A humán mikrobiom és ennek gyakorlati jelentősége a klinikumban

Schwab Richárd dr.
Diavitas - MIND Klinika Zrt

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1. **Bevezetés**
2. Microbiome
3. Barrier és gyulladás
4. Daganatok
5. Klinikai gyakorlat

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ALCÍM: Mennyire tarthatók oki kezelésnek a legnagyobb népegészségügyi jelentőségű (korábban „időskori") kórképek jelenlegi terápiái?

Fertőző betegségek 1928-ig (A. Fleming / penicillin)

- Simple tertian spikes 3 days => P ovale &
- Simple quartan spikes 4 days => P.
- Malignant tertian => Cerebral malaria
- Typhoid fever
- Pel-Ebstein - cyclical: Hogdkin's lymphoma
- Intermittent: abscess / septic
- Step ladder rise: typhoid

- **Hypertension**
- **Diabetes**
- **Obesity**
- **Reflux disease**
- **Atherosclerosis**
- **Alzheimer's (deg.)**
- **R.Arthritis (deg.)**

=> We desperately need the "causative link" to disease pathology just like with antibiotics...

3

Blood Pressure Categories

BLOOD PRESSURE CATEGORY	SYSTOLIC mm Hg (upper number)		DIASTOLIC mm Hg (lower number)
NORMAL	LESS THAN 120	and	LESS THAN 80
ELEVATED	120 – 129	and	LESS THAN 80
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 1	130 – 139	or	80 – 89
HIGH BLOOD PRESSURE (HYPERTENSION) STAGE 2	140 OR HIGHER	or	90 OR HIGHER
HYPERTENSIVE CRISIS (consult your doctor immediately)	HIGHER THAN 180	and/or	HIGHER THAN 120

4

A gyógyszerpiac (USA)

The guideline authors said that the impact of the new guideline will be greatest among younger people. They said **the prevalence of hypertension in people under the age of 45 would triple among men and double among women.**
The **prevalence** of hypertension will increase from 31.9% under JNC7 criteria to **45.6%**. **This works out to 103.3 million people** who will be categorized as having high blood pressure.
In the new guideline **antihypertensive drug therapy is recommended for 36.2% of US adults, or 81.9 million adults**, while 21.4 million are recommended for nonpharmacologic therapy only. The new guideline increases the number of US adults recommended for drug therapy by 4.2m.

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A „két genomunk”

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METHOD: 16s rRNA sequencing with NGS

16s rRNA is a component of the 30S small subunit of prokaryotic ribosomes. It has highly conserved primer binding sites and contains hypervariable regions that can provide species-specific signature sequences useful for identification of bacteria.

As a result, 16S rRNA gene sequencing has become prevalent in medical microbiology as a rapid and cheap alternative to phenotypic methods of bacterial identification.

Although it was originally used to identify bacteria, 16S sequencing was subsequently found to be capable of reclassifying bacteria into completely new species,[17] or even genera.[18][19] It has also been used to describe new species that have never been successfully cultured

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A Humán Mikrobiom

- A bél „mikrobiom” (amit korábban bélflóraként ismertünk és mikrobiotaként is ismert) több ezer milliárd mikroorganizmusból áll.
- A benne élő fajok sokasága (diverzitás) és épsége/funkciója döntő szerepet játszik a gazdaszervezet egészséges anyagcseréjének kialakulásában.
- A fajok száma természeti népeknél kb 6000 és ezek génállománya 3 milliónál is gazdagabb (kb 150x több, mint a humán genomot alkotó géneké).
- A mikrobiom összesen 2kg tömeget is elérhet. 30%-a nagy hasonlóságot mutat az emberek/rasszok között, 70%-a viszont abszolút egyedi és ránk, szűkebb-tágabb környezetünkre jellemző. A mikrobiomunk tehát egy abszolút egyedi azonosítónk…

www.gutmicrobiotawatch.org/gut-microbiota-info/

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The gut microbiota manages host metabolism

METABOLISM IN 2013

Nature Reviews in Endocrinology 2013

Patrice D. Cani

In 2013, studies in rodents and humans have reaffirmed the essential role of the gut microbiota in host metabolism. More importantly, several converging results have increased our knowledge regarding the taxa and functions of the gut microbiota that contribute to the management of energy homeostasis, glucose metabolism and metabolic inflammation.

Cani, P. D. *Nat. Rev. Endocrinol.* **10**, 74–76 (2014); published online 10 December 2013; doi:10.1038/nrendo.2013.240

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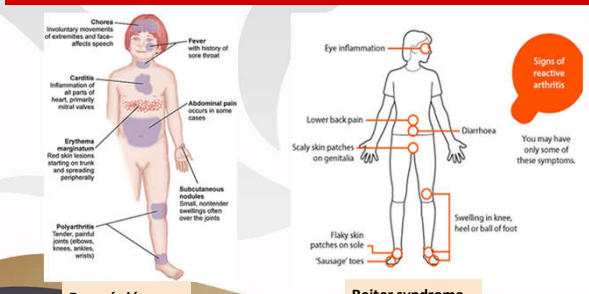
Klasszikus mikrobiom asszociált betegség modellek



12

eLife. 2013 Nov 5;2:e01202. doi: 10.7554/eLife.01202

Expansion of intestinal Prevotella copri correlates with enhanced susceptibility to arthritis.

