lasting approximately four months: ALT reached a peak of 202 IU/L, while AST reached 270 IU/L. However these measures normalized in the following months. Currently, at 38 months on the Protocol, her chronic headaches have disappeared and she no longer suffers from asthma, frequent viral gastrointestinal illnesses and recurrent bouts of pneumonia and bronchitis. Her cognitive abilities, pain and fatigue have improved dramatically.

Safety Profile of Olmesartan

- In placebo-controlled trials, the only side effect that occurred in >1% of olmesartan-treated patients vs. placebo-treated patients was dizziness (3% vs. 1%).
- Frequency of adverse events is not dose related.
- Olmesartan, with or without hydrochlorothiazide, was well tolerated over two years of treatment.

Source: Clin Ther. 2004;26 Suppl A:A28-32.

- Olmesartan has no clinically significant effects on laboratory parameters.

Source: J Hum Hypertens. 2002;16 Suppl 2:S13-6.

- CS-866 [olmesartan] was safe and well tolerated at doses of up to 160 mg/day…. [Olmesartan] has no serious adverse effects.

Source: J Clin Pharmacol. 2001;41:515-27.

Future Directions

This profound reaction occurs in ~98% of patients with chronic disease. Help us characterize how this treatment affects microbial populations.