Plenary: Gut Microbiome and Pre-Autoimmune Diseases - Functional Immunology in Clinical Practice

Jeffrey Bland, PhD, FACN, CNS

Gut Microbiome and Pre-Autoimmune Diseases

Functional Immunology in Clinical Practice

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Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK

Nathalie Conrad, PhD • Shivani Misra, PhD • Jan Y Verbakel, PhD • Prof Geert Verbeke, PhD •

Autoimmune diseases affect approximately one in ten individuals, and their burden continues to increase over time at varying rates across individual diseases. The socioeconomic, seasonal, and regional disparities observed among several autoimmune disorders in our study suggest environmental factors in disease pathogenesis. The inter-relations between autoimmune diseases are commensurate with shared pathogenetic mechanisms or predisposing factors, particularly among connective tissue diseases and among endocrine diseases.

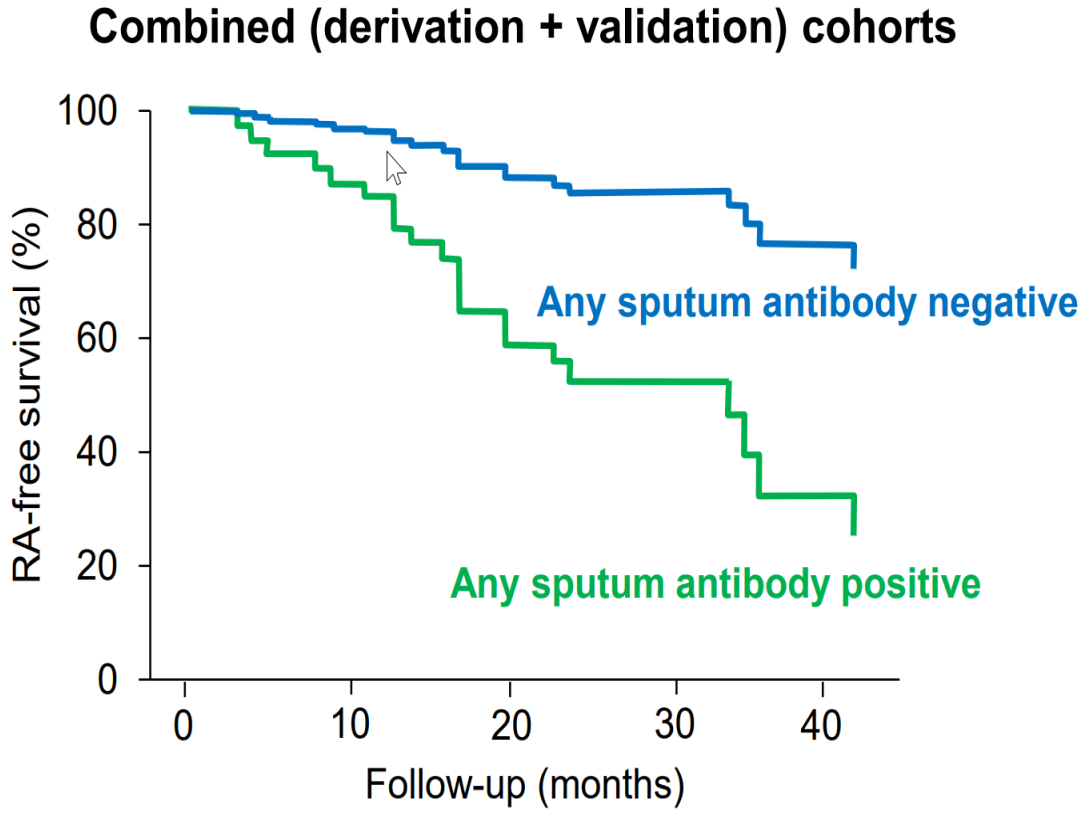
THE LANCET

VOLUME 401, ISSUE 10391, P1878-1890, JUNE 03, 2023

Sputum antibodies predict the development of rheumatoid arthritis

- Anti-CCP IgG+ individuals without inflammatory arthritis (IA) on physical examination (n=66)
  - Derivation (2013–2019, n=39) and validation (2019–2021, n=27) cohorts
  - Blood and saline-induced sputum samples were assessed for anti-CCP IgG and IgA and RF IgM and IgA
  - Patients were followed for ≥12 months and up to 5 years for the development of RA or IA
- 33% developed RA over a median of 17 months
  - Prevalence of any sputum antibody was 67% vs 20% in patients who did vs did not develop RA (combined cohort, P<0.001; sensitivity 67%; specificity 80%)
  - Strongest association was for anti-CCP IgA

Any sputum antibody+ (adjusted: sex, serum RF+)
HR 4.2 (95% CI: 1.7, 10.4), P=0.002



Sputum seropositivity may be associated with future RA in anti-CCP+ individuals without clinical arthritis

Food and Immune Function

Food: the tuberculosis vaccine we already have

Something marvellous occurred in the USA in the 20th century. Between 1900 and 1944, deaths from tuberculosis plummeted from about 200 people per 100 000 to approximately 50 people per 100 000 population.[1] There was no widely available treatment or vaccine for tuberculosis at the time. So why was tuberculosis in retreat? The force driving this trend is believed to be socioeconomic transformation—better living conditions, better public health action, and better nutrition.[2]

Improved nutrition probably played an outsized role as macronutrient and micronutrient deficiencies can blunt adaptive and innate immune responses and alter the inflammatory milieu, which leaves hosts vulnerable to *Mycobacterium tuberculosis* and its most severe consequences.[2] The sharp rise of tuberculosis incidence and mortality during the Dutch Hunger Winter (1944–45) was a potent reminder of the speed with which the onset of undernutrition can destabilise tuberculosis elimination efforts.[3] Conversely, British prisoners of war, who received supplemental rations rich in protein and calories, had much lower tuberculosis incidence and mortality rates than Russian prisoners.[4] A prospective cohort analysis from the USA has showed that a BMI of lower than 18·5 kg/m^2 is associated with a 12-fold increased risk of tuberculosis disease.[5] However, nutritional support, which had been the cornerstone of tuberculosis treatment in sanatoria became deprioritised after the results of the landmark Madras study in 1961, which showed that multidrug outpatient therapy was effective in treating tuberculosis.[6] The discourse on tuberculosis elimination has increasingly become restricted to the biomedical realm in the intervening decades.

Nutritional supplementation to prevent tuberculosis incidence in household contacts of patients with pulmonary tuberculosis in India (RATIONS): a field-based, open-label, cluster-randomised, controlled trial

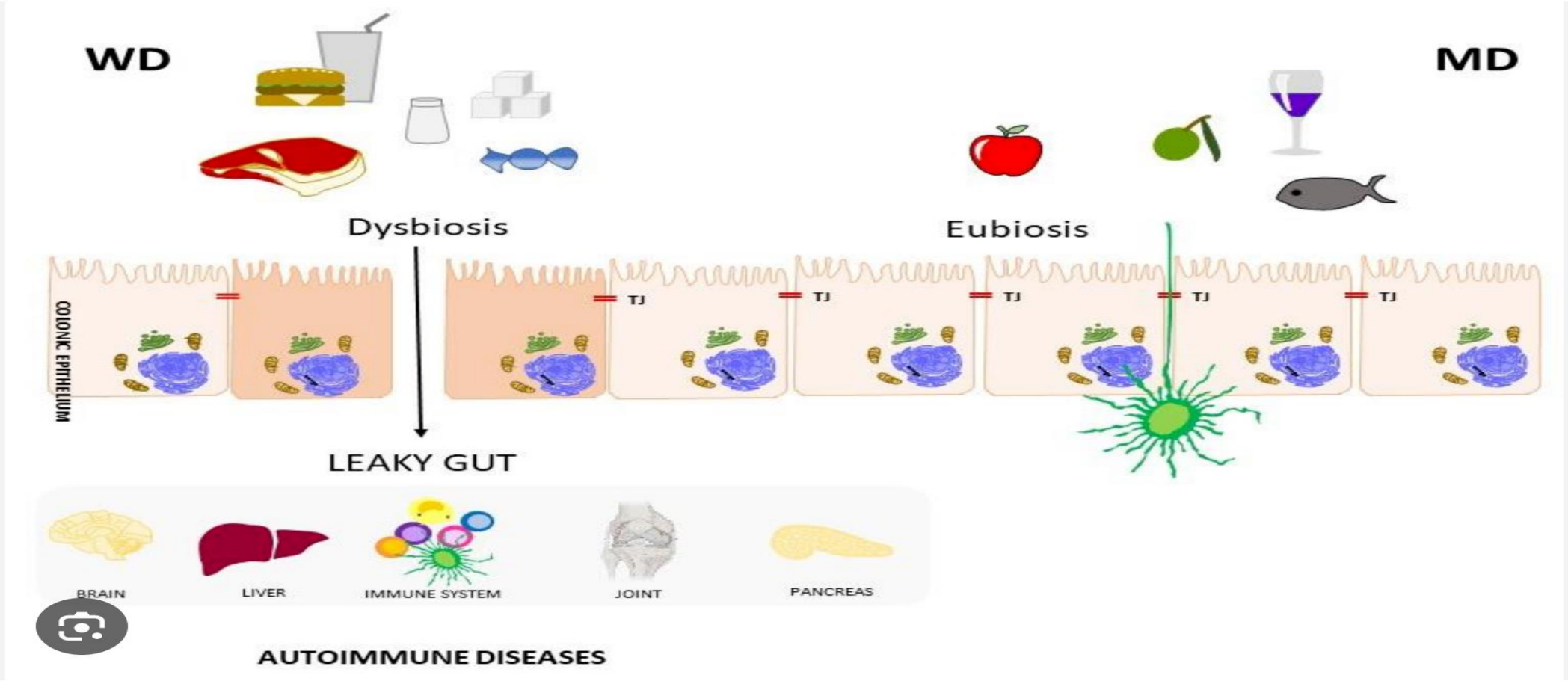
The RATIONS trial[9] makes a convincing argument that inexpensive nutritional interventions are an integral component of tuberculosis elimination efforts alongside drugs and vaccines. Food-based interventions will assuredly have positive externalities fa beyond tuberculosis. Malnutrition traps individuals in a state of poverty directly through reduction in physical productivity and increased health-care costs as well as indirectly through cognitive losses and missed schooling.[13] Thus, nutritional interventions reflect a holistic, human-centred approach that can help us reduce tuberculosis incidence along with inequity. Access to affordable and nutrient-replete food was the tuberculosis vaccine that drove massive reductions in tuberculosis incidence and associated mortality in countries such as the USA and UK at the turn of the 20th century. Bhargava and colleagues have shown its continued relevance in the 21st century.

Impact of Mediterranean Diet on Disease Activity and Gut Microbiota Composition of Rheumatoid Arthritis Patients

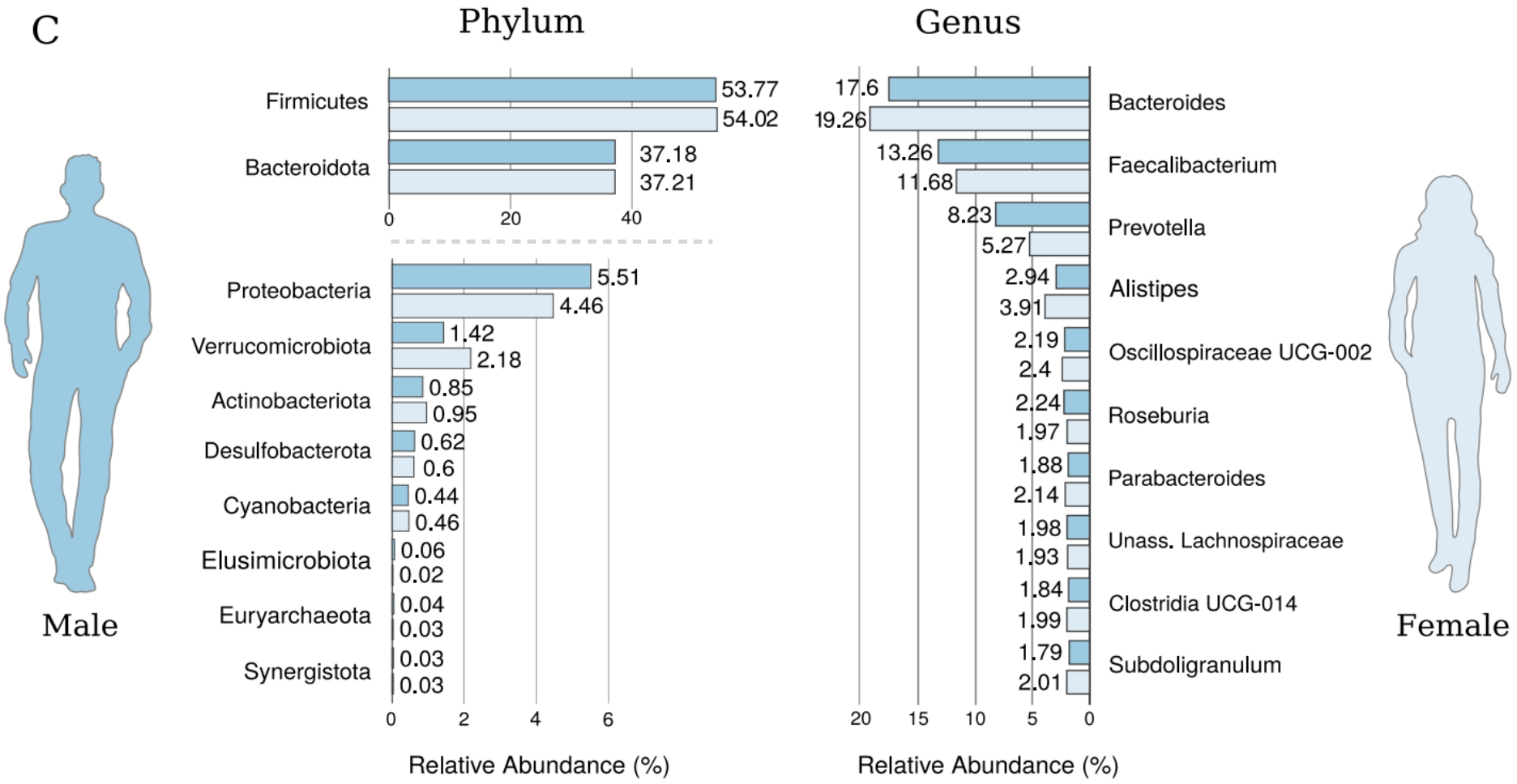
with contrasting results. We investigate the protective effect of the Mediterranean diet (MD) on disease a obiota profile in RA patients. Sixty consecutive RA patients were enrolled upon filling a validated 14-item questionnaire for the assessment of adherence to the Mediterranean diet (Prevention with Mediterranean Diet-PREDIMED). Then, 16S analysis was employed to explore the gut microbiota within the two cohorts of patients. Patients with high adherence to MD (20) had a significantly lower C-reactive protein ($p < 0.037$) and disease activity ($p < 0.034$) than the 40 patients with low/moderate adherence to MD. An inverse association between MD and disease activity was confirmed by multivariate analysis after adjustments for all the different demographic, clinical and serologic variables. A healthier gut microbiota composition was observed in the high adherence group, with a significant decrease in Lactobacillaceae and an almost complete absence of *Prevotella copri* with respect to the low/moderate adherence group. In conclusion, our findings support the protective role of MD on disease activity and microbiota composition in RA patients, and suggest the feasibility of shifting the habitual diet to modulate the gut microbiota and promote the benefits associated with MD.