Scher JU[1], Sczesnak A, Longman RS, Segata N, Ubeda C, Bielski C, Rostron T, Cerundolo V, Pamer EG, Abramson SB, Huttenhower C, Littman DR

Author information

Abstract

Rheumatoid arthritis (RA) is a prevalent systemic autoimmune disease, caused by a combination of genetic and environmental factors. Animal models suggest a role for intestinal bacteria in supporting the systemic immune response required for joint inflammation. Here we performed 16S sequencing on 114 stool samples from rheumatoid arthritis patients and controls, and shotgun sequencing on a subset of 44 such samples. We identified the presence of Prevotella copri as strongly correlated with disease in new-onset untreated rheumatoid arthritis (NORA) patients. Increases in Prevotella abundance correlated with a reduction in Bacteroides and a loss of reportedly beneficial microbes in NORA subjects. We also identified unique Prevotella genes that correlated with disease. Further, colonization of mice revealed the ability of P. copri to dominate the intestinal microbiota and resulted in an increased sensitivity to chemically induced colitis. This work identifies a potential role for P. copri in the pathogenesis of RA. DOI: http://dx.doi.org/10.7554/eLife.01202.001.

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Hepatology. 2016 Mar;63(3):764-75. doi: 10.1002/hep.28356. Epub 2016 Jan 13.

The severity of nonalcoholic fatty liver disease is associated with gut dysbiosis and shift in the metabolic function of the gut microbiota.

Boursier J[1,2], Mueller O[3], Barret M[4], Machado M[5], Fizanne L[2], Araujo-Perez F[6], Guy CD[7], Seed PC[3,6], Rawls JF[3], David LA[3], Hunault G[2], Oberti F[1,2], Calès P[1,2], Diehl AM[5].

Author information

Abstract

Several animal studies have emphasized the role of gut microbiota in nonalcoholic fatty liver disease (NAFLD). However, data about gut dysbiosis in human NAFLD remain scarce in the literature, especially studies including the whole spectrum of NAFLD lesions. We aimed to evaluate the association between gut dysbiosis and severe NAFLD lesions, that is, nonalcoholic steatohepatitis (NASH) and fibrosis, in a well-characterized population of adult NAFLD. Fifty-seven patients with biopsy-proven NAFLD were enrolled. Taxonomic composition of gut microbiota was determined using 16S ribosomal RNA gene sequencing of stool samples. Thirty patients had F0/F1 fibrosis stage at liver biopsy (10 with NASH), and 27 patients had significant F≥2 fibrosis (25 with NASH). Bacteroides abundance was significantly increased in NASH and F≥2 patients, whereas Prevotella abundance was decreased. Ruminococcus abundance was significantly higher in F≥2 patients. By multivariate analysis, Bacteroides abundance was independently associated with NASH and Ruminococcus with F≥2 fibrosis. Stratification according to the abundance of these two bacteria generated three patient subgroups with increasing severity of NAFLD lesions. Based on imputed metagenomic profiles, Kyoto Encyclopedia of Genes and Genomes pathways significantly related to NASH and fibrosis F≥2 were mostly related to carbohydrate, lipid, and amino acid metabolism.

CONCLUSION: NAFLD severity associates with gut dysbiosis and a shift in metabolic function of the gut microbiota. We identified Bacteroides as independently associated with NASH and Ruminococcus with significant fibrosis. Thus, gut microbiota analysis adds information to classical predictors of NAFLD severity and suggests novel metabolic targets for pre-/probiotics therapies.

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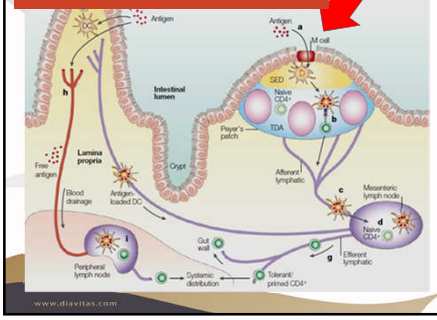
Az intestinális barrier



M-sejtek*

- Antigén "mintavétel"
- A bél barrier sérülés és potenciális pathogén invázióra "felkészülés"
- Energia-igényes
- "Szennyezett" (=diverz antigén környezetben) kevésbé aktív
- minél homogénebb az antigén "kontaminációval" (=alacsonyabb a diverzitás) annál aktívabb

* microfold sejtek

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Non-alcoholic fatty liver and the gut microbiota.

Mol Metab. 2016 Jun 14;5(9):782-94.

Bashiardes S[1], Shapiro H[1], Rozin S[1], Shibolet O[2], Elinav E[1].

Author information

Abstract

BACKGROUND: Non-alcoholic fatty liver (NAFLD) is a common, multi-factorial, and poorly understood liver disease whose incidence is globally rising. NAFLD is generally asymptomatic and associated with other manifestations of the metabolic syndrome. Yet, up to 25% of NAFLD patients develop a progressive inflammatory liver disease termed non-alcoholic steatohepatitis (NASH) that may progress towards cirrhosis, hepatocellular carcinoma, and the need for liver transplantation. In recent years, several lines of evidence suggest that the gut microbiome represents a significant environmental factor contributing to NAFLD development and its progression into NASH. Suggested microbiome-associated mechanisms contributing to NAFLD and NASH include dysbiosis-induced deregulation of the gut endothelial barrier function, which facilitates systemic bacterial translocation, and intestinal and hepatic inflammation. Furthermore, increased microbiome-modulated metabolites such as lipopolysaccharides, short chain fatty acids (SCFAs), bile acids, and ethanol, may affect liver pathology through multiple direct and indirect mechanisms.

SCOPE OF REVIEW: Herein, we discuss the associations, mechanisms, and clinical implications of the microbiome's contribution to NAFLD and NASH. Understanding these contributions to the development of fatty liver pathogenesis and its clinical course may serve as a basis for development of therapeutic microbiome-targeting approaches for treatment and prevention of NAFLD and NASH.

