Scientific References from,

"Fire In The Hole Intestinal Permeability: Precursor to Autoimmune Disease and a Comprehensive Approach to Healing the Gut"

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1. **Watad A, et al. Is autoimmunology a discipline of its own? A big data-based bibliometric and scientometric analyses." Autoimmunity. 2017 Mar 23:1-6.**
https://www.ncbi.nlm.nih.gov/pubmed/28332868

ABSTRACT

Autoimmunology is a super-specialty of immunology specifically dealing with autoimmune disorders. To assess the extant literature concerning autoimmune disorders, bibliometric and scientometric analyses (namely, research topics/keywords co-occurrence, journal co-citation, citations, and scientific output trends - both crude and normalized, authors network, leading authors, countries, and organizations analysis) were carried out using open-source software, namely, VOSviewer and SciCurve. A corpus of 169,519 articles containing the keyword "autoimmunity" was utilized, selecting PubMed/MEDLINE as bibliographic thesaurus. Journals specifically devoted to autoimmune disorders were six and covered approximately 4.15% of the entire scientific production. Compared with all the corpus (from 1946 on), these specialized journals have been established relatively few decades ago. Top countries were the United States, Japan, Germany, United Kingdom, Italy, China, France, Canada, Australia, and Israel. Trending topics are represented by the role of microRNAs (miRNAs) in the ethiopathogenesis of autoimmune disorders, contributions of genetics and of epigenetic modifications, role of vitamins, management during pregnancy and the impact of gender. New subsets of immune cells have been extensively investigated, with a focus on interleukin production and release and on Th17 cells. Autoimmunology is emerging as a new discipline within immunology, with its own bibliometric properties, an identified scientific community and specifically devoted journals.

2. **Morris Z S, et al. "The answer is 17 years, what is the question: understanding time lags in translational research." J R Soc Med 2011 104: 510.**
http://www.ncbi.nlm.nih.gov/pubmed/22179294

ABSTRACT

This study aimed to review the literature describing and quantifying time lags in the health research translation process. Papers were included in the review if they quantified time lags in the development of health interventions. The study identified 23 papers. Few were comparable as different studies use different measures, of different things, at different time points. We concluded that the current state of knowledge of time lags is of limited use to those responsible for R&D and knowledge transfer who face difficulties in knowing what they should or can do to reduce time lags. This effectively 'blindfolds' investment decisions and risks wasting effort. The study concludes that understanding lags first requires agreeing models, definitions and measures, which can be applied in practice. A second task would be to develop a process by which to gather these data.

3. **Madan RA, et al. "From clinical trials to clinical practice: therapeutic cancer vaccines for the treatment of prostate cancer." Expert Rev Vaccines. 2011 Jun;10(6):743-53.**
https://www.ncbi.nlm.nih.gov/pubmed/21692697

ABSTRACT

Therapeutic options for patients with metastatic castration-resistant prostate cancer are increasing, spurring an urgent need to better understand which treatments are best for individual patients. The recent approval of a first-in-class agent, sipuleucel-T, has intensified this need. This therapeutic cancer vaccine has demonstrated a survival advantage in two Phase III trials, but does not alter progression in the short term. Therefore, a new therapeutic approach for patients with metastatic castration-resistant prostate cancer is taking shape, based on broader understanding of available therapies. This new clinical approach seeks to maximize patient benefit from treatment, minimize associated toxicities, and may have far-reaching implications for other therapeutic cancer vaccines currently in clinical development.

4. **Vuilleumier N, et al. "Autoantibodies to apolipoprotein A-1 as a biomarker of cardiovascular autoimmunity." World J Cardiol. 2014 May 26;6(5):314-26.**
http://www.ncbi.nlm.nih.gov/pubmed/24944761

ABSTRACT

Immune-driven inflammation plays an important part in atherogenesis and is therefore believed to be key to the development of cardiovascular disease (CVD), which is currently the leading cause of death in the Western world. By fulfilling some of the Koch postulates, atherogenesis has even been proposed to be considered as an autoimmune disease, raising the hope that CVD could be prevented by immunomodulation. Nevertheless, the role of the immune system and autoimmune reactions in atherosclerosis appear to be a double edged-sword, with both pro-atherogenic and anti-atherogenic attributes. Hence, if immunomodulation is to become a therapeutic option for atherosclerosis and CVD, it will be crucial to correctly identify patients who might benefit from targeted suppression of deleterious autoimmune responses. This could be achieved, for example, by the detection of disease-associated autoantibodies. In this work, we will review the currently available clinical, in vitro, and animal studies dedicated to autoantibodies against apolipoprotein A-1 (anti-apoA-1 IgG), the major proteic fraction of high density lipoprotein. Current clinical studies indicate that high levels of anti-apoA-1 IgG are associated with a worse cardiovascular prognosis. In addition, in vitro and animal studies indicate a pro-inflammatory and pro-atherogenic role, supporting the hypothesis that these autoantibodies may play a direct causal role in CVD, and furthermore that they could potentially represent a therapeutic target for CVD in the future.

5. **"Living Planet Report. Risk and Resilience in a new era." Published by WWF**
http://www.ncbi.nlm.nih.gov/pubmed/24944761

NO ABSTRACT AVAILABLE

6. **Fasono A, Shea-Donohue T. "Mechanisms of Disease: the role of intestinal barrier function in the pathogenesis of gastrointestinal autoimmune diseases." Nat Clin Prac Gastro & Hep Sept 2005 Vol 2 No 9.**
http://www.nature.com/nrgastro/journal/v2/n9/full/ncpgasthep0259.html

SUMMARY

The primary functions of the gastrointestinal tract have traditionally been perceived to be limited to the digestion and absorption of nutrients and electrolytes, and to water homeostasis. A more attentive analysis of the anatomic and functional arrangement of the gastrointestinal tract, however, suggests that another extremely important function of this organ is its ability to regulate the trafficking of macromolecules between the environment and the host through a barrier mechanism. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to nonself-antigens. When the finely tuned trafficking of macromolecules is dysregulated in genetically susceptible individuals, both intestinal and extraintestinal autoimmune disorders can occur. This new paradigm subverts traditional theories underlying the development of autoimmunity, which are based on molecular mimicry and/or the bystander effect, and suggests that the autoimmune process can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing intestinal barrier function. Understanding the role of the intestinal barrier in the pathogenesis of gastrointestinal disease is an area of translational research that encompasses many fields and is currently receiving a great deal of attention. This review is timely given the increased interest in the role of a 'leaky gut' in the pathogenesis of gastrointestinal diseases and the advent of novel treatment strategies, such as the use of probiotics.

7. **Ménard S, et al. "Multiple facets of intestinal permeability and epithelial handling of dietary antigens." Mucosal Immunol. 2010 May;3(3):247-59.**
http://www.ncbi.nlm.nih.gov/pubmed/20404811

ABSTRACT

The intestinal epithelium, the largest interface between the host and environment, regulates fluxes of ions and nutrients and limits host contact with the massive load of luminal antigens. Local protective and tolerogenic immune responses toward luminal content depend on antigen sampling by the gut epithelial layer. Whether, and how exaggerated, the entrance of antigenic macromolecules across the gut epithelium might initiate and/or perpetuate chronic inflammation as well as the respective contribution of paracellular and transcellular permeability remains a matter of debate. To this extent, experimental studies involving the in vivo assessment of intestinal

permeability using small inert molecules do not necessarily correlate with the uptake of larger dietary antigens. This review analyzes both the structural and functional aspects of intestinal permeability with special emphasis on antigen handling in healthy and diseased states and consequences on local immune responses to food antigens.

8. **Arbuckle R, et al. "Development of Autoantibodies before the Clinical Onset of Systemic Lupus Erythematosus." NEJM:2003;349:1526-1533.**
http://www.nejm.org/doi/full/10.1056/NEJMoa021933#t=articleResults

ABSTRACT

BACKGROUND
Although much is known about the natural history of systemic lupus erythematosus (SLE), the development of SLE autoantibodies before the diagnosis of the disease has not been extensively explored. We investigated the onset and progression of autoantibody development before the clinical diagnosis.

METHODS
The Department of Defense Serum Repository contains approximately 30 million specimens prospectively collected from more than 5 million U.S. Armed Forces personnel. We evaluated serum samples obtained from 130 persons before they received a diagnosis of SLE, along with samples from matched controls.