Microorganisms **2020**, *8*, 1989;

Proposed Impact of Mediterranean Diet on Autoimmune Diseases



The Spanish gut microbiome reveals links between microorganisms and Mediterranean diet



Scientific Reports | (2021) 11:21602 | https://doi.org/10.1038/s41598-021-01002-1

Nutrients and Immune Function

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality

Wafaie W. Fawzi, M.B., B.S., Dr.P.H., Gernard I. Msamanga, M.D., Sc.D., Donna Spiegelman, Sc.D., Ruilan Wei, Ph.D., Saidi Kapiga, M.D., Sc.D., Eduardo Villamor, M.D., Dr.P.H., Davis Mwakagile, M.D., M.Med., Ferdinand Mugusi, M.D., M.Med., Ellen Hertzmark, M.A., Max Essex, D.V.M., Ph.D., and David J. Hunter, M.B., B.S., Sc.D.

RESULTS

Of 271 women who received multivitamins, 67 had progression to World Health Organization (WHO) stage 4 disease or died — the primary outcome — as compared with 83 of 267 women who received placebo (24.7 percent vs. 31.1 percent; relative risk, 0.71; 95 percent confidence interval, 0.51 to 0.98; P=0.04). This regimen was also associated with reductions in the relative risk of death related to the acquired immunodeficiency syndrome (0.73; 95 percent confidence interval, 0.51 to 1.04; P=0.09), progression to WHO stage 4 (0.50; 95 percent confidence interval, 0.28 to 0.90; P=0.02), or progression to stage 3 or higher (0.72; 95 percent confidence interval, 0.58 to 0.90; P=0.003). Multivitamins also resulted in significantly higher CD4+ and CD8+ cell counts and significantly lower viral loads. The effects of receiving vitamin A alone were smaller and for the most part not significantly different from those produced by placebo. Adding vitamin A to the multivitamin regimen reduced the benefit with regard to some of the end points examined.

CONCLUSIONS

Multivitamin supplements delay the progression of HIV disease and provide an effective, low-cost means of delaying the initiation of antiretroviral therapy in HIV-infected women.

Optimal Nutritional Status for a Well-Functioning Immune System Is an Important Factor to Protect against Viral Infections

Philip C. Calder [1], Anitra C. Carr [2], Adrian F. Gombart [3] and Manfred Eggersdorfer [4,*]

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Abstract: Public health practices including handwashing and vaccinations help reduce the spread and impact of infections. Nevertheless, the global burden of infection is high, and additional measures are necessary. Acute respiratory tract infections, for example, were responsible for approximately 2.38 million deaths worldwide in 2016. The role nutrition plays in supporting the immune system is well-established. A wealth of mechanistic and clinical data show that vitamins, including vitamins A, B_6, B_{12}, C, D, E, and folate; trace elements, including zinc, iron, selenium, magnesium, and copper; and the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid play important and complementary roles in supporting the immune system. Inadequate intake and status of these nutrients are widespread, leading to a decrease in resistance to infections and as a consequence an increase in disease burden. Against this background the following conclusions are made: (1) supplementation with the above micronutrients and omega-3 fatty acids is a safe, effective, and low-cost strategy to help support optimal immune function; (2) supplementation above the Recommended Dietary Allowance (RDA), but within recommended upper safety limits, for specific nutrients such as vitamins C and D is warranted; and (3) public health officials are encouraged to include nutritional strategies in their recommendations to improve public health.

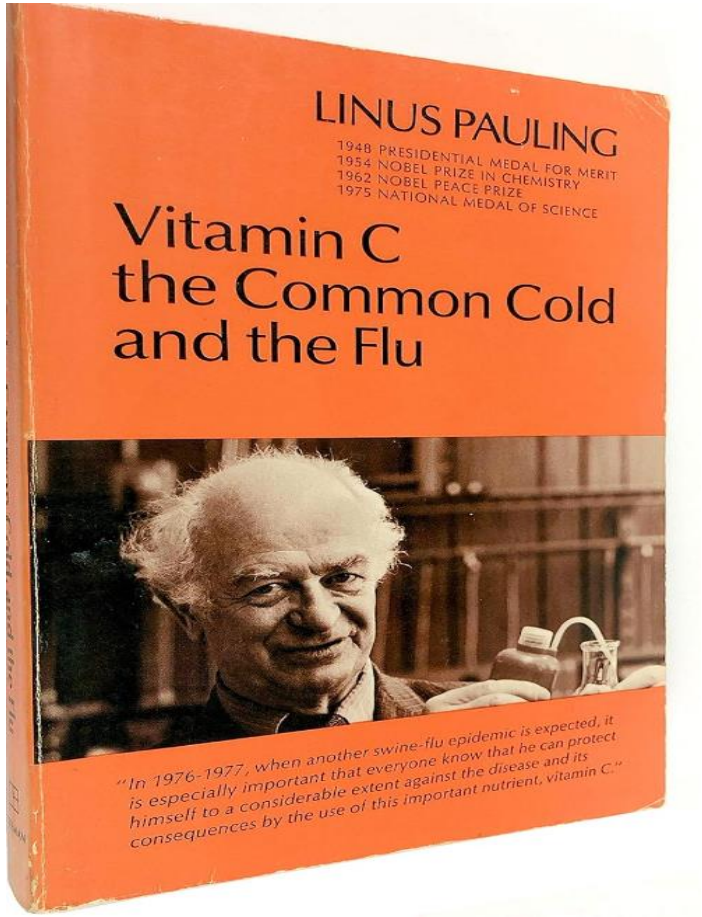
Nutrients **2020**, *12*, 1181;

The Role of Micronutrients in Support of the Immune Response against Viral Infections

Viral infections are a leading cause of morbidity and mortality worldwide, and the importance of public health practices including handwashing and vaccinations in reducing their spread is well established. Furthermore, it is well known that proper nutrition can help support optimal immune function, reducing the impact of infections. Several vitamins and trace elements play an important role in supporting the cells of the immune system, thus increasing the resistance to infections. Other nutrients, such as omega-3 fatty acids, help sustain optimal function of the immune system. The main aim of this manuscript is to discuss of the potential role of micronutrients supplementation in supporting immunity, particularly against respiratory virus infections. Literature analysis showed that in vitro and observational studies, and clinical trials, highlight the important role of vitamins A, C, and D, omega-3 fatty acids, and zinc in modulating the immune response. Supplementation with vitamins, omega 3 fatty acids and zinc appears to be a safe and low-cost way to support optimal function of the immune system, with the potential to reduce the risk and consequences of infection, including viral respiratory infections. Supplementation should be in addition to a healthy diet and fall within recommended upper safety limits set by scientific expert bodies. Therefore, implementing an optimal nutrition, with micronutrients and omega-3 fatty acids supplementation, might be a cost-effective, underestimated strategy to help reduce the burden of infectious diseases worldwide

Nutrients **2020**, *12*, 3198;

The Book that “Birthed” the Nutritional Supplement Industry



National Library of Medicine
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Vitamin C and the Common Cold

Studies on vitamin C

Go to:

Researchers from the Cochrane Collaboration – an international network of researchers – looked into the question of whether taking large doses of vitamin C can protect against colds or relieve the symptoms. To find out, they analyzed studies comparing vitamin C with a product that didn't contain any active ingredients (a placebo).

29 studies, involving more than 11,000 children and adults, tested whether the regular use of supplements containing at least 200 mg of Vitamin C prevented colds. Most of the studies tested a dose of 1,000 or more milligrams of vitamin C per day. Some of the participants took the vitamin C over a period of several years.

Research results

Go to:

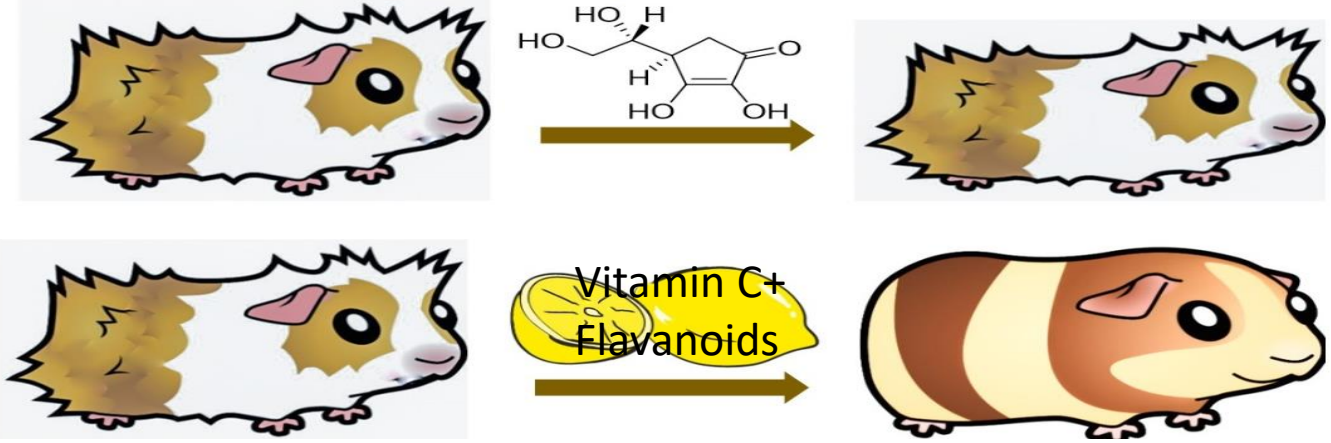
The studies showed that it wasn't possible to prevent colds by taking vitamin C every day over a longer period of time. But doing so did shorten the amount of time that people were ill by about 10 percent. In other words, a cold that would have lasted ten days was over in nine days. The cold symptoms were also a bit milder in people who always took vitamin C. These results have now been confirmed by other researchers as well, especially regarding use in children. It didn't shorten the length of colds in men and women who started taking it only after they became ill.

Some of the studies looked at whether vitamin C can prevent colds in people exposed to short periods of very strenuous physical activity, often in connection with extremely cold temperatures. Examples include marathon runners or soldiers doing winter exercises in a mountainous region.The study participants started taking vitamin C two to three weeks before the very strenuous activities, with the aim of preventing colds. It was found that doing so reduced their risk of developing a cold by about half.