MAJOR CONCLUSIONS: Intestinal host-microbiome interactions play diverse roles in the pathogenesis and progression of NAFLD and NASH. Elucidation of the mechanisms driving these microbial effects on the pathogenesis of NAFLD and NASH may enable to identify new diagnostic and therapeutic targets of these common metabolic liver diseases. This article is part of a special issue on microbiota.

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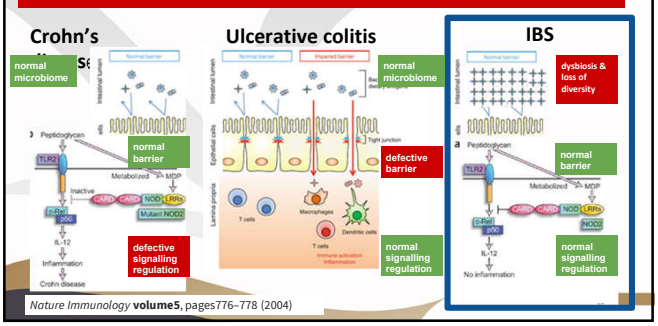
Pathogen Associated Molecular Patterns (PAMP's) and IBD



Nature Immunology **volume5**, pages776–778 (2004)

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United European Gastroenterol J. 2018 Feb;6(1):112-122. doi: 10.1177/2050640617708953. Epub 2017 May 5.

The gut microbiota, bile acids and their correlation in primary sclerosing cholangitis associated with inflammatory bowel disease.

Torres J[1,2], Palmela C[1], Brito H[3], Bao X[4], Rupoi H[5], Moura-Santos P[6], Pereira da Silva J[7], Oliveira A[8], Vieira C[9], Perez K[10], Itzkowitz SH[2], Colombel JF[2], Humbert L[10], Raimbeau D[10], Cravo M[1], Rodrigues CM[5], Hu J[4].

Author information

Abstract

BACKGROUND: Patients with primary sclerosing cholangitis associated with inflammatory bowel disease (PSC-IBD) have a very high risk of developing colorectal neoplasia. Alterations in the gut microbiota and/or gut bile acids could account for the increase in this risk. However, no studies have yet investigated the net result of cholestasis and a potentially altered bile acid pool interacting with a dysbiotic gut flora in the inflamed colon of PSC-IBD.

AIM: The aim of this study was to compare the gut microbiota and stool bile acid profiles, as well as and their correlation in patients with PSC-IBD and inflammatory bowel disease alone.

METHODS: Thirty patients with extensive colitis (15 with concomitant primary sclerosing cholangitis) were prospectively recruited and fresh stool samples were collected. The microbiota composition in stool was profiled using bacterial 16S rRNA sequencing. Stool bile acids were assessed by high-performance liquid chromatography tandem mass spectrometry.

RESULTS: The total stool bile acid pool was significantly reduced in PSC-IBD. Although no major differences were observed in the individual bile acid species in stool, their overall combination allowed a good separation between PSC-IBD and inflammatory bowel disease. Compared with inflammatory bowel disease alone, PSC-IBD patients demonstrated a different gut microbiota composition with enrichment in *Ruminococcus* and *Fusobacterium* genus compared with inflammatory bowel disease. At the operational taxonomic unit level major shifts were observed within the *Firmicutes* (73%) and *Bacteroidetes* phyla (17%). Specific microbiota-bile acid correlations were observed in PSC-IBD, where 12% of the operational taxonomic units strongly correlated with stool bile acids, compared with only 0.4% in non-PSC-IBD.

CONCLUSIONS: Patients with PSC-IBD had distinct microbiota and microbiota-stool bile acid correlations as compared with inflammatory bowel disease. Whether these changes are associated with, or may predispose to, an increased risk of colorectal neoplasia needs to be further clarified.

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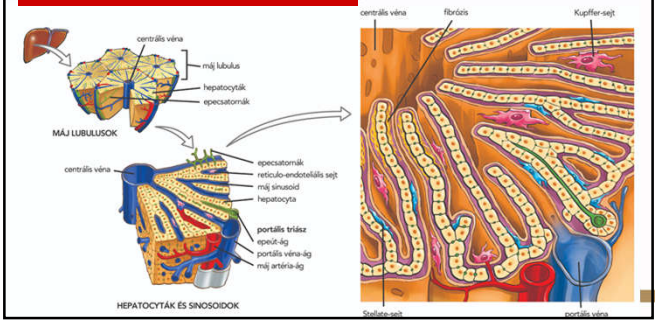
A sinusoid keringés

KLINIKAI ONKOLÓGIA | 2019;6(1):25–33.



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Sci Adv. 2019 Jan 23;5(1):eaau3333. doi: 10.1126/sciadv.aau3333. eCollection 2019 Jan.

Porphyromonas gingivalis in Alzheimer's disease brains: Evidence for disease causation and treatment with small-molecule inhibitors.