RESULTS
In 115 of the 130 patients with SLE (88 percent), at least one SLE autoantibody tested was present before the diagnosis (up to 9.4 years earlier; mean, 3.3 years). Antinuclear antibodies were present in 78 percent (at a dilution of 1:120 or more), anti–double-stranded DNA antibodies in 55 percent, anti-Ro antibodies in 47 percent, anti-La antibodies in 34 percent, anti-Sm antibodies in 32 percent, anti–nuclear ribonucleoprotein antibodies in 26 percent, and antiphospholipid antibodies in 18 percent. Antinuclear, antiphospholipid antibodies, anti-Ro, and anti-La antibodies were present earlier than anti-Sm and anti–nuclear ribonucleoprotein antibodies (a mean of 3.4 years before the diagnosis vs. 1.2 years, P=0.005). Anti–double-stranded DNA antibodies, with a mean onset 2.2 years before the diagnosis, were found later than antinuclear antibodies (P=0.06) and earlier than anti–nuclear ribonucleoprotein antibodies (P=0.005). For many patients, the earliest available serum sample was positive; therefore, these measures of the average time from the first positive antibody test to the diagnosis are underestimates of the time from the development of antibodies to the diagnosis. Of the 130 initial matched controls, 3.8 percent were positive for one or more autoantibodies.

CONCLUSIONS
Autoantibodies are typically present many years before the diagnosis of SLE. Furthermore, the appearance of autoantibodies in patients with SLE tends to follow a predictable course, with a progressive accumulation of specific autoantibodies before the onset of SLE, while patients are still asymptomatic.

9. **Rogers M, et al. "Antigenic Challenge in the Etiology of Autoimmune Disease in Women." J Autoimmun. 2012 May; 38(2-3): J97–J102.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3242155/

ABSTRACT

Infection has long been implicated as a trigger for autoimmune disease. Other antigenic challenges include receipt of allogeneic tissue or blood resulting in immunomodulation. We investigated antigenic challenges as possible risk factors for autoimmune disease in women using the Health and Retirement Study, a nationally representative longitudinal study, linked to Medicare files, years 1991–2007. The prevalence of autoimmune disease (rheumatoid arthritis, Hashimoto's disease, Graves' disease, systemic lupus erythematosus, celiac disease, systemic sclerosis, Sjögren syndrome and multiple sclerosis) was 1.4% in older women (95% CI: 1.3%, 1.5%) with significant variation across regions of the United States. The risk of autoimmune disease increased by 41% (95% CI of incidence rate ratio (IRR): 1.10, 1.81) with a prior infection-related medical visit. The risk of autoimmune disease increased by 90% (95% CI of IRR: 1.36, 2.66) with a prior transfusion without infection. Parity was not associated with autoimmune disease. Women less than 65 years of age and Jewish women had significantly elevated risk of developing autoimmune disease, as did individuals with a history of heart disease or end-stage renal disease. Antigenic challenges, such as infection and allogeneic blood transfusion, are significant risk factors for the development of autoimmune disease in older women.

10. **Trasande L, et al. "Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis." Andrology. 2016 Jul;4(4):565-72.**
https://www.ncbi.nlm.nih.gov/pubmed/27003928

ABSTRACT

A previous report documented that endocrine disrupting chemicals contribute substantially to certain forms of disease and disability. In the present analysis, our main objective was to update a range of health and economic costs that can be reasonably attributed to endocrine disrupting chemical exposures in the European Union, leveraging new burden and disease cost estimates of female reproductive conditions from accompanying report. Expert panels evaluated the epidemiologic evidence, using adapted criteria from the WHO Grading of Recommendations Assessment, Development and Evaluation Working Group, and evaluated laboratory and animal evidence of endocrine disruption using definitions recently promulgated by the Danish Environmental Protection Agency. The Delphi method was used to make decisions on the strength of the data. Expert panels consensus was achieved for probable (>20%) endocrine disrupting chemical causation for IQ loss and associated intellectual disability; autism; attention deficit hyperactivity disorder; endometriosis; fibroids; childhood obesity; adult obesity; adult diabetes; cryptorchidism; male infertility, and mortality associated with reduced testosterone. Accounting for probability of causation, and using the midpoint of each range for probability of causation, Monte Carlo simulations produced a median annual cost of €163 billion (1.28% of EU Gross Domestic Product) across 1000 simulations. We conclude that endocrine disrupting chemical exposures in the EU are likely to contribute substantially to disease and dysfunction across the life course with costs in the hundreds of billions of Euros per year. These estimates represent only

those endocrine disrupting chemicals with the highest probability of causation; a broader analysis would have produced greater estimates of burden of disease and costs.

11. **Ruff WE, Kriegel MA. "Autoimmune host-microbiota interactions at barrier sites and beyond." Trends Mol Med. 2015 Apr;21(4):233-44.**
https://www.ncbi.nlm.nih.gov/pubmed?term=25771098

ABSTRACT

The microbiota is considered to be an important factor influencing the pathogenesis of autoimmunity at both barrier sites and internal organs. Impinging on innate and adaptive immunity, commensals exert protective or detrimental effects on various autoimmune animal models. Human microbiome studies of autoimmunity remain largely descriptive, but suggest a role for dysbiosis in autoimmune disease. Humanized gnotobiotic approaches have advanced our understanding of immune-commensal interactions, but little is known about the mechanisms in autoimmunity. We propose that, similarly to infectious agents, the microbiota mediates autoimmunity via bystander activation, epitope spread, and, particularly under homeostatic conditions, via crossreactivity. This review presents an overview of the current literature concluding with outstanding questions in this field.

12. **Campuzano-Maya G "Cure of alopecia areata after eradication of Helicobacter pylori: A new association?" World J Gastroenterol. 2011 Jul 14; 17(26): 3165–3170.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3158418/

ABSTRACT

Alopecia areata is a disease of the hair follicles, with strong evidence supporting autoimmune etiology. Alopecia areata is frequently associated with immune-mediated diseases with skin manifestations such as psoriasis and lichen planus, or without skin manifestations such as autoimmune thyroiditis and idiopathic thrombocytopenic purpura. Helicobacter pylori (H. pylori) infection is present in around 50% of the world's population and has been associated with a variety of immune-mediated extra-digestive disorders including autoimmune thyroiditis, idiopathic thrombocytopenic purpura, and psoriasis. A case of a 43-year old man with an 8-mo history of alopecia areata of the scalp and beard is presented. The patient was being treated by a dermatologist and had psychiatric support, without any improvement. He had a history of dyspepsia and the urea breath test confirmed H. pylori infection. The patient went into remission from alopecia areata after H. pylori eradication. If such an association is confirmed by epidemiological studies designed for this purpose, new therapeutic options could be available for these patients, especially in areas where infection with H. pylori is highly prevalent.

13. **Eshraghian A. "Epidemiology of Helicobacter pylori infection among the healthy population in Iran and countries of the Eastern Mediterranean Region: A systematic review of prevalence and risk factors." World J Gastroenterol. 2014 Dec 14; 20(46): 17618–17625.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4265624/

ABSTRACT

AIM:
To investigate the epidemiology of Helicobacter pylori (H. pylori) infection among the healthy asymptomatic population in Iran and countries of the Eastern Mediterranean Region.

METHODS: A computerized English language literature search of PubMed, ISI Web of Science, Scopus, and Google Scholar was performed in September 2013. The terms, "Eastern Mediterranean Regional Office (EMRO)" and "Helicobacter pylori", "H. pylori" and "prevalence" were used as key words in titles and/or abstracts. A complementary literature search was also performed in the following countries: Afghanistan, Bahrain, Djibouti, Egypt, Iran, Iraq, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Pakistan, Palestine, Qatar, Saudi Arabia, Somalia, Sudan, Syria, Tunisia, The United Arab Emirates, and Yemen.

RESULTS:
In the electronic search, a total of 308 articles were initially identified. Of these articles, 26 relevant articles were identified and included in the study. There were 10 studies from Iran, 5 studies from the Kingdom of Saudi Arabia, 4 studies from Egypt, 2 from the United Arab Emirates, and one study from Libya, Oman, Tunisia, and Lebanon, respectively. The overall prevalence of H. pylori infection in Iran, irrespective of time and age group, ranged from 30.6% to 82%. The overall prevalence of H. pylori infection, irrespective of time and age group, in other EMRO countries ranged from 22% to 87.6%.

CONCLUSION:
The prevalence of H. pylori in EMRO countries is still high in the healthy asymptomatic population. Strategies to improve sanitary facilities, educational status, and socioeconomic status should be implemented to minimize H. pylori infection.