Albert Szent-Gyrogyi
1937 Nobel Prize for Discovery of Vitamin C

The presence vital amines (vitamins) at the interface of chemistry and nutrition, proposed by Casimir Funk in the early 20th century, proved to be a useful paradigm by which to discover a host of dietary chemicals that were essential for human health. The initial investigation of Funk's proposed anti-scurvy factor by Axel Holst and Theodor Frölich followed by the Nobel prize winning work of Albert Szent-Györgyi is considered to a be a triumph of modern nutrition research. However, the studies undertaken by Szent-Györgyi, Joseph Svirbely, C. G. King and many others indicated the presence of another compound or compounds needed to accompany Vitamin C to completely remedy scurvy symptoms. Subsequent experimental evidence led to the proposal of vitamin P (permeability) as an essential phytochemical nutrient. In certain pathological conditions characterized by an increased permeability or fragility of the capillary wall, highly purified or synthetic ascorbic acid was ineffective for reducing the permeability, whereas the condition was readily cured by administration of extracts of Hungarian red pepper or lemon juice. However, attempts to isolate and characterize vitamin P gave confusing and sometimes irreproducible results, which today can be interpreted as rooted in the unrecognized chemical complexity of the scorbutic diets and tested anti-scorbutic preparations. As investigations continued, several flavonoids and a few coumarins were shown to have vitamin P activity. The historic inability to define a single compound and specific mode of action led to general skepticism about vitamin P. The reasonable conclusion is that several abundant and metabolically related plant constituents fill this essential role in human nutrition at the interface of human health, metabolism, and chemistry.

Vitamin P (ie. Permeability) was later identified as flavonoids that came along with Vitamin C (ie. Anti-scorbutic or Ascorbic Acid) in foods such as Paprika



Vitamin C+Flavonoids

frontiers in Public Health

SYSTEMATIC REVIEW
published: 16 February 2022
doi: 10.3389/fpubh.2022.814669

Flavonoids for Treating Viral Acute Respiratory Tract Infections: A Systematic Review and Meta-Analysis of 30 Randomized Controlled Trials

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Citation:

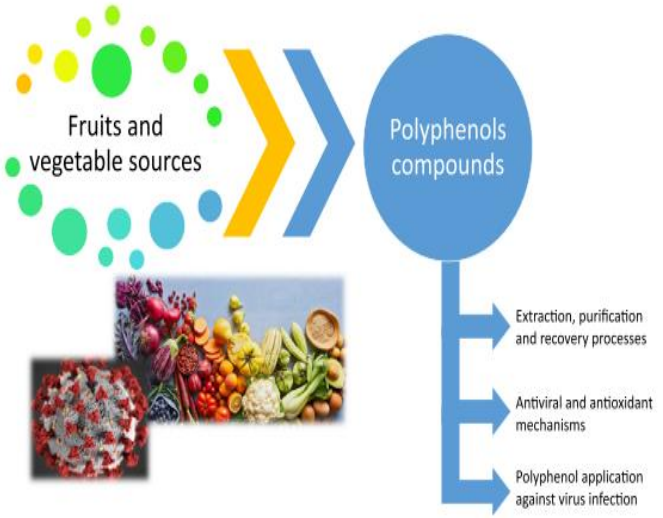
Background: This meta-analysis aimed to investigate the efficacy and safety of flavonoids in treating viral acute respiratory tract infections (ARTIs).

Methods: Randomized controlled trials (RCTs) were entered into meta-analyses performed separately for each indication. Efficacy analyses were based on changes in disease-specific symptom scores. Safety was analyzed based on the pooled data from all eligible trials, by comparing the incidence of adverse events between flavonoids and the control.

Results: In this study, thirty RCTs (n = 5,166) were included. In common cold, results showed that the flavonoids group decreased total cold intensity score (CIS), the sum of sum of symptom intensity differences (SSID) of CIS, and duration of inability to work vs. the control group. In influenza, the flavonoids group improved the visual analog scores for symptoms. In COVID−19, the flavonoids group decreased the time taken for alleviation of symptoms, time taken for SARS-CoV−2 RT-PCR clearance, the RT-PCR positive subjects at day 7, time to achievement of the normal status of symptoms, patients needed oxygen, patients hospitalized and requiring mechanical ventilation, patients in ICU, days of hospitalization, and mortality vs. the control group. In acute non-streptococcal tonsillopharyngitis, the flavonoids group decreased the tonsillitis severity score (TSS) on day 7. In acute rhinosinusitis, the flavonoids group decreased the sinusitis severity score (SSS) on day 7, days off work, and duration of illness. In acute bronchitis, the flavonoids group decreased the bronchitis severity score (BSS) on day 7, days off work, and duration of illness. In bronchial pneumonia, the flavonoids group decreased the time to symptoms disappearance, the level of interleukin−6

Polyphenols and their potential role to fight viral diseases: An overview

Fruits, vegetables, spices, and herbs are a potential source of phenolic acids and polyphenols. These compounds are known as natural by-products or secondary metabolites of plants, which are present in the daily diet and provide important benefits to the human body such as antioxidant, anti-inflammatory, anticancer, anti-allergic, antihypertensive and antiviral properties, among others. Plentiful evidence has been provided on the great potential of polyphenols against different viruses that cause widespread health problems. As a result, this review focuses on the potential antiviral properties of some polyphenols and their action mechanism against various types of viruses such as coronaviruses, influenza, herpes simplex, dengue fever, and rotavirus, among others. Also, it is important to highlight the relationship between antiviral and antioxidant activities that can contribute to the protection of cells and tissues of the human body. The wide variety of action mechanisms of antiviral agents, such as polyphenols, against viral infections could be applied as a treatment or prevention strategy; but at the same time, antiviral polyphenols could be used to produce natural antiviral drugs.



Science of the Total Environment 801 (2021) 149719

Microbiome and Immune Function

Influence of Microbiota on Vaccine Effectiveness: "Is the Microbiota the Key to Vaccine-induced Responses?"

Vaccines are one of the most powerful tools for preventing infectious diseases. To effectively fight pathogens, vaccines should induce potent and long-lasting immune responses that are specific to the pathogens. However, not all vaccines can induce effective immune responses, and the responses vary greatly among individuals and populations. Although several factors, such as age, host genetics, nutritional status, and region, affect the effectiveness of vaccines, increasing data have suggested that the gut microbiota is critically associated with vaccine-induced immune responses. In this review, I discuss how gut microbiota affects vaccine effectiveness based on the clinical and preclinical data, and summarize possible underlying mechanisms related to the adjuvant effects of microbiota. A better understanding of the link between vaccine-induced immune responses and the gut microbiota using high-throughput technology and sophisticated system vaccinology approaches could provide crucial insights for designing effective personalized preventive and therapeutic vaccination strategies.

J Microbiol. 2023; 61(5): 483–494.

Utilization of gut environment-mediated control system of host immunity in the development of vaccine adjuvants

Vaccination is one of the most powerful strategies for the preventive and therapeutic control of infectious diseases and other diseases such as cancer. To maximize the effectiveness of vaccines, it is necessary to modify the immune responses by means of adjuvants. The gut environment, including commensal bacteria and dietary components, has been proven to be able to mediate host immunity. An understanding of gut microbiota–related regulation of immune responses has revealed the potential adjuvanticity of particular microbiota-derived compounds, driving exploration into their development as vaccine adjuvants. In this review, we discuss how commensal bacteria and compounds derived from them regulate host immune responses, and we propose the potential application of these compounds as vaccine adjuvants.

Vaccine 40 (2022) 5399–5403

Elie Mechnikov, M.D.- Discovery of Innate Immunity

Ilya Ilyich Mechnikov, also spelled Élie Metchnikoff, was a Russian zoologist of Romanian noble ancestry best known for his pioneering research in immunology. He and Paul Ehrlich were jointly awarded the 1908 Nobel Prize in Physiology or Medicine "in recognition of their work on immunity".

THE PROLONGATION OF LIFE

OPTIMISTIC STUDIES

BY

ÉLIE METCHNIKOFF

SUB-DIRECTOR OF THE PASTEUR INSTITUTE, PARIS

THE ENGLISH TRANSLATION

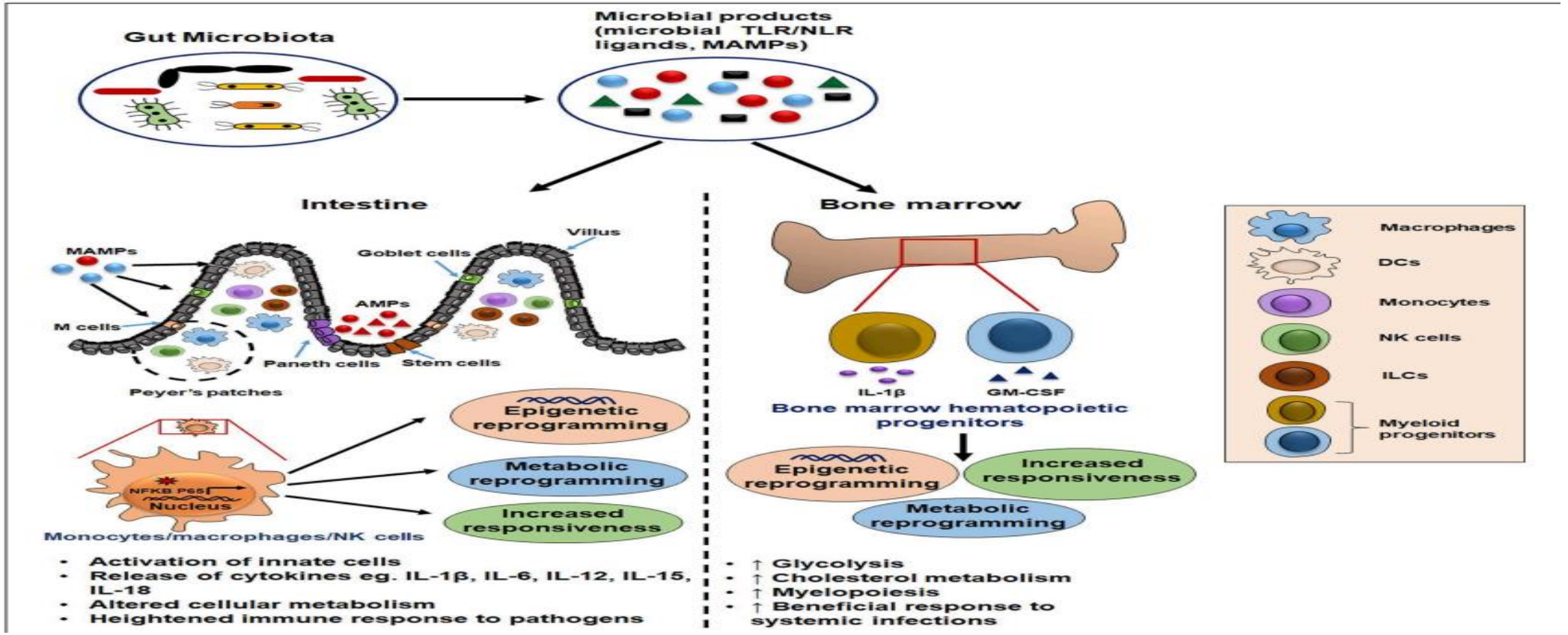
EDITED BY

P. CHALMERS MITCHELL

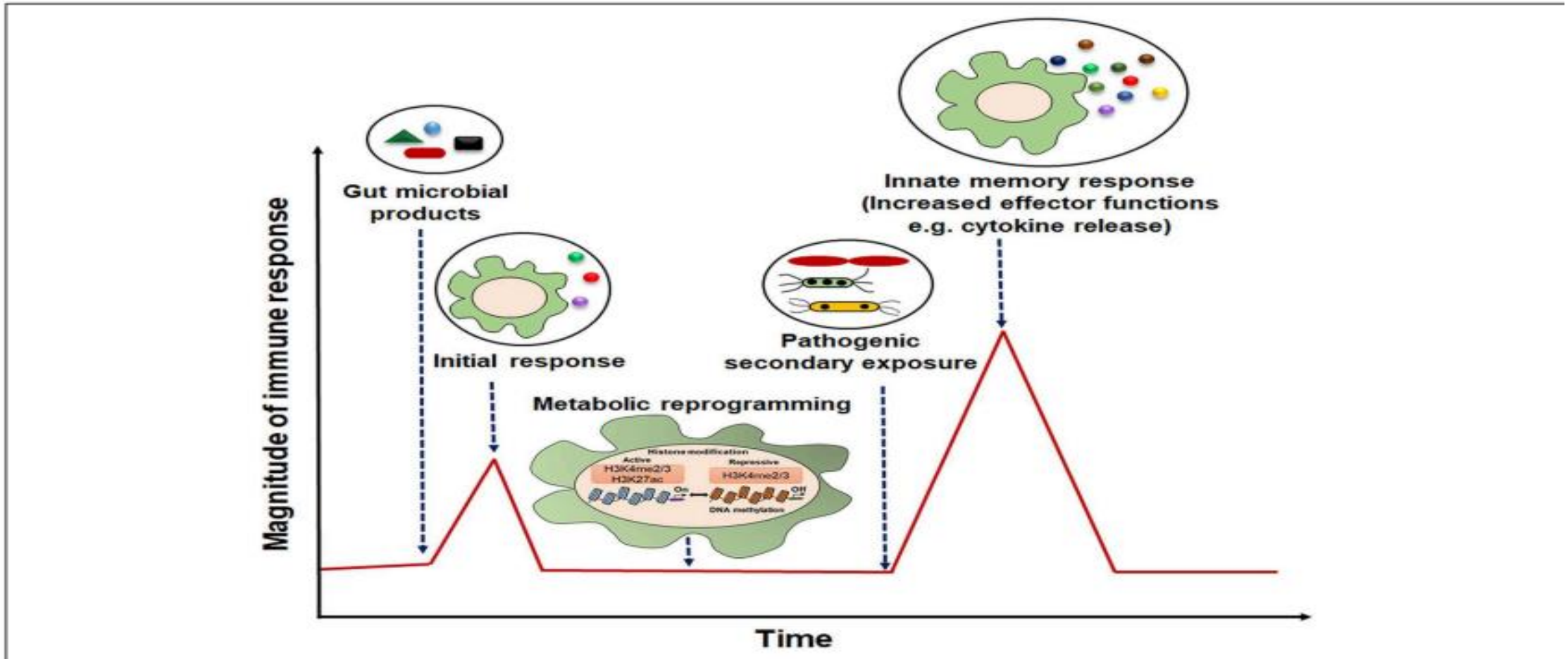
M.A., D.Sc. Oxon., Hon. LL.D., F.R.S.