Dominy SS[1], Lynch C[1], Ermini F[1], Benedyk M[2,3], Marczyk A[2], Konradi A[1], Nguyen M[1], Haditsch U[1], Raha D[1], Griffin C[1], Holsinger LJ[1], Arastu-Kapur S[1], Kaba S[1], Lee A[1], Ryder MI[4], Potempa B[5], Mydel P[2,6], Hellvard A[3,6], Adamowicz K[2], Hasturk H[7,8], Walker GD[9], Reynolds EC[9], Faull RLM[10], Curtis MA[11,12], Dragunow M[11,13], Potempa J[2,5]

Author information

Abstract

Porphyromonas gingivalis, the keystone pathogen in chronic periodontitis, was identified in the brain of Alzheimer's disease patients. Toxic proteases from the bacterium called gingipains were also identified in the brain of Alzheimer's patients, and levels correlated with tau and ubiquitin pathology. Oral *P. gingivalis* infection in mice resulted in brain colonization and increased production of $A\beta_{1-42}$, a component of amyloid plaques. Further, gingipains were neurotoxic in vivo and in vitro, exerting detrimental effects on tau, a protein needed for normal neuronal function. To block this neurotoxicity, we designed and synthesized small-molecule inhibitors targeting gingipains. Gingipain inhibition reduced the bacterial load of an established *P. gingivalis* brain infection, blocked $A\beta_{1-42}$ production, reduced neuroinflammation, and rescued neurons in the hippocampus. These data suggest that gingipain inhibitors could be valuable for treating *P. gingivalis* brain colonization and neurodegeneration in Alzheimer's disease.

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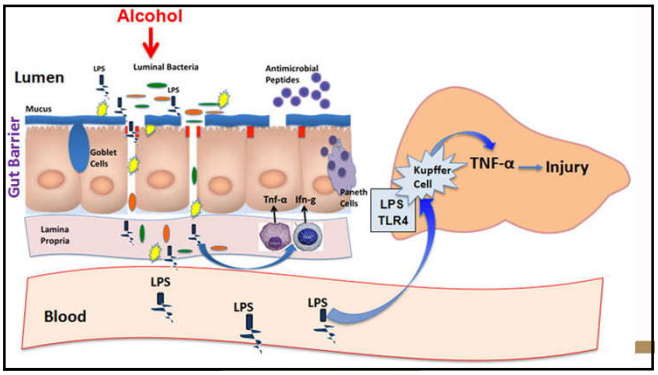

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Infect Immun. 2016 Jun 23;84(7):2141-2148. doi: 10.1128/IAI.01305-15. Print 2016 Jul.

Endothelial Cell Response to Fusobacterium nucleatum.

Mendes RT[1,2], Nguyen D[1], Stephens D[1], Pamuk F[1,3], Fernandes D[2], Van Dyke TE[1], Kantarci A[4].

Author information

Abstract

Vascular response is an essential aspect of an effective immune response to periodontal disease pathogens, as new blood vessel formation contributes to wound healing and inflammation. Gaining a greater understanding of the factors that affect vascular response may then contribute to future breakthroughs in dental medicine. In this study, we have characterized the endothelial cell response to the common bacterium Fusobacterium nucleatum, an important bridging species that facilitates the activity of late colonizers of the dental biofilm. Endothelial cells were infected with Fusobacterium nucleatum (strain 25586) for periods of 4, 12, 24, or 48 h. Cell proliferation and tube formation were analyzed, and expression of adhesion molecules (CD31 and CD34) and vascular endothelial growth factor (VEGF) receptors 1 and 2 was measured by fluorescence-activated cell sorter (FACS) analysis. Data indicate that F. nucleatum impaired endothelial cell proliferation and tube formation. The findings suggest that the modified endothelial cell response acts as a mechanism promoting the pathogenic progression of periodontal diseases and may potentially suggest the involvement of periodontopathogens in systemic diseases associated with periodontal inflammation.

PMID: 27185790 PMCID: PMC4936358 DOI: 10.1128/IAI.01305-15

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Diabetol Metab Syndr. 2017 Sep 22;9:73. doi: 10.1186/s13098-017-0271-8. eCollection 2017.

The promotion of nephropathy by _Porphyromonas gingivalis_ lipopolysaccharide via toll-like receptors.

Kajiwara K[1], Takata S[1], To TT[2], Takara K[1], Hatakeyama Y[3], Tamaoki S[1], Darveau RP[4], Ishikawa H[5], Sawa Y[6].

Author information

Abstract

BACKGROUND: Recently, we reported that toll-like receptor (TLR)2 and TLR4 localized on the glomerular endothelium in the glomeruli of streptozotocin (STZ)-induced type 1 diabetic mice and high fat diet feed-induced type 2 diabetic mice, and that periodontal pathogen Porphyromonas gingivalis LPS (Pg-LPS) administration lowered the survival rate of diabetic mice. The present study aims to examine the effect of TLR4 blocking on the suppression of Pg-LPS-induced diabetic nephropathy.

METHODS: The survival rate and morphological/biochemical features for streptozotocin-induced diabetic mice with Pg-LPS and TLR4 blocker eritoran administration were investigated by reporter gene assay, urine and blood analysis, immunohistochemistry, and real time-PCR.

RESULTS AND CONCLUSIONS: All of the diabetic mice administered Pg-LPS were euthanized within the survival period of almost all of the diabetic mice. The blood urea nitrogen and creatinine, expression of TLR2 and TGF-b, and type 1 collagen accumulation, in the diabetic mice increased significantly with the Pg-LPS administration. In spite of the limited TLR4 activation with Pg-LPS, the TLR4 blocker eritoran decreased blood urea nitrogen and creatinine, and raised the survival rate of the Pg-LPS-administered diabetic mice slightly. The high expression levels of TLR2, TGF-b, and type 1 collagen in Pg-LPS-administered diabetic mice decreased with eritoran. Nuclear STAT3 which enhances TLR2 expression was detected in the TLR2-expressing glomeruli of diabetic mice. The TLR2 and STAT3 gene expression increased by the Pg-LPS administration but decreased with eritoran. These may suggest that Pg-LPS-induced diabetic nephropathy is mainly dependent on TLR2 signaling on glomerular endothelial cells, and that TLR4 blocker eritoran may play a role to slow the progress of diabetic nephropathy.