14. **Vojdani A1, et al. "Environmental triggers and autoimmunity." Autoimmune Dis. 2014;2014:798029.**
https://www.ncbi.nlm.nih.gov/pubmed/25610638

NO ABSTRACT AVAILABLE

15. **Hollon J, et al. "Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity." Nutrients. 2015 Feb 27;7(3):1565-76.**
http://www.ncbi.nlm.nih.gov/pubmed/25734566

ABSTRACT

BACKGROUND:
Intestinal exposure to gliadin leads to zonulin upregulation and consequent disassembly of intercellular tight junctions and increased intestinal permeability. We aimed to study response to gliadin exposure, in terms of barrier function and cytokine secretion, using intestinal biopsies obtained from four groups: celiac patients with active disease (ACD), celiac patients in remission (RCD), non-celiac patients with gluten sensitivity (GS) and non-celiac controls (NC).

METHODS:
Ex-vivo human duodenal biopsies were mounted in microsnapwells and luminally incubated with either gliadin or media alone. Changes in transepithelial electrical resistance were monitored over 120 min. Media was subsequently collected and cytokines quantified.

RESULTS:
Intestinal explants from all groups (ACD (n = 6), RCD (n = 6), GS (n = 6), and NC (n = 5)) demonstrated a greater increase in permeability when exposed to gliadin vs. media alone. The increase in permeability in the ACD group was greater than in the RCD and NC groups. There was a greater increase in permeability in the GS group compared to the RCD group. There was no difference in permeability between the ACD and GS groups, between the RCD and NC groups, or between the NC and GS groups. IL-10 was significantly greater in the media of the NC group compared to the RCD and GS groups.

CONCLUSIONS:
Increased intestinal permeability after gliadin exposure occurs in all individuals. Following gliadin exposure, both patients with gluten sensitivity and those with active celiac disease demonstrate a greater increase in intestinal permeability than celiacs in disease remission. A higher concentration of IL-10 was measured in the media exposed to control explants compared to celiac disease in remission or gluten sensitivity.

16. **Venter C, et al. "Very low prevalence of IgE mediated wheat allergy and high levels of cross-sensitisation between grass and wheat in a UK birth cohort." Clinical and Translational Allergy20166:22**
https://www.ncbi.nlm.nih.gov/pubmed/27335632

ABSTRACT

Background
Patients often report adverse reactions to wheat. Interpretation of sensitization to wheat pollen and flour with/without sensitization to grass pollen is a clinical problem.

Aim
We set out to determine the prevalence of wheat allergy in a birth cohort (10/11 year olds) and investigate the usefulness of performing skin prick tests (SPT), specific IgE tests and component resolved diagnostics to wheat pollen and flour.

Methods
The Food Allergy and Intolerance Research (FAIR) birth cohort included babies born on the Isle of Wight (UK) between September 2001–August 2002 (n = 969). Children were followed up at 1, 2, 3 and 10/11 years. 588 children had SPTs to wheat pollen and grass during the 10 year follow-up. 294 children underwent further SPT to wheat flour and 246 had specific IgE testing to wheat and grass.

Results
Eight children underwent oral food challenges (OFC). We diagnosed 0.48 % (4/827; 95 % CI 0–1 %) children with wheat allergy based on OFC. 16.3 % (96/588) were sensitized to grass pollen, 13.4 % (79/588) to wheat pollen; 78 % (75/96) sensitized to both. Only one child was sensitized to wheat flour and wheat pollen, but not grass pollen. For specific IgE, 15.0 % (37/246) and 36.2 % (89/246) were sensitized to wheat and grass pollen, with 40.5 % (36/89) sensitized to both. Of the 37 children sensitized to wheat, 3 (8.1 %) were sensitized to omega 5 gliadin, 1 (2.7 %) to wheat lipid transfer protein and 1 to wheat gliadin.

Conclusion
Clinicians should be aware of the high level of cross-sensitization when performing tests to wheat and grass pollen i.e. sensitisation to wheat specific IgE and wheat pollen SPT should be assessed in the presence of grass pollen SPT and/or specific IgE.

17. Vader W, et al. "The gluten response in children with celiac disease is directed toward multiple gliadin and glutenin peptides." Gastroenterology. 2002 Jun;122(7):1729-37.
http://www.ncbi.nlm.nih.gov/pubmed/12055577

ABSTRACT

BACKGROUND & AIMS:
Gluten (GLU)-specific T-cell responses in HLA-DQ2 positive adult celiac disease (CD) patients are directed to an immunodominant alpha-gliadin (GLIA) peptide that requires deamidation for T-cell recognition. The aim of the current study was to determine which GLU peptide(s) are involved early in disease.

METHODS:
We have characterized the GLU-specific T-cell response in HLA-DQ2 positive children with recent onset CD.

RESULTS:
We found that 50% of these patients do not respond to the alpha-GLIA peptide but to a diverse set of GLIA and glutenin (GLT) peptides, including 6 novel epitopes. Moreover, individual patients respond to distinct (combinations of) GLU peptides. T-cell cross-reactivity toward homologous GLIA and GLT peptides was observed, which might play a role in the initial spreading of the GLU-specific

T-cell response. Although all pediatric patients displayed deamidation-dependent responses, deamidation-independent responses were found in the majority of patients as well. Finally, T-cell responses to 3 of these novel GLU peptides were found in adult CD patients.

CONCLUSIONS:
The diversity of the GLU-specific T-cell response is far greater than was previously appreciated. Both adult and young CD patients can respond to a diverse repertoire of GLU peptides. The observation that T-cell responses to 3 of the novel peptides are independent of deamidation indicates that T-cell responses can be initiated toward native GLU peptides. The possibility that deamidation drives the GLU response toward immunodominant T-cell stimulatory peptides after disease initiation is discussed.

18. Choung RS, et al. "Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays." PLoS One. 2016 Jan 29;11(1):e0147777.
http://www.ncbi.nlm.nih.gov/pubmed/26824466

ABSTRACT

BACKGROUND:
Most antibodies recognize conformational or discontinuous epitopes that have a specific 3-dimensional shape; however, determination of discontinuous B-cell epitopes is a major challenge in bioscience. Moreover, the current methods for identifying peptide epitopes often involve laborious, high-cost peptide screening programs. Here, we present a novel microarray method for identifying discontinuous B-cell epitopes in celiac disease (CD) by using a silicon-based peptide array and computational methods.

METHODS:
Using a novel silicon-based microarray platform with a multi-pillar chip, overlapping 12-mer peptide sequences of all native and deamidated gliadins, which are known to trigger CD, were synthesized in situ and used to identify peptide epitopes.

RESULTS:
Using a computational algorithm that considered disease specificity of peptide sequences, 2 distinct epitope sets were identified. Further, by combining the most discriminative 3-mer gliadin sequences with randomly interpolated3- or 6-mer peptide sequences, novel discontinuous epitopes were identified and further optimized to maximize disease discrimination. The final discontinuous epitope sets were tested in a confirmatory cohort of CD patients and controls, yielding 99% sensitivity and 100% specificity.

CONCLUSIONS:
These novel sets of epitopes derived from gliadin have a high degree of accuracy in differentiating CD from controls, compared with standard serologic tests. The method of ultra-high-density peptide microarray described here would be broadly useful to develop high-fidelity diagnostic tests and explore pathogenesis.

19. **O'Bryan T. The Autoimmune Fix: How to Stop the Hidden Autoimmune Damage That Keeps You Sick, Fat, and Tired Before It Turns Into Disease, Emmaus, PA: Rodale Press, ISBN 978-1-62336-700-8, 2016.**

NO ABSTRACT AVAILABLE

20. **Bischoff SC, et al. "Intestinal permeability--a new target for disease prevention and therapy." BMC Gastroenterol. 2014 Nov 18;14:189.**
http://www.ncbi.nlm.nih.gov/pubmed/25407511

ABSTRACT

Data are accumulating that emphasize the important role of the intestinal barrier and intestinal permeability for health and disease. However, these terms are poorly defined, their assessment is a matter of debate, and their clinical significance is not clearly established. In the present review, current knowledge on mucosal barrier and its role in disease prevention and therapy is summarized. First, the relevant terms 'intestinal barrier' and 'intestinal permeability' are defined. Secondly, the key element of the intestinal barrier affecting permeability are described. This barrier represents a huge mucosal surface, where billions of bacteria face the largest immune system of our body. On the one hand, an intact intestinal barrier protects the human organism against invasion of microorganisms and toxins, on the other hand, this barrier must be open to absorb essential fluids and nutrients. Such opposing goals are achieved by a complex anatomical and functional structure the intestinal barrier consists of, the functional status of which is described by 'intestinal permeability'. Third, the regulation of intestinal permeability by diet and bacteria is depicted. In particular, potential barrier disruptors such as hypoperfusion of the gut, infections and toxins, but also selected over-dosed nutrients, drugs, and other lifestyle factors have to be considered. In the fourth part, the means to assess intestinal permeability are presented and critically discussed. The means vary enormously and probably assess different functional components of the barrier. The barrier assessments are further hindered by the natural variability of this functional entity depending on species and genes as well as on diet and other environmental factors. In the final part, we discuss selected diseases associated with increased intestinal permeability such as critically illness, inflammatory bowel diseases, celiac disease, food allergy, irritable bowel syndrome, and--more recently recognized--obesity and metabolic diseases. All these diseases are characterized by inflammation that might be triggered by the translocation of luminal components into the host. In summary, intestinal permeability, which is a feature of intestinal barrier function, is increasingly recognized as being of relevance for health and disease, and therefore,
this topic warrants more attention.