Secretary of the Zoological Society of London; Corresponding Member of the Academy of Natural Sciences of Philadelphia

Potential Role of Gut Microbiota in Induction and Regulation of Innate Immune Memory



Chronobiology of Improved Innate Immune Function



Resetting tolerance in autoimmune disease

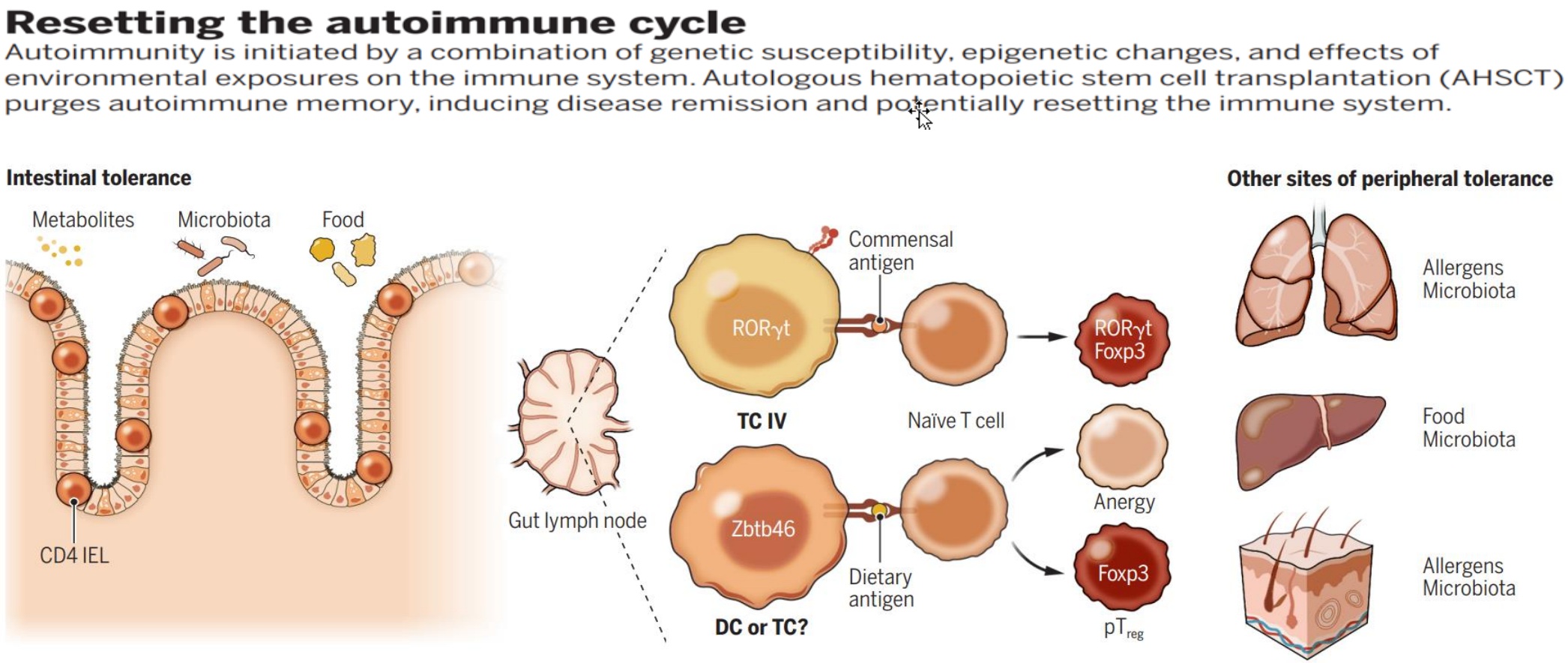


Fig. 1. The intestine as a model tissue for investigation of peripheral tolerance. Identification of the mechanisms underlying intestinal pT_{reg} generation in response to commensal and dietary antigens, including newly characterized tolerogenic APCs, provides a framework for investigation of peripheral tolerance at other tissue sites. Outside of the intestine, it is not clear whether distinct APCs and niche factors, including microbial products, regulate pT_{reg} differentiation, or whether commensal-specific T_{regs} within the skin, lung, and liver are also distinguished by expression of RORγt.

Epigenetics, Microbiome and Autoimmune Diseases

NIH National Institutes of Health
Office of Nutrition Research

Interactions Between Diet, the Gut Microbiome, and Epigenetics that Influence Health and Disease

Thursday, July 27, 2023 | 2:00 – 4:00 pm ET

Registration: https://scgcorp.zoom.us/webinar/register/WN_ekgzgEynQsmJy6H7YJN0-A

Registration for this virtual seminar is first-come, first-served until capacity is reached or through Tuesday, July 26, 2023. If you require reasonable accommodations to participate, please contact mdennis@scgcorp.com at least 10 days before the meeting to discuss your needs.

This virtual seminar will explore how dietary intake and metabolism by the gut microbiome can alter host epigenetics, potentially shaping phenotype and influencing health and disease. It is a collaboration between the Microbiome, Diet, and Health Interrelationships and Foundational Nutrition Science Implementation Working Groups. These workings groups, along with six other topic-based groups, are charged with assisting the NIH Office of Nutrition Research to implement the Strategic Plan for NIH Nutrition Research.

Moderator

Howard A. Young, PhD
Senior Investigator, Cancer Innovation Laboratory,
National Cancer Institute

Speakers

Regulation of Intestinal Health and Disease by Diet-Microbiota-Epigenetic Interactions
Theresa Alenghat, VMD, PhD
Associate Professor, UC Department of Pediatrics,
Cincinnati Children's Hospital Medical Center

Microbiome and Neurodegeneration: Deciphering Gut-Brain Crosstalk
Eva L. Feldman, MD, PhD
James W. Albers Distinguished University Professor,
Russell N. DeJong Professor of Neurology,
University of Michigan

Dietary Epigenetic Modifiers in Cardiovascular Disease: Where Do We Go from Here
Brad Ferguson, PhD
Associate Professor, Department of Nutrition,

Gut microbiota in pre-clinical rheumatoid arthritis: From pathogenesis to preventing progression

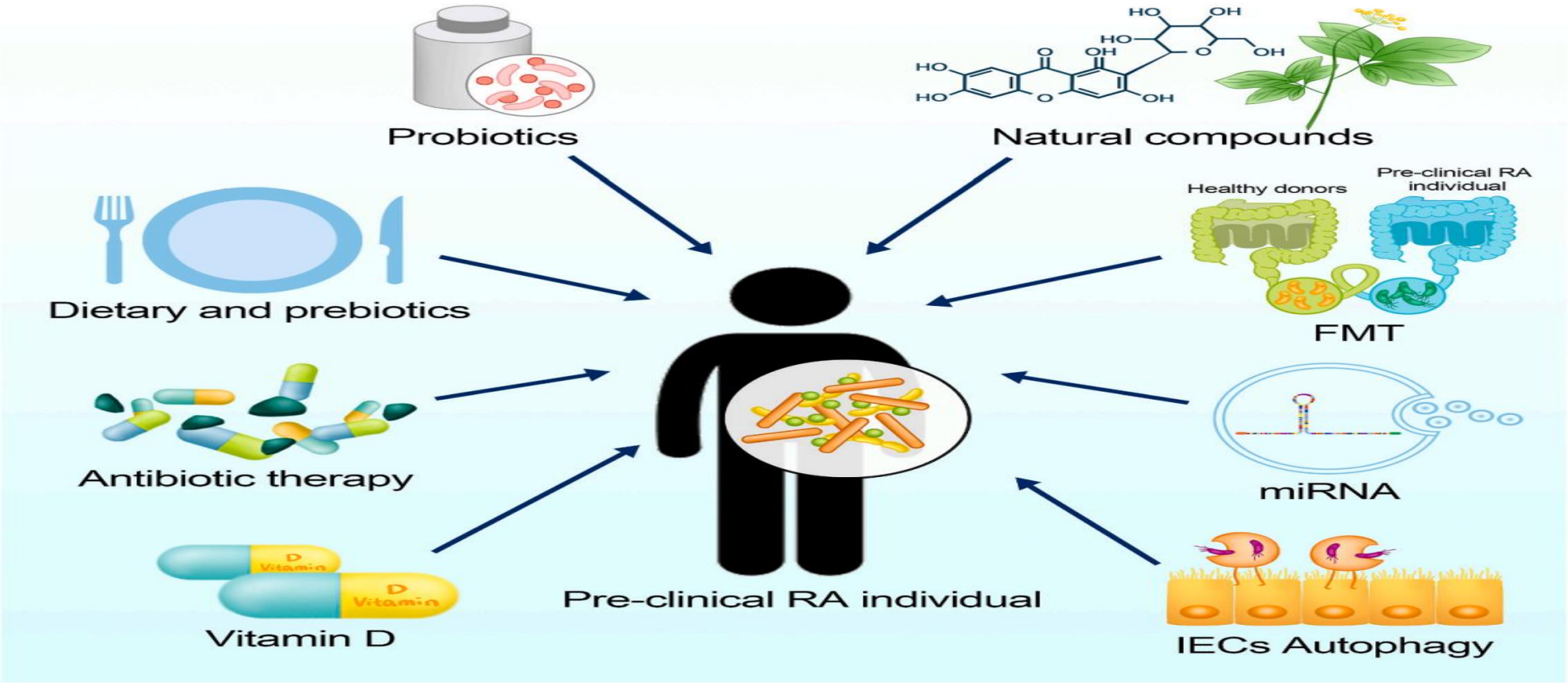


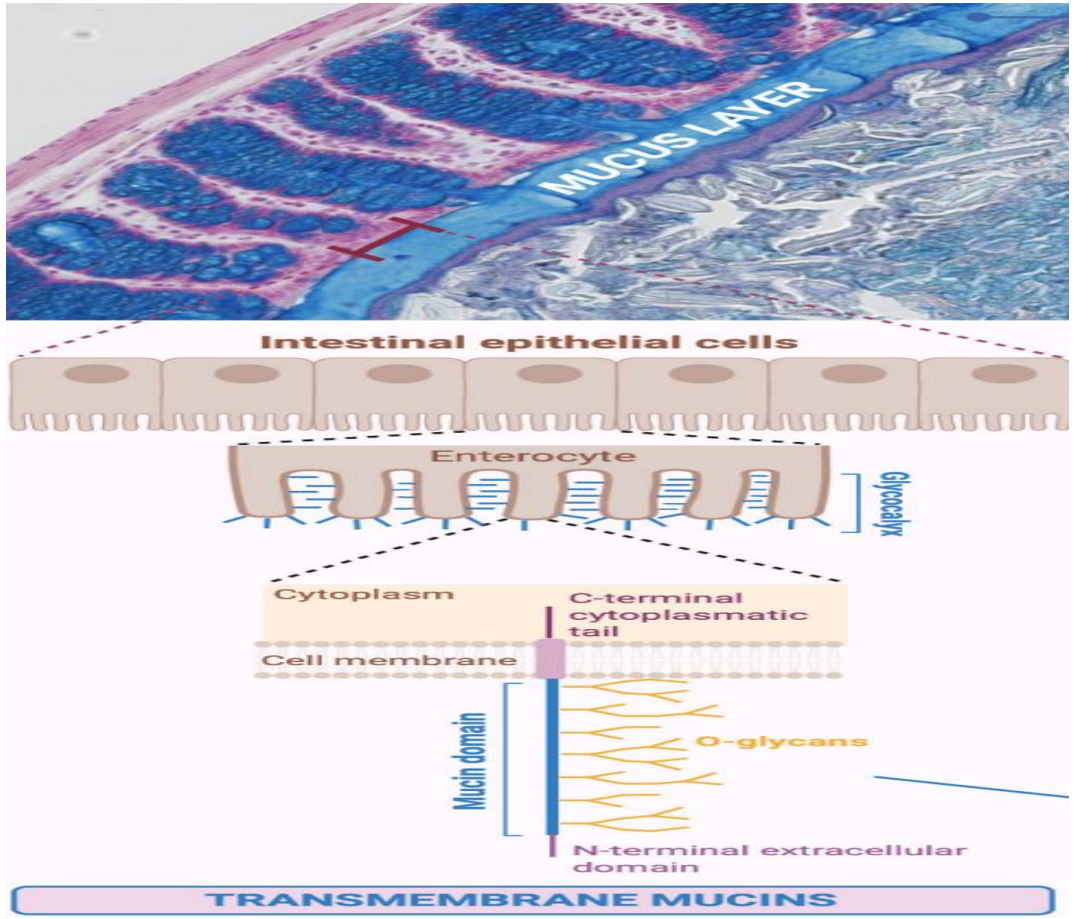
Fig. 2. Potential strategies for gut microbiota based intercention of individuals with pre-clincial RA.