PMID: 29018490 PMCID: PMC5610442 DOI: 10.1186/s13098-017-0271-8

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J Physiol. 2017 Mar 1;595(5):1831-1845. doi: 10.1113/JP273269. Epub 2017 Feb 8.

Western diet induces colonic nitrergic myenteric neuropathy and dysmotility in mice via saturated fatty acid- and lipopolysaccharide-induced TLR4 signalling.

Reichardt F[1], Chassaing B[2], Nezami BG[1], Li G[1], Tabatabavakili S[1], Mwangi S[1], Uppal K[3], Liang B[3], Vijay-Kumar M[4], Jones D[3], Gewirtz AT[2], Srinivasan S[1].

Author information

Abstract

KEY POINTS: A high-fat diet (60% kcal from fat) is associated with motility disorders inducing constipation and loss of nitrergic myenteric neurons in the proximal colon. Gut microbiota dysbiosis, which occurs in response to HFD, contributes to endotoxaemia. High levels of lipopolysaccharide lead to apoptosis in cultured myenteric neurons that express Toll-like receptor 4 (TLR4). Consumption of a Western diet (WD) (35% kcal from fat) for 6 weeks leads to gut microbiota dysbiosis associated with altered bacterial metabolites and increased levels of plasma free fatty acids. These disorders precede the nitrergic myenteric cell loss observed in the proximal colon. Mice lacking TLR4 did not exhibit WD-induced myenteric cell loss and dysmotility. Lipopolysaccharide-induced in vitro enteric neurodegeneration requires the presence of palmitate and may be a result of enhanced NO production. The present study highlights the critical role of plasma saturated free fatty acids that are abundant in the WD with respect to driving enteric neuropathy and colonic dysmotility.

ABSTRACT: The consumption of a high-fat diet (HFD) is associated with myenteric neurodegeneration, which in turn is associated with delayed colonic transit and constipation. We examined the hypothesis that an inherent increase in plasma free fatty acids (FFA) in the HFD together with an HFD-induced alteration in gut microbiota contributes to the pathophysiology of these disorders. C57BL/6 mice were fed a Western diet (WD) (35% kcal from fat enriched in palmitate) or a purified regular diet (16.9% kcal from fat) for 3, 6, 9 and 12 weeks. Gut microbiota dysbiosis was investigated by fecal lipopolysaccharide (LPS) measurement and metabolomics (linear trap quadrupole-Fourier transform mass spectrometer) analysis. Plasma FFA and LPS levels were assessed, in addition to colonic and ileal nitrergic myenteric neuron quantifications and motility. Compared to regular diet-fed control mice, WD-fed mice gained significantly more weight without blood glucose alteration. Dysbiosis was exhibited after 6 weeks of feeding, as reflected by increased fecal LPS and bacterial metabolites and concomitant higher plasma FFA. The numbers of nitrergic myenteric neurons were reduced in the proximal colon after 9 and 12 weeks of WD and this was also associated with delayed colonic transit. WD-fed Toll-like receptor 4 ($TLR4^{-/-}$ mice did not exhibit myenteric cell loss or dysmotility. Finally, LPS (0.5-2 $ng\,ml^{-1}$) and palmitate (20 and 30 μm) acted synergistically to induce neuronal cell death in vitro, which was prevented by the nitric oxide synthase inhibitor NG-nitro-l-arginine methyl ester. In conclusion, WD-feeding results in increased levels of FFA and microbiota that, even in absence of hyperglycaemia or overt endotoxaemia, synergistically induce TLR4-mediated neurodegeneration and dysmotility.

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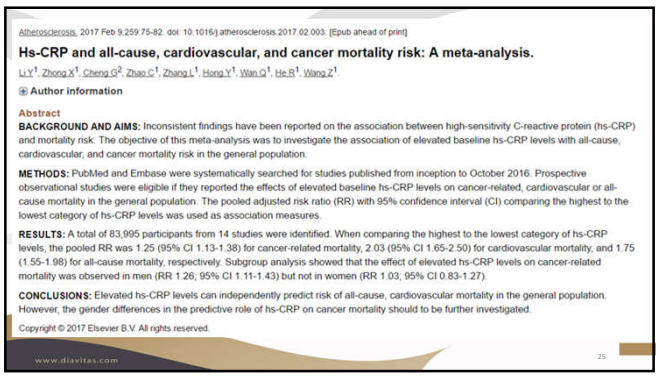

Atherosclerosis. 2017 Feb 9;259:75-82. doi: 10.1016/j.atherosclerosis.2017.02.003. [Epub ahead of print]

Hs-CRP and all-cause, cardiovascular, and cancer mortality risk: A meta-analysis.

Li Y[1], Zhong X[1], Cheng G[2], Zhao C[1], Zhang L[1], Hong Y[1], Wan Q[1], He R[1], Wang Z[1]

Author information

Abstract

BACKGROUND AND AIMS: Inconsistent findings have been reported on the association between high-sensitivity C-reactive protein (hs-CRP) and mortality risk. The objective of this meta-analysis was to investigate the association of elevated baseline hs-CRP levels with all-cause, cardiovascular, and cancer mortality risk in the general population.

METHODS: PubMed and Embase were systematically searched for studies published from inception to October 2016. Prospective observational studies were eligible if they reported the effects of elevated baseline hs-CRP levels on cancer-related, cardiovascular or all-cause mortality in the general population. The pooled adjusted risk ratio (RR) with 95% confidence interval (CI) comparing the highest to the lowest category of hs-CRP levels was used as association measures.