21. **Jiang T, et al. "Apple-Derived Pectin Modulates Gut Microbiota, Improves Gut Barrier Function, and Attenuates Metabolic Endotoxemia in Rats with Diet-Induced Obesity." Nutrients. 2016 Feb 29;8(3):126**
https://www.ncbi.nlm.nih.gov/pubmed/26938554

ABSTRACT

This study was aimed at determining potential effects of apple-derived pectin on weight gain, gut microbiota, gut barrier and metabolic endotoxemia in rat models of diet-induced obesity. The rats received a standard diet (control; Chow group; n = 8) or a high-fat diet (HFD; n = 32) for eight weeks to induce obesity. The top 50th percentile of weight-gainers were selected as diet induced obese rats. Thereafter, the Chow group continued on chow, and the diet induced obese rats were randomly divided into two groups and received HFD (HF group; n = 8) or pectin-supplemented HFD (HF-P group; n = 8) for six weeks. Compared to the HF group, the HF-P group showed attenuated weight gain (207.38 ± 7.96 g vs. 283.63 ± 10.17 g, $p < 0.01$) and serum total cholesterol level (1.46 ± 0.13 mmol/L vs. 2.06 ± 0.26 mmol/L, $p < 0.01$). Compared to the Chow group, the HF group showed a decrease in Bacteroidetes phylum and an increase in Firmicutes phylum, as well as subordinate categories ($p < 0.01$). These changes were restored to the normal levels in the HF-P group. Furthermore, compared to the HF group, the HF-P group displayed improved intestinal alkaline phosphatase (0.57 ± 0.20 vs. 0.30 ± 0.19, $p < 0.05$) and claudin 1 (0.76 ± 0.14 vs. 0.55 ± 0.18, $p < 0.05$) expression, and decreased Toll-like receptor 4 expression in ileal tissue (0.76 ± 0.58 vs. 2.04 ± 0.89, $p < 0.01$). The HF-P group also showed decreased inflammation (TNFα: 316.13 ± 7.62 EU/mL vs. 355.59 ± 8.10 EU/mL, $p < 0.01$; IL-6: 51.78 ± 2.35 EU/mL vs. 58.98 ± 2.59 EU/mL, $p < 0.01$) and metabolic endotoxemia (2.83 ± 0.42 EU/mL vs. 0.68 ± 0.14 EU/mL, $p < 0.01$). These results suggest that apple-derived pectin could modulate gut microbiota, attenuate metabolic endotoxemia and inflammation, and consequently suppress weight gain and fat accumulation in diet induced obese rats.

22. **Fawley J, Gourlay DM. "Intestinal alkaline phosphatase: a summary of its role in clinical disease." J Surg Res. 2016 May 1;202(1):225-34**
https://www.ncbi.nlm.nih.gov/pubmed/27083970

ABSTRACT

Over the past few years, there is increasing evidence implicating a novel role for Intestinal Alkaline Phosphatase (IAP) in mitigating inflammatory mediated disorders. IAP is an endogenous protein expressed by the intestinal epithelium that is believed to play a vital role in maintaining gut homeostasis. Loss of IAP expression or function is associated with increased intestinal inflammation, dysbiosis, bacterial translocation and subsequently systemic inflammation. As these events are a cornerstone of the pathophysiology of many diseases relevant to surgeons, we sought to review recent research in both animal and humans on IAP's physiologic function, mechanisms of action and current research in specific surgical diseases.

23. Giuseppina Frasca,et al. "Gelatin tannate reduces the proinflammatory effects of lipopolysaccharide in human intestinal epithelial cells." Clin Exp Gastroenterol. 2012; 5: 61–67.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3358810/

ABSTRACT

Background
Gelatin tannate is a mixture of tannic acid and gelatin. Tannic acid has astringent properties, due to its capacity to form protein–macromolecular complexes, as well as antibacterial and antioxidant properties. However, little is known about its anti-inflammatory properties.

Purpose
To evaluate the anti-inflammatory activity of gelatin tannate by quantifying the suppression of key molecules produced during inflammatory events in lipopolysaccharide (LPS)-stimulated human intestinal cells.

Methods
Intercellular adhesion molecule-1 (ICAM-1) expression was determined by Western blot analysis; interleukin-8 (IL-8) and tumor necrosis factor-α (TNF-α) concentrations were measured by enzyme-linked immunosorbent assays in Caco-2 cells 24 hours after treatment with LPS (1 μg/mL) in presence of different concentrations of gelatin tannate.

Results
ICAM-1 is induced on a wide variety of cells by inflammatory stimuli such as LPS. Our results have shown gelatin tannate as a potent inhibitor of ICAM-1 expression in LPS-stimulated Caco-2 cells. IL-8 and TNF-α are important inflammatory mediators, recruiting neutrophils and T-lymphocytes. Together with LPS, adding gelatin tannate at different concentrations induced a dose-dependent inhibition of IL-8 and TNF-α released by Caco-2 cells.

Conclusion
These results suggest that gelatin tannate exerts anti-inflammatory effects by inhibiting the specific cytokines and adhesion molecules involved in several inflammatory disorders.

24. Lopetuso LR, et al. "The therapeutic management of gut barrier leaking: the emerging role for mucosal barrier protectors." Eur Rev Med Pharmacol Sci. 2015;19(6):1068-76.
https://www.ncbi.nlm.nih.gov/pubmed/25855934

ABSTRACT

OBJECTIVE:
Gut barrier is a functional unit organized as a multi-layer system and its multiple functions are crucial for maintaining gut homeostasis. Numerous scientific evidences showed a significant association between gut barrier leaking and gastro-intestinal/extra-intestinal diseases.

MATERIALS AND METHODS:
In this review we focus on the relationship between gut barrier leaking and human health. At the same time we speculate on the possible new role of gut barrier protectors in enhancing and restoring gut barrier physiology with the final goal of promoting gut health.

RESULTS:
The alteration of the equilibrium in gut barrier leads to the passage of the luminal contents to the underlying tissues and thus into the bloodstream, resulting in the activation of the immune response and in the induction of gut inflammation. This permeability alteration is the basis for the pathogenesis of many diseases, including infectious enterocolitis, inflammatory bowel diseases, irritable bowel syndrome, small intestinal bacterial overgrowth, celiac disease, hepatic fibrosis, food intolerances and also atopic manifestations. Many drugs or compounds used in the treatment of gastrointestinal disease are able to alter the permeability of the intestinal barrier. Recent data highlighted and introduced the possibility of using gelatin tannate, a mucosal barrier protector, for an innovative approach in the management of intestinal diseases, allowing an original therapeutic orientation with the aim of enhancing mucus barrier activity and restoring gut barrier.

CONCLUSIONS:
These results suggest how the mucus layer recovering, beside the gut microbiota modulation, exerted by gut barrier protectors could be a useful weapon to re-establish the physiological intestinal homeostasis after an acute and chronic injury.

25. Marco ML, et al.“Health benefits of fermented foods: microbiota and beyond.” Curr Opin Biotechnol. 2016 Dec 17;44:94-102.
https://www.ncbi.nlm.nih.gov/pubmed/27998788

ABSTRACT

Fermented foods and beverages were among the first processed food products consumed by humans. The production of foods such as yogurt and cultured milk, wine and beer, sauerkraut and kimchi, and fermented sausage were initially valued because of their improved shelf life, safety, and organoleptic properties. It is increasingly understood that fermented foods can also have enhanced nutritional and functional properties due to transformation of substrates and formation of bioactive or bioavailable end-products. Many fermented foods also contain living microorganisms of which some are genetically similar to strains used as probiotics. Although only a limited number of clinical studies on fermented foods have been performed, there is evidence that these foods provide health benefits well-beyond the starting food materials.

