Microbiome-induced proteome dysbiosis in autoimmune disease
So far we have heard a lot about ‘Personalized’ Medicine resulting from observation of the disease process…

I will focus on ‘Predictive’ and ‘Preventative’ Medicine – which can only result from an understanding
The 1000 Genomes Project is an international collaboration which has mapped the genomes of more than 2500 individuals and published studies of SNPs and other human genetic variations.
DNA contamination in the 1000 Genomes Project

Abstract

Background: *In silico* Biology is increasingly important and is of great value in the analysis of DNA data. While the problem of contamination is well recognised in experimental data, the corresponding problem of database corruption has received less attention.

Results: Mapping 50 billion next generation DNA sequences from the 1000 Genome Project against published genomes reveals many that are contaminating *Mycoplasma* but are not included in the reference human genome.
Man is a Superorganism

‘The Economist’, Aug 18, 2018

‘Man is a Superorganism’

The fetus lives in a sterile world, protected by its mother's gut and cover the surface of the environment it is born into. But it's time we in fact born dirty - bacteria where they begin to shape our immune system. Whether or this collection of gut is beneficial or harmful remains to be seen.
Eric Alm’s MIT group: “Ecology drives a global network of gene exchange.”
Helicobacter pylori is found in carotid Plaque (as is Porphyromonas gingivalis), and in peripheral blood. Dave Relman first reported microbial DNA in blood (.. and in amniotic fluid (2008)). Gut microbiome changes in fact seem to be a result of systemic immune dysfunction. The genomes accumulate gradually during life. Genes from the metagenome suppress innate immunity, and thus determine the clinical dysfunction, and the disease symptoms.
Columbia: TEM photograph taken of a monocyte from the vitreous of a sarcoidosis patient showing hundreds of tiny coccoids (in colonies) have parasitized this cell. The very phagocytes which are supposed to kill bacterial pathogens are providing safe haven for them.
Bacteria exposed to antibiotics rapidly develop mutations that allow them to develop resistance to the drugs, and this process is fairly understood. Scientists have now explained the evolution of bacterial resistance to infected agents: cells of the immune system called macrophages—immune system cells that engulf foreign elements like bacteria—are rapidly captured. The same E. coli mutant that evaded engulfment by one macrophage successfully evaded engulfment by another, suggesting that the resistance mechanism is common.

By Laasya Samhita | December 12, 2012

Published in *PLOS Pathogens*
Computational microscope

...how living cells respond and battle diseases
Molecular Mimicry

*Identical function*
Multiple Sclerosis, OND and controls

The Proteome

A result of the Interactome due to persistent infection within Nucleated cells.
The Proteome is huge.
12,788 cDNA Microarray was used to profile gene expression in U937 macrophages infected with *M. tuberculosis*.

“463 differentially expressed genes .. 97 unknown .. intracellular signaling, cytoskeletal rearrangement, apoptosis, transcriptional regulation, cell surface receptors, cell-mediated immunity as well as a variety of cellular metabolic pathways.”
Persistent EBV does not
regulate VDR more than 10-fold.

Note that the most pronounced effect
is in the immature lymphoblastoid cell
lines (LCL) after 1.5 years of exposure.

Species Known to act on VDR:
- Mycobacterium tuberculosis,
- Aspergillus fumigatus,
In order to survive inside human phagocytic cells, microbes have had to evolve to knock out the VDR, so that they don’t have to deal with the cell’s innate defenses. Homo sapiens, and only in Homo sapiens, one Nuclear Receptor expresses genes for TLR2, as well as the Cathelicidin antimicrobial peptides, all of which are essential to host defense.
Activates VDR

eg: Gliotoxin (Aspergillus)

VDR

RXR

Activated VDR

Translates genes

Reactivates Innate Immunity
Therapy NOT 'Personalized'

* MONOTHERAPY*

* NO OTHER DRUGS*

25-D held at < 12 ng/ml
Interactome inside phagocytic cells, causing dysfunction in cell metabolism which we know as 'autoimmune' disease.

Clinical collaborators have demonstrated proof of concept, with more than a decade of observational data from treating a variety of idiopathic diagnoses. The endpoint achieved is often reported as 'cure.' By preventing the intracellular microbiome from overcoming the host innate immunity, we can...
Question Time
How much disease is there among patients who not only have cancer, but also other diseases. So-called chronic diseases like diabetes, COPD, cardiovascular disease, arthritis, depression, and other conditions can greatly affect the type of care needed, the cure rate, and overall survival rate. Other diseases can also have a negative impact on cancer diagnosis and five-year survival rate. For example, among cancer the five-year survival rate among patients with one or two other chronic diseases is 64 percent, while it is 50 percent among patients with three or more diseases. This data is from the Central Denmark Region and was published in a special edition of a recent issue of the European Journal of Cancer.
Direct damage by pathogen

Host resistance mechanisms

Damage caused by immune response

‘Immunopathology’

Ruslan Medzhitov, “Host Defense Strategies”
Projected chronic disease in USA

49% of US adults, 133 million, have at least one chronic disease (2004)