RESULTS: A total of 83,995 participants from 14 studies were identified. When comparing the highest to the lowest category of hs-CRP levels, the pooled RR was 1.25 (95% CI 1.13-1.38) for cancer-related mortality, 2.03 (95% CI 1.65-2.50) for cardiovascular mortality, and 1.75 (1.55-1.98) for all-cause mortality, respectively. Subgroup analysis showed that the effect of elevated hs-CRP levels on cancer-related mortality was observed in men (RR 1.26; 95% CI 1.11-1.43) but not in women (RR 1.03; 95% CI 0.83-1.27).

CONCLUSIONS: Elevated hs-CRP levels can independently predict risk of all-cause, cardiovascular mortality in the general population. However, the gender differences in the predictive role of hs-CRP on cancer mortality should to be further investigated.

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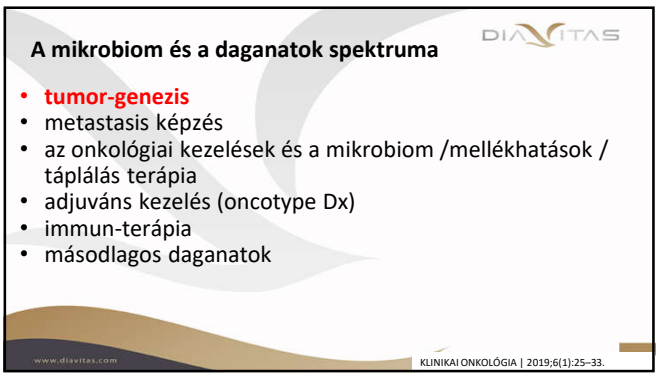

DIAVITAS

A mikrobiom és a daganatok spektruma

- **tumor-genezis**
- metastasis képzés
- az onkológiai kezelések és a mikrobiom /mellékhatások / táplálás terápia
- adjuváns kezelés (oncotype Dx)
- immun-terápia
- másodlagos daganatok

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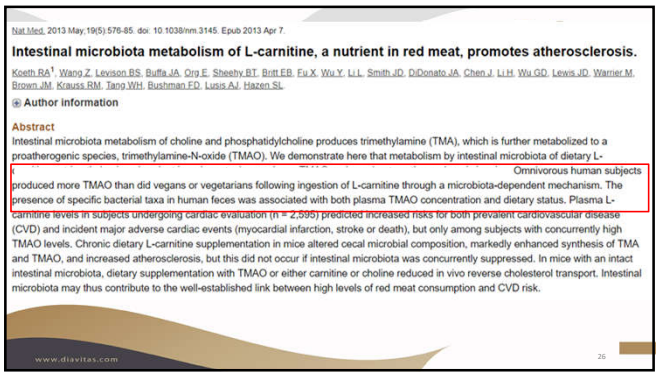

Nat Med. 2013 May;19(5):576-85. doi: 10.1038/nm.3145. Epub 2013 Apr 7.

Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis.

Koeth RA[1], Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, Britt EB, Fu X, Wu Y, Li L, Smith JD, DiDonato JA, Chen J, Li H, Wu GD, Lewis JD, Warrier M, Brown JM, Krauss RM, Tang WH, Bushman FD, Lusis AJ, Hazen SL

Author information

Abstract

Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is further metabolized to a proatherogenic species, trimethylamine-N-oxide (TMAO). We demonstrate here that metabolism by intestinal microbiota of dietary L-

Omnivorous human subjects produced more TMAO than did vegans or vegetarians following ingestion of L-carnitine through a microbiota-dependent mechanism. The presence of specific bacterial taxa in human feces was associated with both plasma TMAO concentration and dietary status. Plasma L-carnitine levels in subjects undergoing cardiac evaluation (n = 2,595) predicted increased risks for both prevalent cardiovascular disease (CVD) and incident major adverse cardiac events (myocardial infarction, stroke or death), but only among subjects with concurrently high TMAO levels. Chronic dietary L-carnitine supplementation in mice altered cecal microbial composition, markedly enhanced synthesis of TMA and TMAO, and increased atherosclerosis, but this did not occur if intestinal microbiota was concurrently suppressed. In mice with an intact intestinal microbiota, dietary supplementation with TMAO or either carnitine or choline reduced in vivo reverse cholesterol transport. Intestinal microbiota may thus contribute to the well-established link between high levels of red meat consumption and CVD risk.

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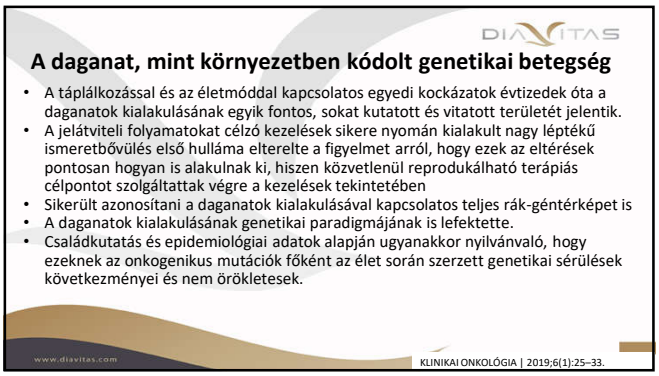

DIAVITAS

A daganat, mint környezetben kódolt genetikai betegség

- A táplálkozással és az életmóddal kapcsolatos egyedi kockázatok évtizedek óta a daganatok kialakulásának egyik fontos, sokat kutatott és vitatott területét jelentik.
- A jelátviteli folyamatokat célzó kezelések sikere nyomán kialakult nagy léptékű ismeretbővülés első hulláma elterelte a figyelmet arról, hogy ezek az eltérések pontosan hogyan is alakulnak ki, hiszen közvetlenül reprodukálható terápiás célpontot szolgáltattak végre a kezelések tekintetében
- Sikerült azonosítani a daganatok kialakulásával kapcsolatos teljes rák-géntérképet is
- A daganatok kialakulásának genetikai paradigmájának is lefektette.
- Családkutatás és epidemiológiai adatok alapján ugyanakkor nyilvánvaló, hogy ezeknek az onkogenikus mutációk főként az élet során szerzett genetikai sérülések következményei és nem örökletesek.