Liyan Lin et al., *Journal of Autoimmunity*, https://doi.org/10.1016/j.jaut.2023.103001

Mucus barrier, mucins and gut microbiota: the expected slimy partners?

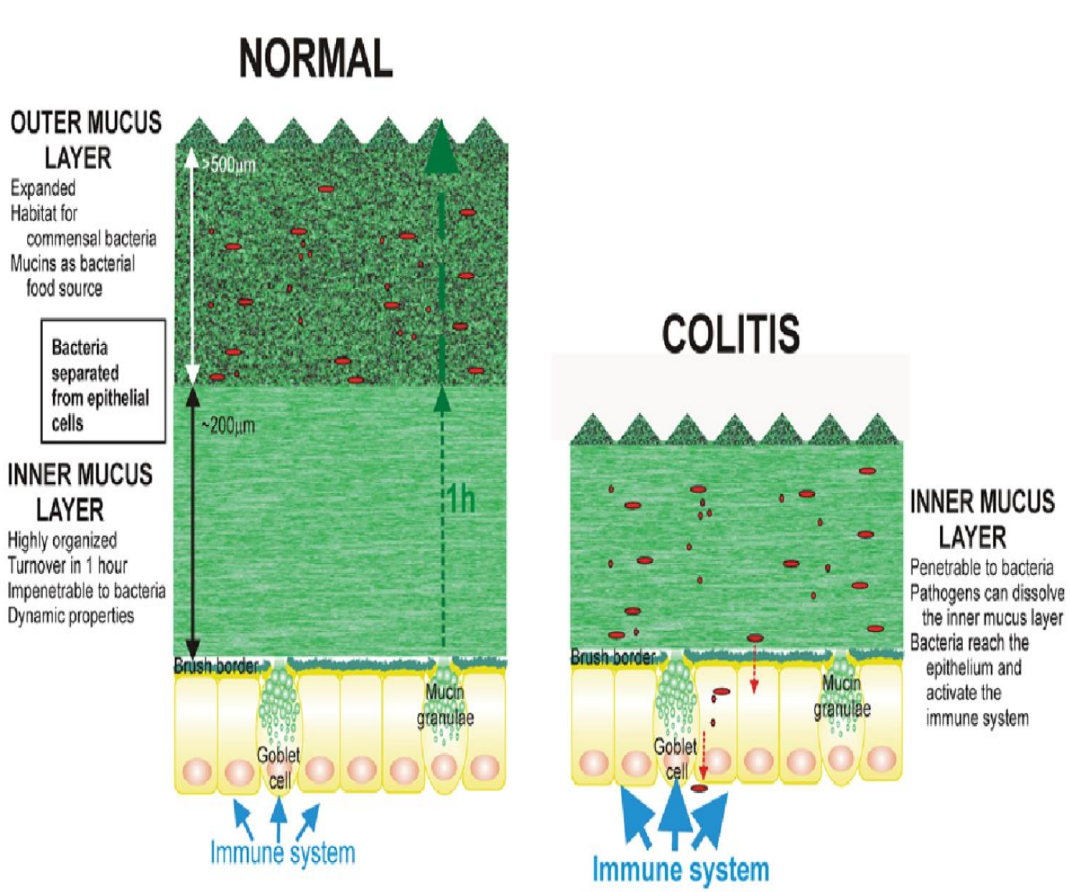
Key messages

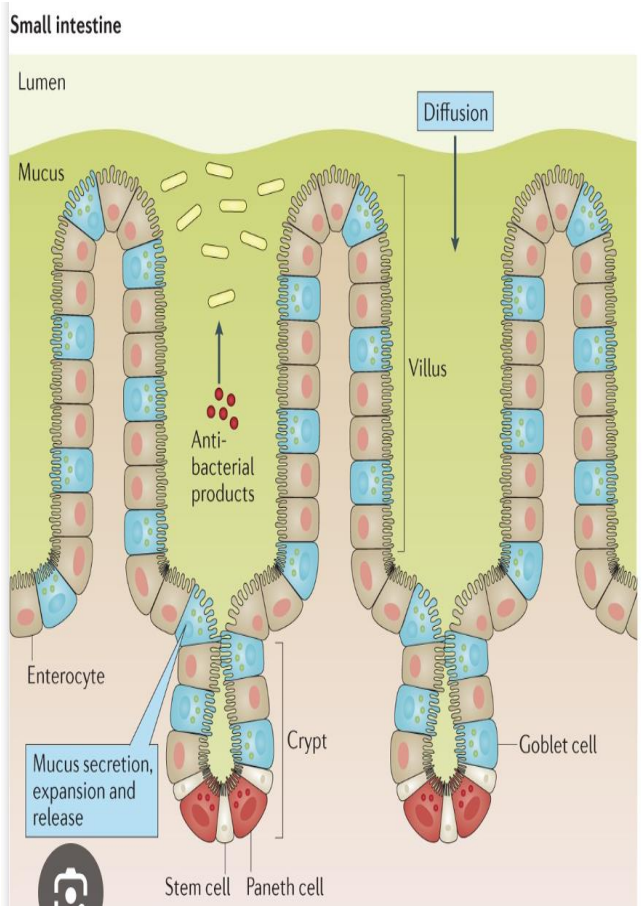
- The gut mucus layer is vital for maintaining intestinal health.
- The regulation of the intestinal mucus barrier and glycobiology are very complex and dynamic systems still poorly understood.
- There is a complex bidirectional interaction between host glycans and gut microbes.
- Gut microbiota composition is an important factor contributing to the regulation of the intestinal mucus barrier function.
- Specific nutrients or potential next-generation beneficial bacteria can be used to prevent, improve or maintain a protective mucus layer.

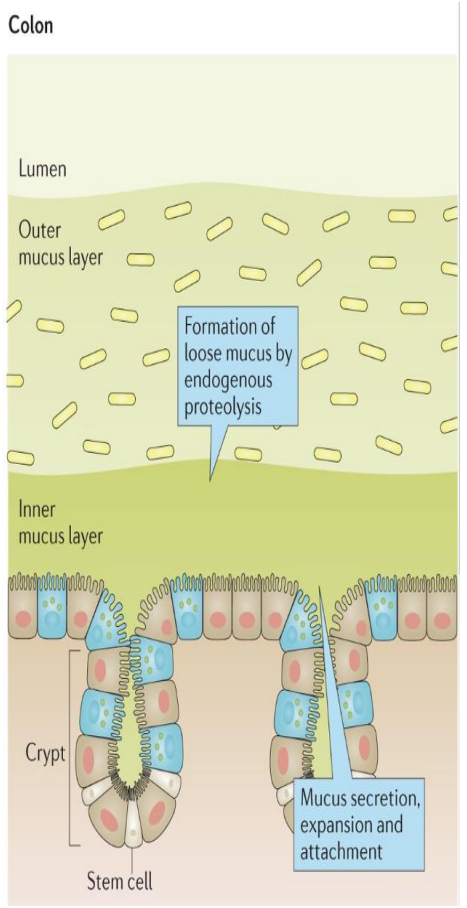


Paone P, Cani PD. *Gut* 2020;**69**:2232–2243. doi:10.1136/gutjnl-2020-322260

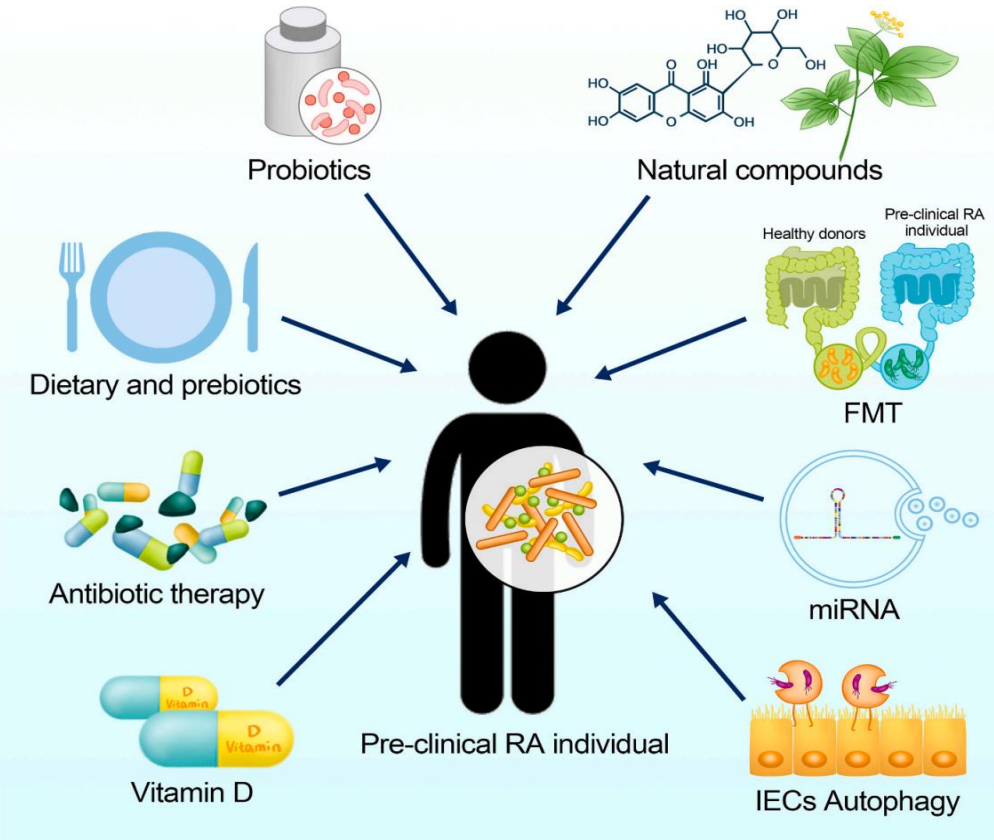
Mucin 1 and Mucin 2 Layers and Immune System Interrelationship







Gut microbiota in pre-clinical rheumatoid arthritis: From pathogenesis to preventing progression



Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by progressive polyarthritis that leads to cartilage and bone damage. Pre-clinical RA is a prolonged state before clinical arthritis and RA develop, in which autoantibodies (antibodies against citrullinated proteins, rheumatoid factors) can be present due to the breakdown of immunologic self-tolerance. As early treatment initiation before the onset of polyarthritis may achieve sustained remission, optimize clinical outcomes, and even prevent RA progression, the pre-clinical RA stage is showing the prospect to be the window of opportunity for RA treatment.

Growing evidence has shown the role of the gut microbiota in inducing systemic inflammation and polyarthritis via multiple mechanisms, which may involve molecular mimicry, impaired intestinal barrier function, gut microbiota-derived metabolites mediated immune regulation, modulation of the gut microbiota's effect on immune cells, intestinal epithelial cells autophagy, and the interaction between the microbiome and human leukocyte antigen alleles as well as microRNAs.

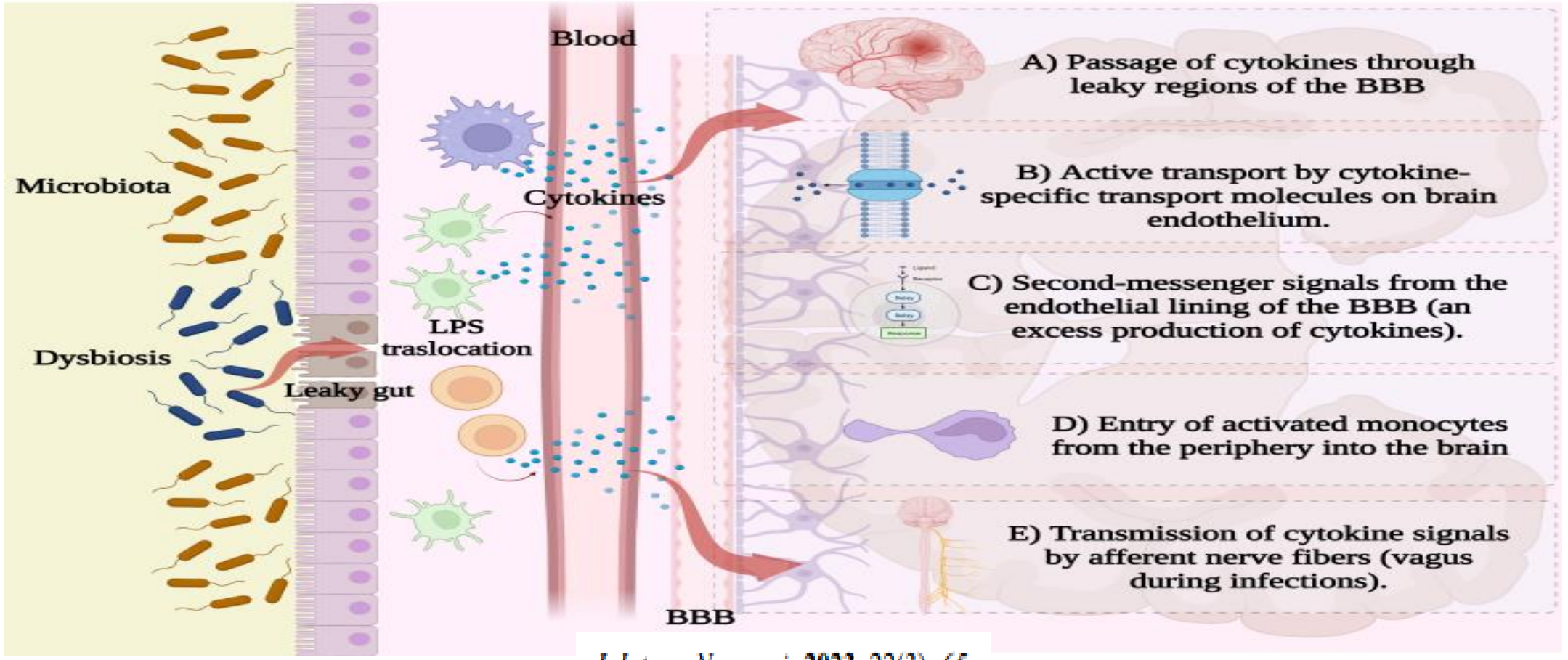
Journal of Autoimmunity

Liyan Lin et al., *Journal of Autoimmunity*, https://doi.org/10.1016/j.jaut.2023.103001