26. **Cantorna MT, Mahon BD. "Mounting evidence for vitamin D as an environmental factor affecting autoimmune disease prevalence." Exp Biol Med (Maywood). 2004 Dec;229(11):1136-42.**
http://www.ncbi.nlm.nih.gov/pubmed/15564440

ABSTRACT

Low vitamin D status has been implicated in the etiology of autoimmune diseases such as multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease. The optimal level of vitamin D intake required to support optimal immune function is not known but is likely to be at least that required for healthy bones. Experimentally, vitamin D deficiency results in the increased incidence of autoimmune disease. Mechanistically, the data point to a role for vitamin D in the development of self-tolerance. The vitamin D hormone (1,25-dihydroxy vitamin D(3)) regulates T helper cell (Th1) and dendritic cell function while inducing regulatory T-cell function. The net result is a decrease in the Th1-driven autoimmune response and decreased severity of symptoms. This review discusses the accumulating evidence pointing to a link between vitamin D and autoimmunity. Increased vitamin D intakes might decrease the incidence and severity of autoimmune diseases and the rate of bone fracture.

27. **Gniadecki R, et al. "1,25-dihydroxyvitamin D3 stimulates the assembly of adherens junctions in keratinocytes: involvement of protein kinase C." Endocrinology. 1997 Jun;138(6):2241-8.**
http://www.ncbi.nlm.nih.gov/pubmed/9165007

ABSTRACT

Signaling via intercellular junctions plays an important role in the regulation of growth and differentiation of epithelial cells. Loss of cell-cell contacts has been implicated in carcinogenesis, tumor progression, and metastasis. Here, we investigated whether 1,25-dihydroxyvitamin D3 [1,25-(OH)2D3] was able to stimulate the assembly of adherens junctions and/or desmosomes in cultured human keratinocytes. After 4-day incubation, 1,25-(OH)2D3 caused assembly of adherens junctions, but not desmosomes. The adherens junctions were identified upon known ultrastructural criteria and evidence of the translocation of specific junctional proteins (E-cadherin, P-cadherin, alpha-catenin, and vinculin) to the cell-cell borders. The presence of alpha-catenin and vinculin at cell-cell borders indicated that the adherens junctions were functional. This was further supported by showing that anti E-cadherin antibody inhibited the 1,25-(OH)2D3-induced keratinocyte stratification. A relation between protein kinase C and adherens junction regulation was noticed. 1,25-(OH)2D3-dependent formation of junctions was blocked by the inhibitors of protein kinase C, bisindolylmaleimide and 1-(5-isoquinolinylsulfonyl)-2-methyl-piperazine (H-7), and treatment of keratinocytes with 1,25-(OH)2D3 caused a rapid activation of protein kinase C and its translocation to the membranes. Formation of intercellular contacts may be an important mechanism of 1,25-(OH)2D3 action in hyperproliferative and neoplastic diseases.

28. **Visser J, et al. "Tight Junctions, Intestinal Permeability, and Autoimmunity Celiac Disease and Type 1 Diabetes Paradigms." Ann N Y Acad Sci. May 2009; 1165: 195-205.**
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2886850/

ABSTRACT

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on celiac disease (CD), an autoimmune enteropathy, and type 1 diabetes (T1D), a hyperglycosaemia caused by a destructive autoimmune process targeting the insulin-producing pancreatic islet cells. Even if environmental factors and genetic susceptibility are clearly involved in the pathogenesis of autoimmunity, for most autoimmune disorders there is no or little knowledge about the causing agent or genetic makeup underlying the disease. In this respect, CD represents a unique autoimmune disorder because a close genetic association with HLA-DQ2 or HLA-DQ8 haplotypes and, more importantly, the environmental trigger (the gliadin fraction of gluten-containing grains wheat, barley, and rye) are known. Conversely, the trigger for autoimmune destruction of pancreatic ß cells in T1D is unclear. Interestingly, recent data suggest that gliadin is also involved in the pathogenesis of T1D. There is growing evidence that increased intestinal permeability plays a pathogenic role in various autoimmune diseases including CD and T1D. Therefore, we hypothesize that besides genetic and environmental factors, loss of intestinal barrier function is necessary to develop autoimmunity. In this review, each of these components will be briefly reviewed.

29. **Kong J, et al. "Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier." Am J Physiol Gastrointest Liver Physiol. 2008 Jan;294(1):G208-16**
http://www.ncbi.nlm.nih.gov/pubmed/17962355

ABSTRACT

Emerging evidence supports a pathological link between vitamin D deficiency and the risk of inflammatory bowel disease (IBD). To explore the mechanism we used the dextran sulfate sodium (DSS)-induced colitis model to investigate the role of the vitamin D receptor (VDR) in mucosal barrier homeostasis. While VDR(+/+) mice were mostly resistant to 2.5% DSS, VDR(-/-) mice developed severe diarrhea, rectal bleeding, and marked body weight loss, leading to death in 2 wk. Histological examination revealed extensive ulceration and impaired wound healing in the colonic epithelium of DSS-treated VDR(-/-) mice. Severe ulceration in VDR(-/-) mice was preceded by a greater loss of intestinal transepithelial electric resistance (TER) compared with VDR(+/+) mice. Confocal and electron microscopy (EM) revealed severe disruption in epithelial junctions in VDR(-/-) mice after 3-day DSS treatment. Therefore, VDR(-/-) mice were much more susceptible to DSS-induced mucosal injury than VDR(+/+) mice. In cell cultures, 1,25-dihydroxy-vitamin D(3) [1,25(OH)(2)D(3)] markedly enhanced tight junctions formed by Caco-2 monolayers by increasing junction protein expression and TER and preserved the structural integrity of tight junctions in the presence of DSS. VDR knockdown with small interfering (si)RNA reduced the junction proteins and TER in Caco-2 monolayers. 1,25(OH)(2)D(3) can also stimulate epithelial cell migration in vitro. These observations suggest that VDR plays a critical role in mucosal barrier homeostasis by preserving the integrity of junction complexes and the healing capacity of the colonic epithelium. Therefore, vitamin D deficiency may compromise the mucosal barrier, leading to increased susceptibility to mucosal damage and increased risk of IBD.

30. Bengmark S. “Nutrition of the critically ill — a 21st-century perspective.” Nutrients. 2013 Jan 14;5(1):162-207.
http://www.ncbi.nlm.nih.gov/pubmed/23344250

ABSTRACT

Health care-induced diseases constitute a fast-increasing problem. Just one type of these health care-associated infections (HCAI) constitutes the fourth leading cause of death in Western countries. About 25 million individuals worldwide are estimated each year to undergo major surgery, of which approximately 3 million will never return home from the hospital. Furthermore, the quality of life is reported to be significantly impaired for the rest of the lives of those who, during their hospital stay, suffered life-threatening infections/sepsis. Severe infections are strongly associated with a high degree of systemic inflammation in the body, and intimately associated with significantly reduced and malfunctioning GI microbiota, a condition called dysbiosis. Deranged composition and function of the gastrointestinal microbiota, occurring from the mouth to the anus, has been found to cause impaired ability to maintain intact mucosal membrane functions and prevent leakage of toxins - bacterial endotoxins, as well as whole bacteria or debris of bacteria, the DNA of which are commonly found in most cells of the body, often in adipocytes of obese individuals or in arteriosclerotic plaques. Foods rich in proteotoxins such as gluten, casein and zein, and proteins, have been observed to have endotoxin-like effects that can contribute to dysbiosis. About 75% of the food in the Western diet is of limited or no benefit to the microbiota in the lower gut. Most of it, comprised specifically of refined carbohydrates, is already absorbed in the upper part of the GI tract, and what eventually reaches the large intestine is of limited value, as it contains only small amounts of the minerals, vitamins and other nutrients necessary for maintenance of the microbiota. The consequence is that the microbiota of modern humans is greatly reduced, both in terms of numbers and diversity when compared to the diets of our paleolithic forebears and the individuals living a rural lifestyle today. It is the artificial treatment provided in modern medical care - unfortunately often the only alternative provided - which constitute the main contributors to a poor outcome. These treatments include artificial ventilation, artificial nutrition, hygienic measures, use of skin-penetrating devices, tubes and catheters, frequent use of pharmaceuticals; they are all known to severely impair the microbiomes in various locations of the body, which, to a large extent, are ultimately responsible for a poor outcome. Attempts to reconstitute a normal microbiome by supply of probiotics have often failed as they are almost always undertaken as a complement to - and not as an alternative to - existing treatment schemes, especially those based on antibiotics, but also other pharmaceuticals.