KLINIKAI ONKOLÓGIA | 2019;6(1):25–33.

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DIAVITAS

1. Bevezetés
2. Microbiome
3. Barrier és gyulladás
4. **Daganatok**
5. Klinikai gyakorlat

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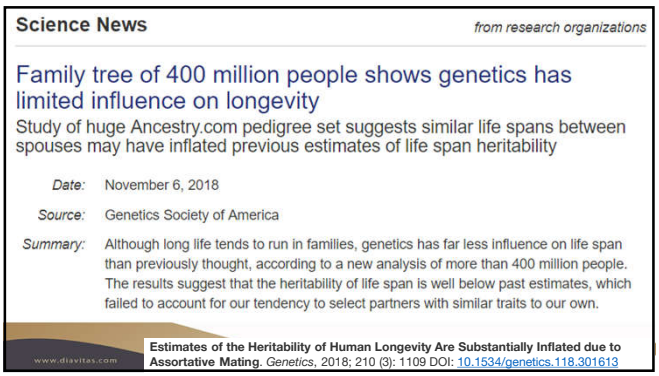

Science News *from research organizations*

Family tree of 400 million people shows genetics has limited influence on longevity

Study of huge Ancestry.com pedigree set suggests similar life spans between spouses may have inflated previous estimates of life span heritability

Date: November 6, 2018

Source: Genetics Society of America

Summary: Although long life tends to run in families, genetics has far less influence on life span than previously thought, according to a new analysis of more than 400 million people. The results suggest that the heritability of life span is well below past estimates, which failed to account for our tendency to select partners with similar traits to our own.

Estimates of the Heritability of Human Longevity Are Substantially Inflated due to Assortative Mating. *Genetics*, 2018; 210 (3): 1109 DOI: 10.1534/genetics.118.301613

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A Helicobacter Pylori

- A vírusok daganatkeltő hatása régóta ismert (Rous sarcoma virus => csirke sarcoma) - 1911 (Peyton Rous - Nobel dij 1966), a 4 gén közül az egyik az src kináz (J. Michael Bishop and Harold E. Varmus - Nobel dij 1989) … továbbiak EBV, HPV….
- Barry Marshall and Robin Warren (1982) gastritis, duodenalis ulcus es gyomorrák
- Globálisan 50% körüli a fertőzöttség, ami nagyobb fejlődő országokban és bizonyítottan emelkedett kockázat gyomorrák tekintetében. De a fertőzött emberek 85%-a egész életében tünetmentes.
- A MALT lymphoma: 72-98%-ban összefüggést mutat a Hp fertőzöttséggel és a Hp eradikáció a fertőzött egyéneknél az esetek 50-95%-ban komplett remissiót eredményez.

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KLINIKAI ONKOLÓGIA | 2019;6(1):25–33.

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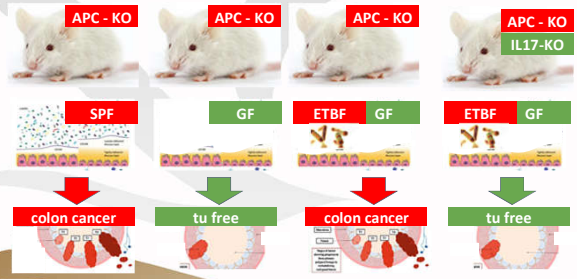
A vastagbélrák - genetikai betegség?



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Cell Host & Microbe, VOLUME 23, ISSUE 2, P203-214.E5, FEBRUARY 14, 2018

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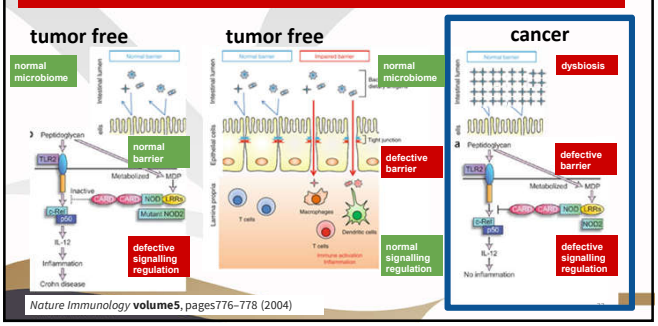
Pathogen Associated Molecular Patterns (PAMP's) and CRC



Nature Immunology **volume5**, pages776–778 (2004)

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45 éves nőbeteg

- A 2016-ban felfedezett CRC (akkor 42 éves)
- családban nem halmozódott
- colon ascendens/ coecum lokalizáció: grade III adenocc gelat. exulc. coli
- stadium: pT4aN2bV0pn0 (7/20 nycs poz, vasc, perineuralis invazio nem volt)
- KRAS vad (SE I-path) => neoadjuváns (FOLFOX) kemoth majd műtét
- PET távoli áttétet nem mutatott
- utána adjuváns chemoth (FOLFOX)

- 2019 januárban met hep., ascites, peritonealis invázió
- Oncompass 58 gén: KDR polymorfizmus, szuper vad tipus
- jelenleg is zajlik Cetuximab + FOLFOX és jól reagál

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1. Bevezetés
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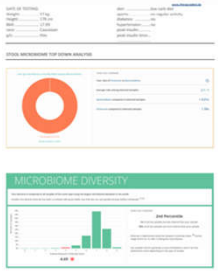
47y female: high dose antibiotics, severy diarrhea, weight loss

- The patient presented with severe diarrhea, weight loss, reactive arthritis, PSVT and skin problems
- Past medical history revealed long, combined antibiotics for sinusitis, multiple food allergies, arrhythmia related to certain foods
- SGT revealed a very severe loss (2% percentile) of the microbiome diversity with high dominance of stool Clostridiales (CD toxin negative)
- High protein and fiber diet improved symptoms but because of the almost complete loss of diversity the patient referred to fecal transplantation program.