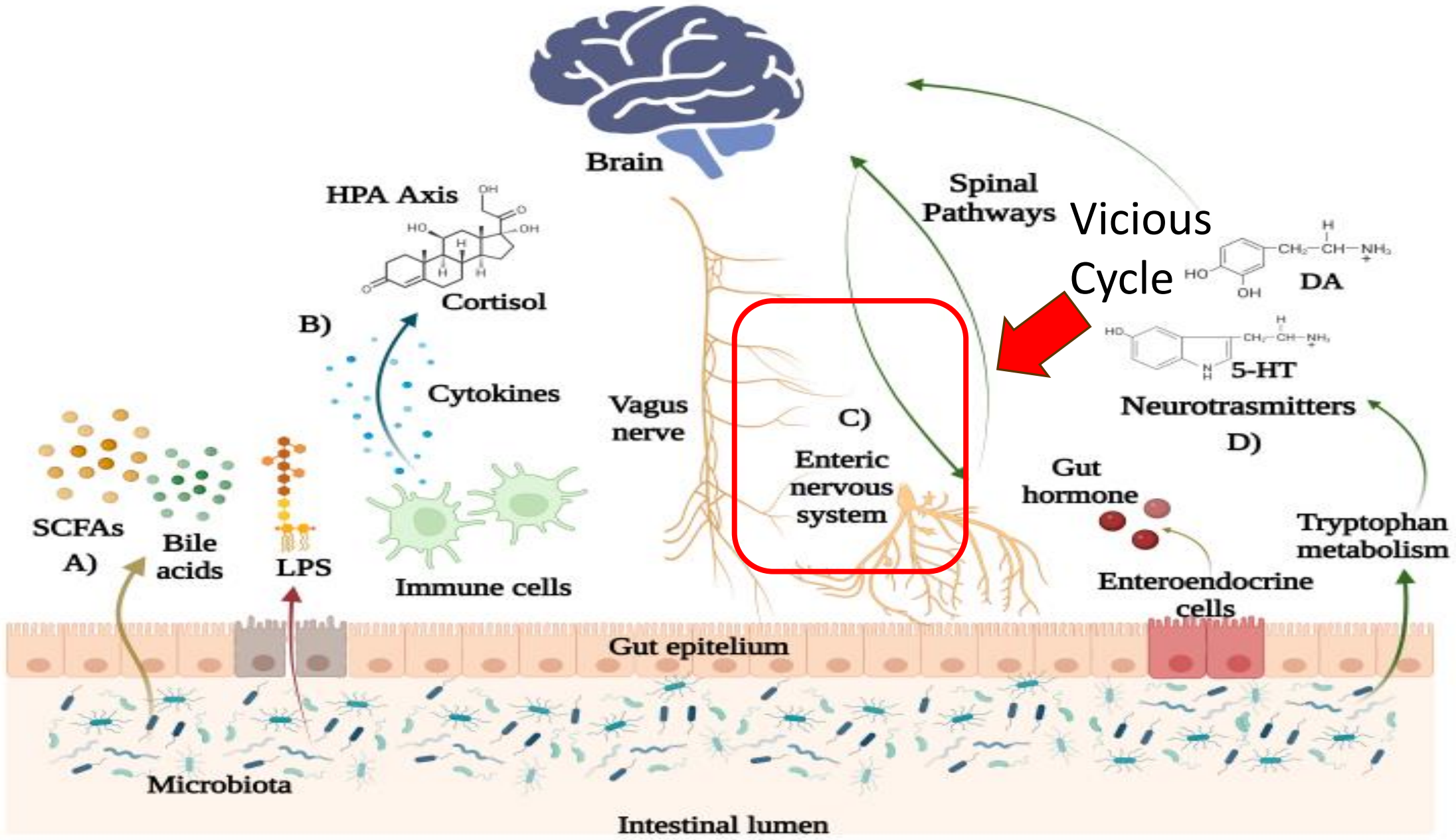
The Role of Neuro-Immune Interaction in Chronic Pain Conditions; Functional Somatic Syndrome, Neurogenic Inflammation, and Peripheral Neuropathy

Functional somatic syndromes are increasingly diagnosed in chronically ill patients presenting with an array of symptoms not attributed to physical ailments. Conditions such as chronic fatigue syndrome, fibromyalgia syndrome, or irritable bowel syndrome are common disorders that belong in this broad category. Such syndromes are characterised by the presence of one or multiple chronic symptoms including widespread musculoskeletal pain, fatigue, sleep disorders, and abdominal pain, amongst other issues. Symptoms are believed to relate to a complex interaction of biological and psychosocial factors, where a definite aetiology has not been established. Theories suggest causative pathways between the immune and nervous systems of affected individuals with several risk factors identified in patients presenting with one or more functional syndromes.

Neuroinflammation, Microbiota-Gut-Brain Axis, and Depression: The Vicious Circle



J. Integr. Neurosci. **2023**; 22(3): 65



J. Integr. Neurosci. **2023**; 22(3): 65

Association of Gut Microbial Genera with Heart Rate Variability in the General Japanese Population: The Iwaki Cross-Sectional Research Study

Abstract: The gut microbiota has become a significant factor associated with health and disease. Although many studies have reported the implications of changes in the gut microbiota on cardiovascular diseases, there are no reports on the relationship between heart rate variability (HRV) and the gut microbiota. Therefore, we investigated the association between gut microbiota abundance and HRV parameters in this cross-sectional study of the general Japanese population. This study included 950 participants of the Iwaki Health Promotion Project who underwent a medical examination in 2019 that included HRV and gut microbiota measurements. At the genus level, multivariate regression analysis showed that higher gut microbial diversity was associated with a higher standard deviation of RR intervals (SDNN). Moreover, a higher SDNN was associated with a higher relative count of *Lachnospiraceae incertae sedis*. *L. incertae sedis* abundance was associated with higher HRV parameters such as SDNN, coefficient of variation of RR intervals, low-frequency component power (LF)/high-frequency component power, and LF. In the general Japanese population, higher gut microbial diversity and *L. incertae sedis* abundance were associated with higher HRV parameters.

Metabolites **2022**, *12*, 730.

Association of Gut Microbial Genera with Heart Rate Variability in the General Japanese Population: The Iwaki Cross-Sectional Research Study

Table 4. Analysis of the association between HRV parameters and the Shannon index.

Characteristics	Univariate			Model 1			Model 2		
	β	95% CI	*p*-Value	β	95% CI	*p*-Value	β	95% CI	*p*-Value
SDNN (ms)	0.681	−2.931 to 4.293	0.711	3.542	0.142 to 6.942	0.041	3.934	0.444 to 7.424	0.027
CVRR (%)	−0.056	−0.458 to 0.346	0.786	0.302	−0.064 to 0.667	0.106	0.346	−0.030 to 0.721	0.071
LF (ms^2)	−38.512	−168.009 to 90.984	0.560	57.731	−67.340 to 182.803	0.365	63.993	−65.218 to 193.205	0.331
HF (ms^2)	3.120	−81.242 to 87.663	0.942	38.975	−44.438 to 122.388	0.359	50.440	−34.732 to 135.612	0.245
LF/HF	−0.014	−1.003 to 0.975	0.978	0.342	−0.647 to 1.331	0.498	0.346	−0.671 to 1.363	0.504
HR (bpm)	−2.232	−4.745 to 0.280	0.082	−1.608	−4.088 to 0.872	0.204	0.676	−4.132 to 0.876	0.202

Model 1: Adjusted for age, sex, and BMI. Model 2: Adjusted for age, sex, BMI, antidiabetic, antihyperlipidemic, antihypertensive, physical activity (non-winter and winter months), smoking, and alcohol consumption. Abbreviations: BMI, body mass index; CI, confidence interval; CVRR, coefficient of variation of RR intervals; HF, high-frequency component power; HR, heart rate; HRV, heart rate variability; LF, low-frequency component power; SDNN, standard deviation of RR intervals.

These results showed that a higher gut microbial diversity was associated with a higher SDNN after adjusting for age, sex, BMI, antidiabetic, antihyperlipidemic, antihypertensive, physical activity, smoking, and alcohol consumption.

Cardiac vagal activity is associated with gut-microbiome patterns in women—An exploratory pilot study

Introduction: A functional reciprocity between the gut microbiome and vagal nerve activity has been suggested, however, human studies addressing this phenomenon are limited.
Methods: Twenty-four-hour cardiac vagal activity (CVA) was assessed from 73 female participants (aged 24.5 ± 4.3 years). Additionally, stool samples were subjected to 16SrRNA gene analysis (V1–V2). Quantitative Insights Into Microbial Ecology (QIIME) was used to analyse microbiome data. Additionally, inflammatory parameters (such as CRP and IL-6) were derived from serum samples.
Results: Daytime CVA correlated significantly with gut microbiota diversity ($r_{sp} = 0.254$, $p = 0.030$), CRP ($r_{sp} = -0.348$, $p = 0.003$), and IL-6 ($r_{sp} = -0.320$, $p = 0.006$). When the group was divided at the median of 24 h CVA (Mdn = 1.322), the following features were more abundant in the high CVA group: *Clostridia* (Linear discriminant analysis effect size (LDA) = 4.195, $p = 0.029$), *Clostridiales* (LDA = 4.195, $p = 0.029$), *Lachnospira* (LDA = 3.489, $p = 0.004$), *Ruminococcaceae* (LDA = 4.073, $p = 0.010$), *Faecalibacterium* (LDA = 3.982, $p = 0.042$), *Lactobacillales* (LDA = 3.317, $p = 0.029$), *Bacilli* (LDA = 3.294, $p = 0.0350$), *Streptococcaceae* (LDA = 3.353, $p = 0.006$), *Streptococcus* (LDA = 3.332, $p = 0.011$). Based on Dirichlet multinomial mixtures two enterotypes could be detected, which differed significantly in CVA, age, BMI, CRP, IL-6, and diversity.
Conclusions: As an indicator of gut-brain communication, gut microbiome analysis could be extended by measurements of CVA to enhance our understanding of signalling *via* microbiota-gut-brain-axis and its alterations through psychobiotics.

DIALOGUES IN CLINICAL NEUROSCIENCE
2022, VOL. 24, NO. 1, 1–9

Immuno-Epigenetics

Hormesis defines the limits of lifespan

This commentary provides a novel synthesis of how biological systems adapt to a broad spectrum of environmental and age-related stresses that are underlying causes of numerous degenerative diseases and debilitating effects of aging. It proposes that the most fundamental, evolutionary-based integrative strategy to sustain and protect health is based on the concept of hormesis. This concept integrates anti-oxidant, anti-inflammatory and cellular repair responses at all levels of biological organization (i.e., cell, organ and organism) within the framework of biphasic dose responses that describe the quantitative limits of biological plasticity in all cells and organisms from bacteria and plants to humans. A major feature of the hormetic concept is that low levels of biological, chemical, physical and psychological stress upregulate adaptive responses that not only precondition, repair and restore normal functions to damaged tissues/organs but modestly overcompensate, reducing ongoing background damage, thereby enhancing health beyond that in control groups, lacking the low level "beneficial" stress. Higher doses of such stress often become counterproductive and eventually harmful.

Ageing Research Reviews 91 (2023) 102074

How does hormesis impact biology, toxicology, and medicine?

