

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

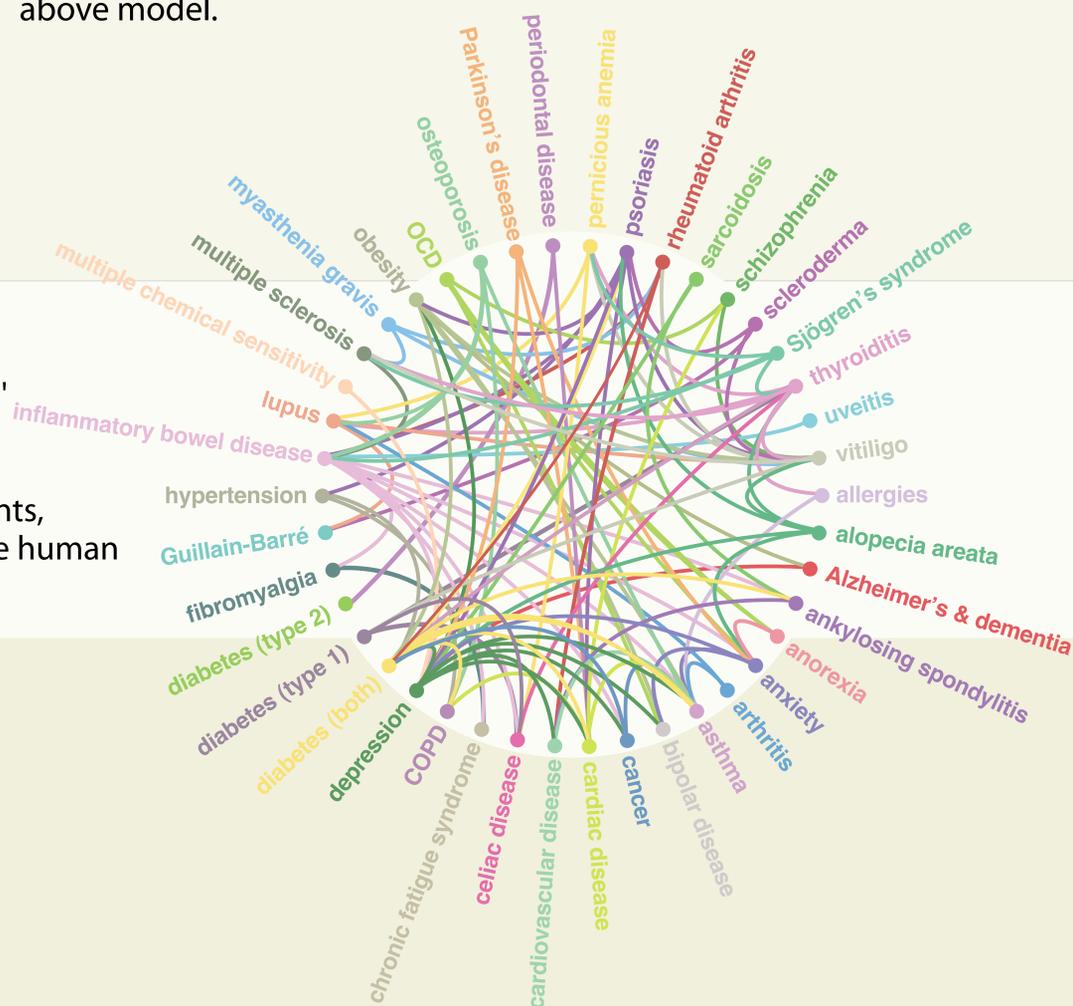
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Recent studies have demonstrated that persistent microbial species such as Mtb, Borrelia, CMV, HIV, and EBV are able to suppress expression of TACO, TLR-2, and key endogenous antimicrobials such as cathelicidin and the beta-Defensins by dysregulating 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-activate 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.



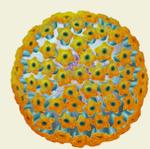
## Microbes downregulate expression of the VDR nuclear receptor



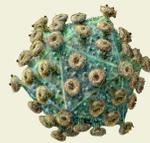
***Mycobacterium tuberculosis***  
Downregulates the VDR 3.3-fold  
Source: Chin Med J (Engl). 2003;116:1070-3.



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

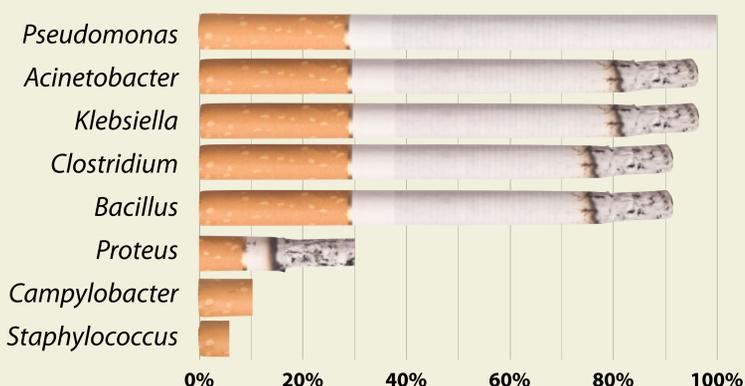


**Epstein Barr Virus (EBV)**  
Downregulates the VDR 32-fold in some B cells  
Source: Experimental Oncology. 2009; 31(2): 92-96.



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

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



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

## 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 *Haemophilus* predisposes to asthma.
- Measles predisposes to secondary bacterial infections.

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## Executive summary