31. **Le Barz M, et al. "Probiotics as Complementary Treatment for Metabolic Disorders." Diabetes Metab J. 2015 Aug;39(4):291-303. doi: 10.4093/dmj.2015.39.4.291.**
https://www.ncbi.nlm.nih.gov/pubmed/26301190

ABSTRACT

Over the past decade, growing evidence has established the gut microbiota as one of the most important determinants of metabolic disorders such as obesity and type 2 diabetes. Indeed, obesogenic diet can drastically alter bacterial populations (i.e., dysbiosis) leading to activation of pro-inflammatory mechanisms and metabolic endotoxemia, therefore promoting insulin resistance and cardiometabolic disorders. To counteract these deleterious effects, probiotic strains have been developed with the aim of reshaping the microbiome to improve gut health. In this review, we focus on benefits of widely used probiotics describing their potential mechanisms of action, especially their ability to decrease metabolic endotoxemia by restoring the disrupted intestinal mucosal barrier. We also discuss the perspective of using new bacterial strains such as butyrate-producing bacteria and the mucolytic Akkermansia muciniphila, as well as the use of prebiotics to enhance the functionality of probiotics. Finally, this review introduces the notion of genetically engineered bacterial strains specifically developed to deliver anti-inflammatory molecules to the gut.

32. **David LA, et al. "Diet rapidly and reproducibly alters the human gut microbiome." Nature. 2014 Jan 23;505(7484):559-63. doi: 10.1038/nature12820.**
https://www.ncbi.nlm.nih.gov/pubmed/24336217

ABSTRACT

Long-term dietary intake influences the structure and activity of the trillions of microorganisms residing in the human gut, but it remains unclear how rapidly and reproducibly the human gut microbiome responds to short-term macronutrient change. Here we show that the short-term consumption of diets composed entirely of animal or plant products alters microbial community structure and overwhelms inter-individual differences in microbial gene expression. The animal-based diet increased the abundance of bile-tolerant microorganisms (Alistipes, Bilophila and Bacteroides) and decreased the levels of Firmicutes that metabolize dietary plant polysaccharides (Roseburia, Eubacterium rectale and Ruminococcus bromii). Microbial activity mirrored differences between herbivorous and carnivorous mammals, reflecting trade-offs between carbohydrate and protein fermentation. Foodborne microbes from both diets transiently colonized the gut, including bacteria, fungi and even viruses. Finally, increases in the abundance and activity of Bilophila wadsworthia on the animal-based diet support a link between dietary fat, bile acids and the outgrowth of microorganisms capable of triggering inflammatory bowel disease. In concert, these results demonstrate that the gut microbiome can rapidly respond to altered diet, potentially facilitating the diversity of human dietary lifestyles.

33. **Oishi K, et al. "Effect of probiotics, Bifidobacterium breve and Lactobacillus casei, on bisphenol A exposure in rats." Biosci Biotechnol Biochem. 2008 Jun;72(6):1409-15.**
https://www.ncbi.nlm.nih.gov/pubmed/18540113

ABSTRACT

Bisphenol A (BPA), a putative endocrine disruptor, may be taken up by humans via the diet and have adverse effects on human health. In this study, we evaluated whether the probiotics, Bifidobacterium breve strain Yakult (BbY) and Lactobacillus casei strain Shirota (LcS), could exert a protective effect against dietary exposure to BPA. A group of rats fed on a diet containing 5% BbY or 5% LcS showed three advantageous effects compared to the control group; (i) the area under the blood concentration-time curve of BPA after its oral administration was significantly decreased, (ii) the amount of BPA excreted in the feces was significantly greater (2.4 times), and (iii) the percentage of BPA bound to the sediment fraction of the feces was significantly higher. These results suggest that BbY and LcS reduced the intestinal absorption by facilitating the excretion of BPA, and that these probiotics may suppress the adverse effects of BPA on human health.

34. **Papista C, et al. "Gluten induces coeliac-like disease in sensitised mice involving IgA, CD71 and transglutaminase 2 interactions that are prevented by probiotics." Lab Invest. 2012 Apr;92(4):625-35. doi: 10.1038/labinvest.2012.13.**
https://www.ncbi.nlm.nih.gov/pubmed/22330344

ABSTRACT

Coeliac disease (CD) is a malabsorptive enteropathy resulting from intolerance to gluten. Environmental factors and the microbiota are suggested to have critical roles in the onset of CD. The CD71 IgA receptor on epithelial cells is responsible for abnormal retrotranscytosis of IgA-gluten peptide complexes from the intestinal lumen into the lamina propria, inducing intestinal inflammation. However, understanding the role of gluten in the CD physiopathology has been hindered by the absence of relevant animal models. Here, we generated a mouse model for CD to study the factors controlling its pathogenesis as well as to investigate the influence of oral delivery of probiotics on disease development. Gluten sensitivity was established by feeding three generations of BALB/c mice a gluten-free diet (G-) followed by gluten challenge (G+) for 30 days. The G+ mice developed villous atrophy, crypt hyperplasia and infiltration of T cells and macrophages in the small intestine. Inflammation was associated with an overexpression of CD71 on the apical side of enterocytes and an increase of plasma cells producing IgA, which colocalised with the CD71. Moreover, IgA colocalised with the transglutaminase 2 (TG2), the production of which was increased in the lamina propria of G+ mice. These mice displayed increased production of cyclooxygenase-2 (COX-2), pro-inflammatory cytokines and IL-15, as well as anti-gliadin and anti-TG2 autoantibodies. The commensal flora-isolated presumptive probiotic Saccharomyces boulardii KK1 strain hydrolysed the 28-kDa α-gliadin fraction, and its oral delivery in G+ mice improved enteropathy development in association with decrease of epithelial cell CD71 expression and local cytokine production. In conclusion, the G+ BALB/c mouse represents a new mouse model for human CD based on histopathological features and expression of common biomarkers. The selected probiotic treatment reversing disease development will allow the study of the role of probiotics as a new therapeutic approach of CD.

35. **Krishnan M, et al. "VSL#3 Probiotic Stimulates T-cell Protein Tyrosine Phosphatase-mediated Recovery of IFN-γ-induced Intestinal Epithelial Barrier Defects." Inflamm Bowel Dis. 2016 Dec;22(12):2811-2823.**
https://www.ncbi.nlm.nih.gov/pubmed/27824650

ABSTRACT

BACKGROUND:
VSL#3 is a probiotic compound that has been used in the treatment of inflammatory bowel disease. T-cell protein tyrosine phosphatase (TCPTP) is the protein product of the inflammatory bowel disease candidate gene, PTPN2, and we have previously shown that it protects epithelial barrier function. The aim of this study was to investigate whether VSL#3 improves intestinal epithelial barrier function against the effects of the inflammatory bowel disease-associated proinflammatory cytokine, interferon-gamma (IFN-γ) through activation of TCPTP.

METHODS:
Polarized monolayers of T84 intestinal epithelial cells were treated with increasing concentrations of VSL#3 to determine effects on TCPTP expression and enzymatic activity. Therapeutic effects of VSL#3 against barrier disruption by IFN-γ were measured by transepithelial electrical resistance and fluorescein isothiocyanate-dextran permeability. A novel TCPTP-deficient HT-29 intestinal epithelial cell line was generated to study the role of TCPTP in mediating the effects of VSL#3. Tight junction protein distribution was assessed with confocal microscopy.

RESULTS:
VSL#3 increased TCPTP protein levels and enzymatic activity, correlating with a VSL#3-induced decrease in IFN-γ signaling. VSL#3 corrected the decrease in transepithelial electrical resistance and the increase in epithelial permeability induced by IFN-γ. Moreover, the restorative effect of VSL#3 against IFN-γ signaling, epithelial permeability defects, altered expression and localization of the tight junction proteins claudin-2, occludin, and zonula occludens-1, were not realized in stable TCPTP/(PTPN2)-deficient HT-29 intestinal epithelial cells.