Edward J. Calabrese[1] and Mark P. Mattson[2,3]

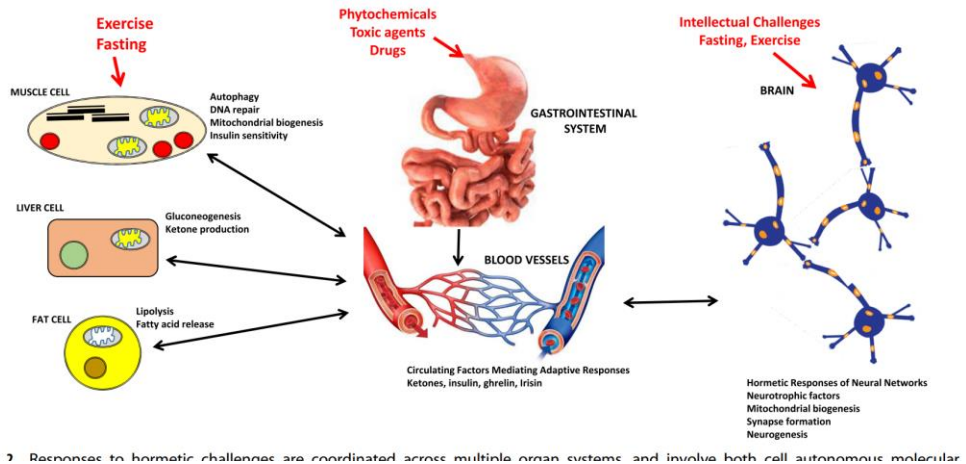
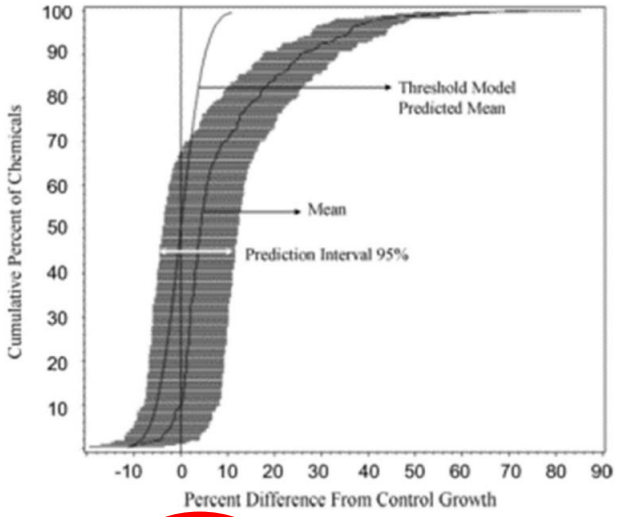


Fig. 2. Responses to hormetic challenges are coordinated across multiple organ systems, and involve both cell autonomous molecular



Hormesis

Published in partnership with the Japanese Society of Anti-Aging Medicine

The Hormesis-Epigenetic Connection

35th Annual
John R. Cameron Symposium

"Epigenetics and Human Health"

Professor Randy L. Jirtle, PhD

SEPT 18, 2023

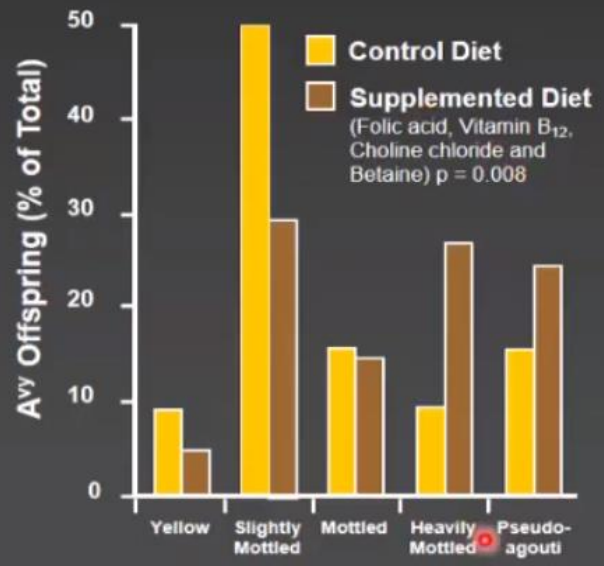
The Agouti Sisters

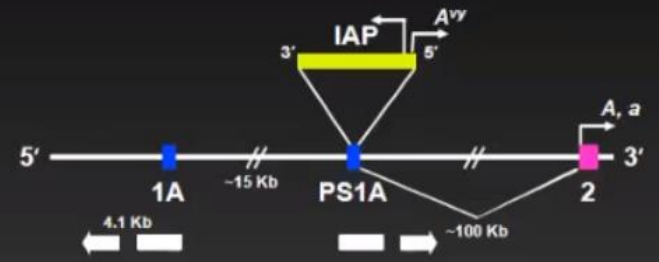
"For every problem in a given discipline of science, there exists a species ideal for its solution."

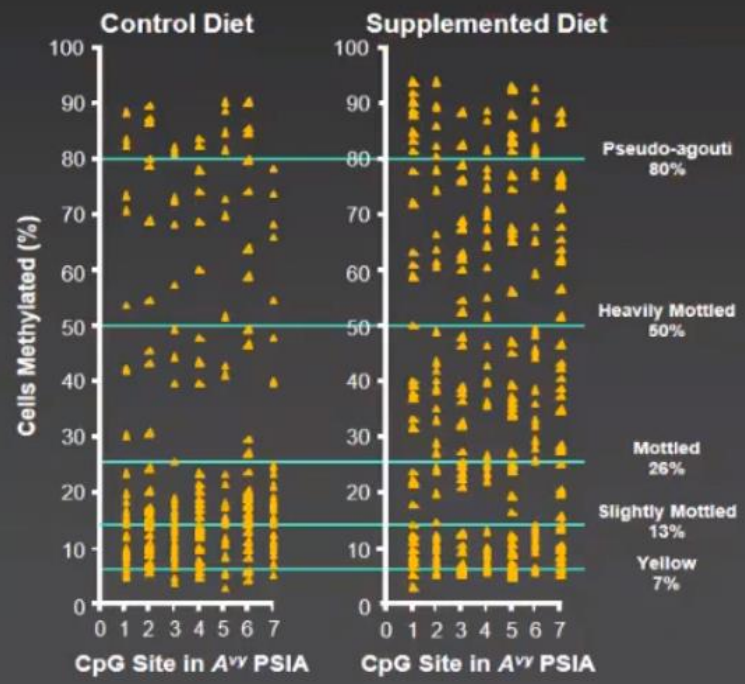
Edward O. Wilson (1929-2021)

Metastable Epiallele

Agouti Viable-yellow (A^{vy}) Locus







Waterland & Jirtle, *Mol. Cell Biol.* 23: 5293-5300, 2003

http://www.geneimprint.com

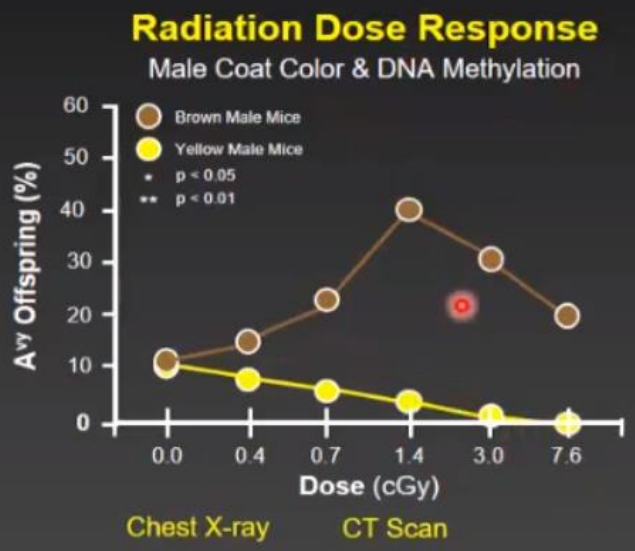
Environmental Epigenetic Studies

Viable yellow Agouti Mice

Waterland & Jirtle, Mol. Cell Biol. 23: 5293-5300, 2003
Dolinoy *et al.*, Environ Health Perspect 114: 567-572, 2006
Dolinoy *et al.*, *PNAS* 104: 13056-13061, 2007

Low Dose X-ray Exposure

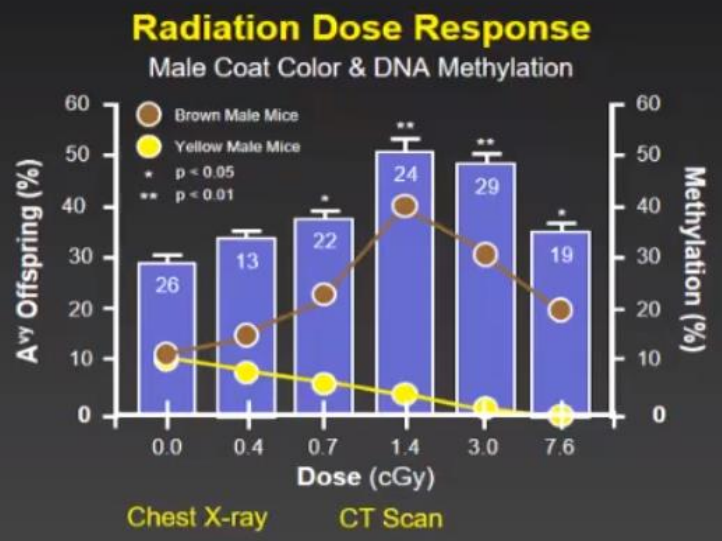
Viable Yellow Agouti Mice



Bernal *et al.* FASEB J: 27: 665-671, 2013

http://www.geneimprint.com

Low Dose X-ray Exposure
Viable Yellow Agouti Mice

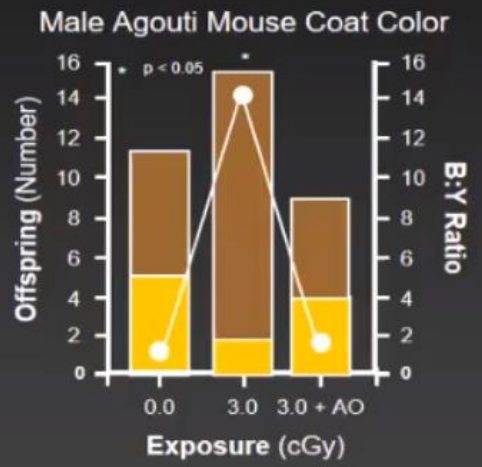


Offspring Coat Color

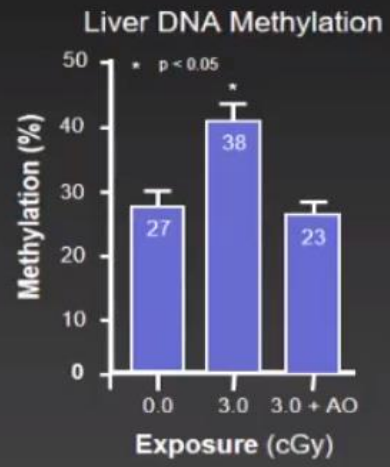
- Low doses of ionizing radiation increase the incidence of brown healthy offspring by enhancing DNA methylation.
- Thus, low doses of X-rays induce a ***positive*** adaptive response in the Avy offspring by altering the epigenome.
- Epigenetic modification of gene transcription is the "*unknown*" mechanism John Moulder referred to in his argument against the credibility of hormesis.

Bernal *et al.* FASEB J: 27: 665-671, 2013

X-ray Exposure
Antioxidant Supplementation



Antioxidant Supplementation
l-selenomethionine
Vitamin C
Vitamin E
Succinate
Alpha-lipoic acid
N-acetyl cysteine



- Antioxidants negate the increased DNA methylation and block the positive adaptive response induced by low doses of X-rays.
- The ***positive*** adaptive response induced by low doses of X-rays is mediated in part through oxidative stress.

Bernal *et al.* FASEB J: 27: 665-671, 2013

Neo-Rosetta Stone

Artist: *James Jirtle*

Future Objectives

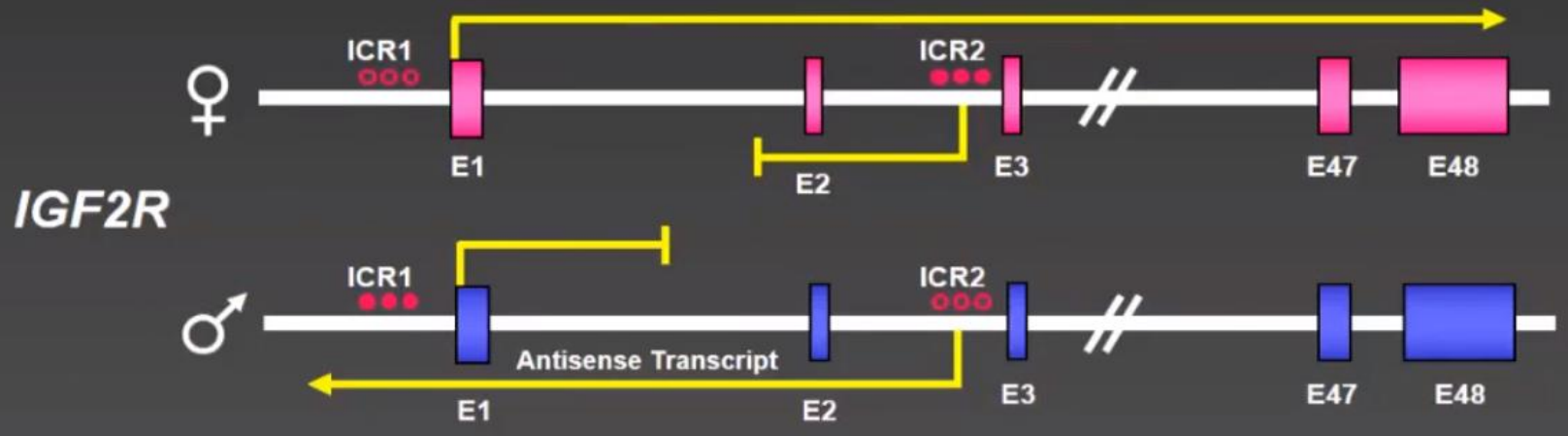
- Identify the complete repertoire of human imprinted genes and their epigenetically-controlled regulatory elements – *The Human Imprintome.*
- Determine whether radiation alters the imprintome in humans, and if so, whether these epigenetic effects are inherited transgenerationally.

Luedi *et al* . Genome Res. 17: 1723–1730, 2007
Skaar *et al* . ILAR J 53: 341-358, 2012
Jima *et al*. Epigenetics 17: 1920-1943, 2022

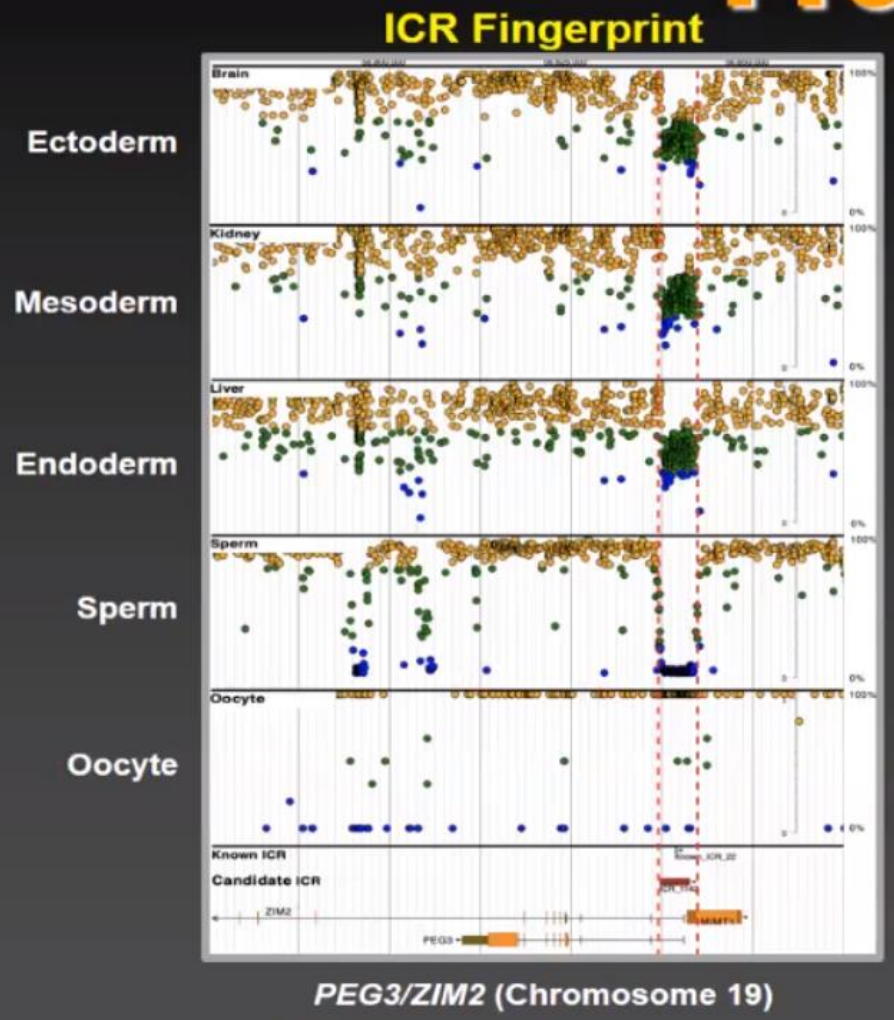
Imprinted Genes

Autosomal Genes with a Sex

Imprinting results in parent-of-origin dependent monoallelic expression.



Human Imprintome Characteristics



***PEG3/ZIM2* (Chromosome 19)**

- Genome-wide DNA methylation sequencing identified 1,488 ICRs in the human imprintome.
- ICRs range from 10 to ~ 4,000 bp with a median length of 248 bp.
- Parental origin of 332 ICRs have been determined, and 46% are maternally methylated (i.e. paternally expressed genes).

ICR= Imprint Control Region

Murphy *et al* Genomics. 71: 110-117, 2001.
Skaar *et al* . ILAR J 53: 341-358, 2012
Jima *et al*. Epigenetics 17: 1920-1943, 2022

Transposable Elements: Targets for Early Nutritional Effects on Epigenetic Gene Regulation

Robert A. Waterland and Randy L. Jirtle*

Early nutrition affects adult metabolism in humans and other mammals, potentially via persistent alterations in DNA methylation. With viable yellow agouti (A^{vy}) mice, which harbor a transposable element in the *agouti* gene, we tested the hypothesis that the metastable methylation status of specific transposable element insertion sites renders them epigenetically labile to early methyl donor nutrition. Our results show that dietary methyl supplementation of *a/a* dams with extra folic acid, vitamin B_{12}, choline, and betaine alter the phenotype of their A^{vy}/a offspring via increased CpG methylation at the A^{vy} locus and that the epigenetic metastability which confers this lability is due to the A^{vy} transposable element.

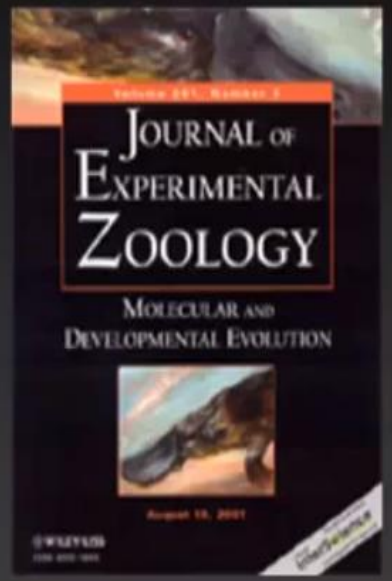
MOLECULAR AND CELLULAR BIOLOGY, Aug. 2003, p. 5293–5300

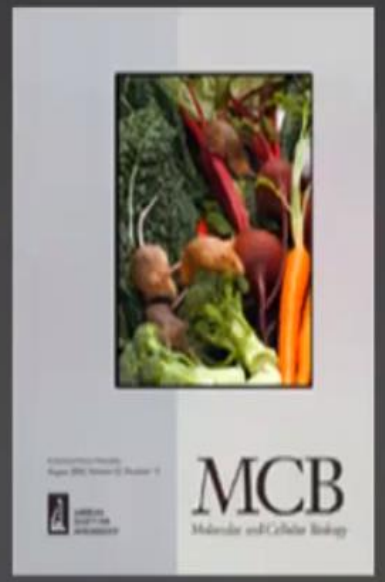
Genomic map of candidate human imprint control regions: the imprintome

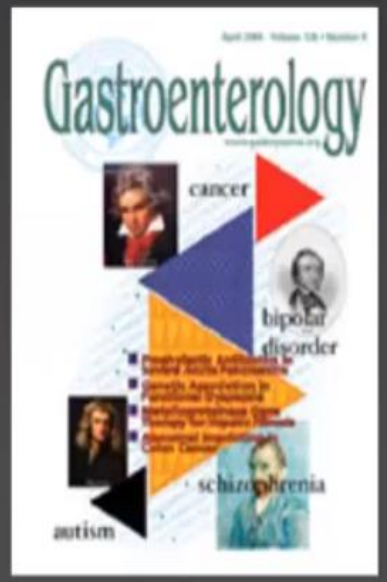
Dereje D. Jima[a,b], David A. Skaar[a,c,d], Antonio Planchart[a,c,d], Alison Motsinger-Reif[b,c,e], Sebnem E. Cevik[d], Sarah S. Park[d,f], Michael Cowley [a,c,d], Fred Wright[a,b], John House[b,c,d,e], Andy Liu[g], Randy L. Jirtle [a,c,d], and Cathrine Hoyo[a,c,d]

Imprinted genes – critical for growth, metabolism, and neuronal function – are expressed from one parental allele. Parent-of-origin-dependent CpG methylation regulates this expression at imprint control regions (ICRs). Since ICRs are established before tissue specification, these methylation marks are similar across cell types. Thus, they are attractive for investigating the developmental origins of adult diseases using accessible tissues, but remain unknown. We determined genome-wide candidate ICRs in humans by performing whole-genome bisulphite sequencing (WGBS) of DNA derived from the three germ layers and from gametes. We identified 1,488 hemi-methylated candidate ICRs, including 19 of 25 previously characterized ICRs (https://humanicr.org/). Gamete methylation approached 0% or 100% in 332 ICRs (178 paternally and 154 maternally methylated), supporting parent-of-origin-specific methylation, and 65% were in well-described CTCF-binding or DNaseI hypersensitive regions. This draft of the human imprintome will allow for the systematic determination of the role of early-acquired imprinting dysregulation in the pathogenesis of human diseases and developmental and behavioural disorders.

EPIGENETICS
2022, VOL. 17, NO. 13, 1920–1943







http://www.geneimprint.com

The science of hope: an interview with Randy Jirtle

Epidemiology studies can only demonstrate significant associations, not cause and effect; however, it appears from the evidence presented in this paper that African–Americans may develop diseases more frequently through changes in the epigenome than through genetic mutations. This indicates that environmental effects on the epigenome may potentially play a bigger role in the formation of diseases and disorders in the African–American population than in people of European ancestry.

This is an important issue to continue studying. If true, even though all populations develop diseases and behavioral disorders, the epigenetic and/or genetic paths that lead there may be different. Consequently, the methods needed to diagnose, prevent and treat these pathologies most effectively may also need to vary among human populations.

EPIGENOMICS, VOL. 14, NO. 6

Modulating epigenetic memory through vitamins and TET: implications for regenerative medicine and cancer treatment

Vitamins A and C represent unrelated sets of small molecules that are essential to the human diet and have recently been shown to intensify erasure of epigenetic memory in naive embryonic stem cells. These effects are driven by complementary enhancement of the ten-eleven translocation (TET) demethylases – vitamin A stimulates TET expression, whereas vitamin C potentiates TET catalytic activity. Vitamin A and C cosupplementation synergistically enhances reprogramming of differentiated cells to the naive state, but overuse may exaggerate instability of imprinted genes. As such, optimizing their use in culture media will be important for regenerative medicine and mammalian transgenics. In addition, mechanistic perception of how these vitamins interact with the epigenome may be relevant for understanding cancer and improving patient treatment.

Epigenomics (2017) 9(6), 863–871

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Multivitamin Supplements and HIV Disease Progression and Mortality

Wafaie W. Fawzi, M.B., B.S., Dr.P.H., Gernard I. Msamanga, M.D., Sc.D., Donna Spiegelman, Sc.D., Ruilan Wei, Ph.D., Saidi Kapiga, M.D., Sc.D., Eduardo Villamor, M.D., Dr.P.H., Davis Mwakagile, M.D., M.Med., Ferdinand Mugusi, M.D., M.Med., Ellen Hertzmark, M.A., Max Essex, D.V.M., Ph.D., and David J. Hunter, M.B., B.S., Sc.D.

ficiency syndrome (0.73; 95 percent confidence interval, 0.51 to 1.04; P=0.09), progression to WHO stage 4 (0.50; 95 percent confidence interval, 0.28 to 0.90; P=0.02), or progression to stage 3 or higher (0.72; 95 percent confidence interval, 0.58 to 0.90; P=0.003). Multivitamins also resulted in significantly higher CD4+ and CD8+ cell counts and significantly lower viral loads. The effects of receiving vitamin A alone were smaller and for the most part not significantly different from those produced by placebo. Adding vitamin A to the multivitamin regimen reduced the benefit with regard to some of the end points examined.

CONCLUSIONS

Multivitamin supplements delay the progression of HIV disease and provide an effective, low-cost means of delaying the initiation of antiretroviral therapy in HIV-infected women.

Summary of Results from Big Bold Health Polyphenol/Bioflavonoid Intervention Trial

Clintrial.gov registered study with 50 apparently healthy men and women

Non-placebo controlled, n-of-1 study protocol

Participants took 800mg of a mixture of flavonoids in Himalayan Tartary Buckwheat including 2-HOBA and D-chiroinositol daily for 90 days

Evaluated immune cell epigenome using specialized Illumina chip with more than 800,000 CpG methylation sites

Results indicated a restructuring of the immune epigenome at specific loci, and alterations in immune cell phenotypes

Using well established immune cell age algorithms it was found that those with elevated immune epigenetic age had statistically significant reduction in immune after the 90 intervention

First study to demonstrate that intervention with a well characterized mixture of flavonoids from Himalayan Tartary Buckwheat at levels that can be achieved through dietary intake results in a measurable restructuring of methylation patterns of metastable epialleles of immune cells in adults associated with favorable alterations associated with immuno-rejuvenation

Integrative Healthcare SYMPOSIUM

Saturday 3:45pm – 4:45pm

Plenary: Gut Microbiome and Pre-Autoimmune Diseases - Functional Immunology in Clinical Practice

Please scan this QR code on you mobile

or tablet device to access the session feedback survey

Plenary: Gut Microbiome and Pre-Autoimmune Diseases - Functional Immunology in Clinical Practice