CONCLUSIONS:
VSL#3 reduces IFN-γ signaling and IFN-γ-induced epithelial barrier defects in a TCPTP-dependent manner. These data point to a key role for TCPTP as a therapeutic target for restoration of barrier function using probiotics.

36. **Vasquez, A. "Reducing Pain and Inflammation Naturally. Part II: New Insights into Fatty Acid Supplementation and Its Effect on Eicosanoid Production and Genetic Expression." Nutritional Perspectives: Journal of the Council on Nutrition;Jan2005, Vol. 28 Issue 1, p5.**
http://chirochat.org/article_files/Article-1726.pdf

ABSTRACT

Doctors and patients can achieve significant success in the treatment of pain and inflammation by using dietary modification along with nutritional, botanical, and fatty acid supplementation. The first article in this series reviewed recent diet research and the basic biochemistry of fatty acid metabolism, and this second article will provide doctors with a profound understanding of the importance of optimal fatty acid supplementation and will review the clinical benefits of this essential therapy. This review contains the most concise, detailed, up-to-date, and clinically relevant description of fatty acid metabolism that has ever been published in a single article.

37. **Caesar R, et al. "Crosstalk between Gut Microbiota and Dietary Lipids Aggravates WAT Inflammation through TLR Signaling." Cell Metab. 2015 Oct 6;22(4):658-68**
https://www.ncbi.nlm.nih.gov/pubmed/26321659

ABSTRACT

Dietary lipids may influence the abundance of circulating inflammatory microbial factors. Hence, inflammation in white adipose tissue (WAT) induced by dietary lipids may be partly dependent on their interaction with the gut microbiota. Here, we show that mice fed lard for 11 weeks have increased Toll-like receptor (TLR) activation and WAT inflammation and reduced insulin sensitivity compared with mice fed fish oil and that phenotypic differences between the dietary groups can be partly attributed to differences in microbiota composition. Trif(-/-) and Myd88(-/-) mice are protected against lard-induced WAT inflammation and impaired insulin sensitivity. Experiments in germ-free mice show that an interaction between gut microbiota and saturated lipids promotes WAT inflammation independent of adiposity. Finally, we demonstrate that the chemokine CCL2 contributes to microbiota-induced WAT inflammation in lard-fed mice. These results indicate that gut microbiota exacerbates metabolic inflammation through TLR signaling upon challenge with a diet rich in saturated lipids.

38. **Clarke JO, Mullin GE. "A review of complementary and alternative approaches to immunomodulation." Nutr Clin Pract. 2008 Feb;23(1):49-62.**
http://www.ncbi.nlm.nih.gov/pubmed/18203964

ABSTRACT

Current Western therapies for inflammatory diseases are suboptimal; increasingly, patients are turning to complementary and alternative medicine for symptom relief and improved quality of life. There is emerging evidence that many of these therapies have the ability to modulate the immune system and disrupt the proinflammatory cascade through a variety of mechanisms, including antioxidant effects, alterations in cell signaling (in particular the nuclear factor (NF)-kappaB pathway), cytokines, proinflammatory mediators, and disruption of bacterial flora. Using inflammatory bowel disease (IBD) as a model of inflammation, we explore the principal complementary and alternative medicine treatments that show promise in this regard, namely, resveratrol, green tea, curcumin, boswellia, fish oil, vitamin D, and probiotics. With each agent, we detail the mechanisms that have been described with regard to immune modulation, discuss the medical conditions for which it has been evaluated, and explore the data to date for the prevention or treatment of IBD.

39. **"L-Glutamine." Alternative Medicine Review Volume 6, Number 4 2001.**
http://www.anaturalhealingcenter.com/documents/Thorne/monos/glutamine_mono_6.4.pdf

INTRODUCTION

L-glutamine is the most prevalent amino acid in the bloodstream and because human cells readily synthesize it, is usually considered a non-essential amino acid. It is found in high concentration in skeletal muscle, lung, liver, brain, and stomach tissue. Skeletal muscle contains the greatest intracellular concentration of glutamine, comprising up to 60 percent of total body glutamine stores, and is considered the primary storage depot and exporter of glutamine to other tissues. Under certain pathological circumstances the body's tissues need more glutamine than the amount supplied by diet and biosynthesis.

40. Hanaway P. "Balance of flora, galt, and mucosal integrity." Altern Ther Health Med. 2006 Sep-Oct;12(5):52-60.
http://www.ncbi.nlm.nih.gov/pubmed/17017755

ABSTRACT

It is clear that there is a dynamic relationship involving the gastrointestinal flora, environmental inputs (food and other nutrients), and the health of the immune system. Recent research has taught us a great deal about the role of diet and commensal bacteria in promoting health. It appears that Nobel Laureate Eli Metchnikov may have been correct in his assertion that live bacterial cultures are "the elixir of life". We are unlocking a number of secrets about immune system functioning, but we keep coming back to a simple intervention that has an ever-expanding opus of research to support it, and an extremely low toxicity ratio. Future studies will help us to clarify the best strains and the best dosages for individual patients and specific conditions. Assessment of commensal flora and a genomic scan for markers of immunologic dysregulation will be more accurate and more widely available. It appears, however, that the diagnostic and therapeutic tools we have to work with today can make a tremendous difference in reducing the burden of suffering for our patients. If "form follows function," as Buckminster Fuller was fond of saying, then the form of our immune system may be following the precise functions that our commensal flora is dictating. We have the opportunity to encourage breastfeeding, decrease unnecessary antibiotic and antimicrobial usage (especially in the first two years of life), improve oral tolerance with a healthy n-6/n-3 fatty acid ratio, and support the development of a healthy commensal flora. These actions on behalf of our immune systems will pay dividends for years to come.

41. Bengmark S. "Curcumin, an atoxic antioxidant and natural NFkappaB, cyclooxygenase-2, lipooxygenase, and inducible nitric oxide synthase inhibitor: a shield against acute and chronic diseases." JPEN J Parenter Enteral Nutr. 2006 Jan-Feb;30(1):45-51.
http://www.ncbi.nlm.nih.gov/pubmed/16387899

ABSTRACT

BACKGROUND:
The world suffers a tsunami of chronic diseases, and a typhoon of acute illnesses, many of which are associated with the inappropriate or exaggerated activation of genes involved in inflammation. Finding therapeutic agents which can modulate the inflammatory reaction is the highest priority in medical research today. Drugs developed by the pharmaceutical industry have thus far been associated with toxicity and side effects, which is why natural substances are of increasing interest.

METHODS:
A literature search (PubMed) showed almost 1500 papers dealing with curcumin, most from recent years. All available abstracts were read. Approximately 300 full papers were reviewed.

RESULTS:
Curcumin, a component of turmeric, has been shown to be non-toxic, to have antioxidant activity, and to inhibit such mediators of inflammation as NFkappaB, cyclooxygenase-2 (COX-2), lipooxygenase (LOX), and inducible nitric oxide synthase (iNOS). Significant preventive and/or curative effects have been observed in experimental animal models of a number of diseases, including arteriosclerosis, cancer, diabetes, respiratory, hepatic, pancreatic, intestinal and gastric diseases, neurodegenerative and eye diseases.

CONCLUSIONS:
Turmeric, an approved food additive, or its component curcumin, has shown surprisingly beneficial effects in experimental studies of acute and chronic diseases characterized by an exaggerated inflammatory reaction. There is ample evidence to support its clinical use, both as a prevention and a treatment. Several natural substances have greater antioxidant effects than conventional vitamins, including various polyphenols, flavonoids and curcumenoids. Natural substances are worth further exploration both experimentally and clinically.

42. Goozee KG, et al. "Examining the potential clinical value of curcumin in the prevention and diagnosis of Alzheimer's disease." Br J Nutr. 2016 Feb 14;115(3):449-65. doi: 10.1017/S0007114515004687.
https://www.ncbi.nlm.nih.gov/pubmed/26652155

ABSTRACT

Curcumin derived from turmeric is well documented for its anti-carcinogenic, antioxidant and anti-inflammatory properties. Recent studies show that curcumin also possesses neuroprotective and cognitive-enhancing properties that may help delay or prevent neurodegenerative diseases, including Alzheimer's disease (AD). Currently, clinical diagnosis of AD is onerous, and it is primarily based on the exclusion of other causes of dementia. In addition, phase III clinical trials of potential treatments have mostly failed, leaving disease-modifying interventions elusive. AD can be characterised neuropathologically by the deposition of extracellular β amyloid (Aβ) plaques and intracellular accumulation of tau-containing neurofibrillary tangles. Disruptions in Aβ metabolism/clearance contribute to AD pathogenesis. In vitro studies have shown that Aβ metabolism is altered by curcumin, and animal studies report that curcumin may influence brain function and the development of dementia, because of its antioxidant and anti-inflammatory properties, as well as its ability to influence Aβ metabolism. However, clinical studies of curcumin have revealed limited effects to date, most likely because of curcumin's relatively low solubility and bioavailability, and because of selection of cohorts with diagnosed AD, in whom there is already major neuropathology. However, the fresh approach of targeting early AD pathology (by treating healthy, pre-clinical and mild cognitive impairment-stage cohorts) combined with new curcumin formulations that increase bioavailability is renewing optimism concerning curcumin-based therapy. The aim of this paper is to review the current evidence supporting an association between curcumin and modulation of AD pathology, including in vitro and in vivo studies. We also review the use of curcumin in emerging retinal imaging technology, as a fluorochrome for AD diagnostics.

43. Aggarwal BB, Harikumar KB. "Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases." Int J Biochem Cell Biol. 2009 Jan;41(1):40-59.
http://www.ncbi.nlm.nih.gov/pubmed/18662800

ABSTRACT

Although safe in most cases, ancient treatments are ignored because neither their active component nor their molecular targets are well defined. This is not the case, however, with curcumin, a yellow-pigment substance and component of turmeric (Curcuma longa), which was identified more than a century ago. For centuries it has been known that turmeric exhibits anti-inflammatory activity, but extensive research performed within the past two decades has shown that this activity of turmeric is due to curcumin (diferuloylmethane). This agent has been shown to regulate numerous transcription factors, cytokines, protein kinases, adhesion molecules, redox status and enzymes that have been linked to inflammation. The process of inflammation has been shown to play a major role in most chronic illnesses, including neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases. In the current review, we provide evidence for the potential role of curcumin in the prevention and treatment of various proinflammatory chronic diseases. These features, combined with the pharmacological safety and negligible cost, render curcumin an attractive agent to explore further.

44. Keech AM. "Peptide Immunotherapy-Colostrum A Physician's reference guide."
http://www.drkeech.com

"For thousands of years raw colostrum has been consumed to help with all sorts of health challenges. In recent years with the use of modern manufacturing techniques, the benefits of consuming raw colostrum have been preserved in powdered colostrum. In the last ten years more advanced fractionation technologies have allowed the large-scale production of liquid colostrum supplements. Now we are observing a revival in the use of colostrum liquids and powders.

Colostrum Peptides, more commonly known as Proline-rich Polypeptides (PRPs) are isolated in these liquid colostrum products. Peptide Immunotherapy is the scientific classification of how these PRPs modulate or balance the human immune system. Constantly balancing and re-teaching the human immune system how to function through passive transfer is the information key to health in all mammals, including humans. So when our immune system faces daily health challenges, we are equipped and ready to defend ourselves down to the molecular levels … thanks to Colostrum Peptides."

45. **Sajdel-Sulkowska E, and Zabielski R. "Gut Microbiome and Brain-Gut Axis in Autism — Aberrant Development of Gut-Brain Communication and Reward Circuitry." Recent Advances in Autism Spectrum Disorders - Volume I, Prof. Michael Fitzgerald (Ed.), ISBN: 978-953-51-1021-7.**
https://www.intechopen.com/books/recent-advances-in-autism-spectrum-disorders-volume-i/gut-microbiome-and-brain-gut-axis-in-autism-aberrant-development-of-gut-brain-communication-and-rewa

NO ABSTRACT AVAILABLE

Introduction

The function of the gut microbiome and the bidirectional communication between the gastrointestinal tract (GIT) and the brain is increasingly recognized in health and disease and disruption in its composition is not unique to the autistic pathology. However, the bidirectional communication between the gut and the brain, "the gut-brain/brain-gut axis" in autism has been relatively understudied. In general, this communication between gut and brain occurs through a direct neuronal pathway via the vagus nerve, the hormonal pathway of several hormones involved in the regulation of food intake, such as cholecystokinin (CCK), ghrelin, leptin and insulin, and by the immunological signaling pathway involving cytokines. Recent studies indicate that the vagus nerve is involved in immunomodulation as suggested by its ability to attenuate the production of proinflammatory cytokines in experimental models of inflammation (de Jonge and Ullola, 2007). Furthermore, the gut microbiome emerges as a major player not only in the maturation of GIT tissue and the gut brain axis but also in brain maturation, through its effect on both the immune and endocrine systems. Many toxins, toxicants, infectious agents, diet or stress, affect an individual's gut microbiome, which may be especially sensitive during the critical developmental period. Disruption of the developing microbiome may have profound consequences on the developing gut-brain axis including the brain as well as long-term effects on both the physical and psychological development.

46. **J Atheroscler Thromb. "How macrophages are converted to foam cells." 2012;19(10):949-50.**
https://www.ncbi.nlm.nih.gov/pubmed/22785084

NO ABSTRACT AVAILABE

47. **Choung RS, et al. "Determination of B-Cell Epitopes in Patients with Celiac Disease: Peptide Microarrays." PLoS One. 2016 Jan 29;11(1):e0147777.**
http://www.ncbi.nlm.nih.gov/pubmed/26824466

ABSTRACT

BACKGROUND:
Most antibodies recognize conformational or discontinuous epitopes that have a specific 3-dimensional shape; however, determination of discontinuous B-cell epitopes is a major challenge in bioscience. Moreover, the current methods for identifying peptide epitopes often involve laborious, high-cost peptide screening programs. Here, we present a novel microarray method for identifying discontinuous B-cell epitopes in celiac disease (CD) by using a silicon-based peptide array and computational methods.

METHODS:
Using a novel silicon-based microarray platform with a multi-pillar chip, overlapping 12-mer peptide sequences of all native and deamidated gliadins, which are known to trigger CD, were synthesized in situ and used to identify peptide epitopes.

RESULTS:
Using a computational algorithm that considered disease specificity of peptide sequences, 2 distinct epitope sets were identified. Further, by combining the most discriminative 3-mer gliadin sequences with randomly interpolated3- or 6-mer peptide sequences, novel discontinuous epitopes were identified and further optimized to maximize disease discrimination. The final discontinuous epitope sets were tested in a confirmatory cohort of CD patients and controls, yielding 99% sensitivity and 100% specificity.

CONCLUSIONS:
These novel sets of epitopes derived from gliadin have a high degree of accuracy in differentiating CD from controls, compared with standard serologic tests. The method of ultra-high-density peptide microarray described here would be broadly useful to develop high-fidelity diagnostic tests and explore pathogenesis.

48. **Bland, Jeffrey, and Sara H. Benum. *Genetic Nutritioneering*. Los Angeles: Keats Pub., 1999. Print.**

NO ABSTRACT AVAILABLE

Excerpt
"Throughout your life the most profound influences on your health, vitality and function are not the Doctors you have visited or the drugs, surgery, or other therapies you have undertaken. The most profound influences are the cumulative effects of the decisions you make about your diet and lifestyle on the expression of your genes."

DR. THOMAS O'BRYAN DC, CCN, DACBN

About Dr. Tom O'Bryan

Dr. O'Bryan believes in making a difference in the world, one healthy human being at a time. As an internationally recognized and sought after speaker and workshop leader, Dr. O'Bryan specializes in the complications of Non-Celiac Gluten Sensitivity, Celiac Disease and Autoimmune Diseases as they occur inside and outside of the intestines.

In November 2016, Dr. O'Bryan released *Betrayal: The Autoimmune Disease Solution They're Not Telling You,* an investigation into the global effects of issues underlying our autoimmune system and chronic disease. Currently, over 300,000 people world-wide have watched the docu-series.

Dr. O'Bryan is considered the 'Sherlock Holmes' for chronic disease and metabolic disorders. He is a clinician par excellence in treating chronic disease and metabolic disorders from a Functional Medicine Perspective. He holds teaching Faculty positions with the Institute for Functional Medicine and the National University of Health Sciences. He has trained and certified tens of thousands of practitioners around the world in advanced understanding of the impact of wheat sensitivity and the development of individual autoimmune diseases.

His 2016 ground-breaking book*, 'The Autoimmune Fix',* outlines the step-by-step development of degenerative diseases and gives us the tools to identify our dis-ease process years before the symptoms become obvious and turn into full blown diseases. The work became the winner of the *National Book Award* and ranked #1 in several categories on Amazon.com.