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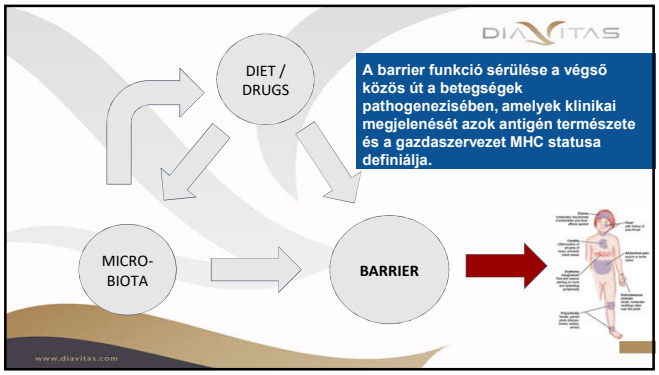

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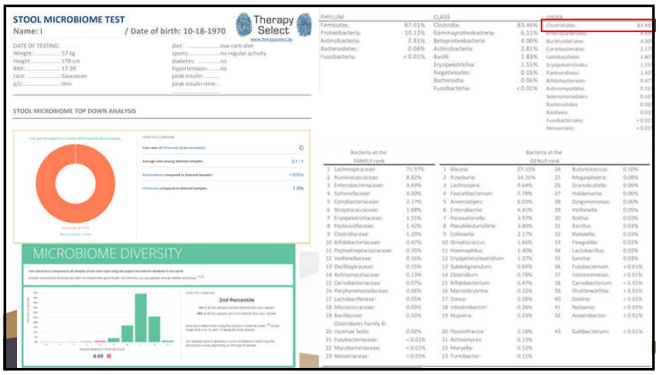

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Aliment Pharmacol Ther. 2015 Sep;42(5):515-28. doi: 10.1111/apt.13302. Epub 2015 Jul 6.

Chemotherapy-driven dysbiosis in the intestinal microbiome.

Montassier E[1,2], Gastinne T[3], Vangay P[4], Al-Ghalith GA[2,4], Bruley des Varannes S[5], Massart S[6], Moreau P[3], Potel G[1], de La Cochetière MF[7], Batard E[1], Knights D[2,8].

Author information

Abstract

BACKGROUND: Chemotherapy is commonly used as myeloablative conditioning treatment to prepare patients for haematopoietic stem cell transplantation (HSCT). Chemotherapy leads to several side effects, with gastrointestinal (GI) mucositis being one of the most frequent. Current models of GI mucositis pathophysiology are generally silent on the role of the intestinal microbiome.

AIM: To identify functional mechanisms by which the intestinal microbiome may play a key role in the pathophysiology of GI mucositis, we applied high-throughput DNA-sequencing analysis to identify microbes and microbial functions that are modulated following chemotherapy.

METHODS: We amplified and sequenced 16S rRNA genes from faecal samples before and after chemotherapy in 28 patients with non-Hodgkin's lymphoma who received the same myeloablative conditioning regimen and no other concomitant therapy such as antibiotics.

RESULTS: We found that faecal samples collected after chemotherapy exhibited significant decreases in abundances of Firmicutes ($P = 0.0002$) and Actinobacteria ($P = 0.002$) and significant increases in abundances of Proteobacteria ($P = 0.0002$) compared to samples collected before chemotherapy. Following chemotherapy, patients had reduced capacity for nucleotide metabolism ($P = 0.0001$), energy metabolism ($P = 0.001$), metabolism of cofactors and vitamins ($P = 0.006$), and increased capacity for glycan metabolism ($P = 0.0002$), signal transduction ($P = 0.0002$) and xenobiotics biodegradation ($P = 0.002$).

CONCLUSIONS: Our study identifies a severe compositional and functional imbalance in the gut microbial community associated with chemotherapy-induced GI mucositis. The functional pathways implicated in our analysis suggest potential directions for the development of intestinal microbiome-targeted interventions in cancer patients.

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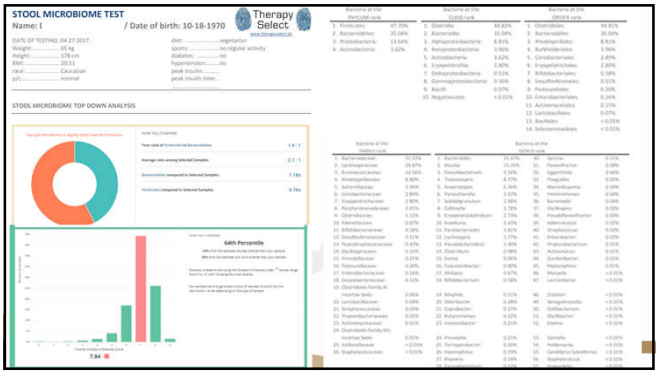

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PROBIOTIKUMOK

Advances in Microbiology, 2013, 3, 212-221
doi:10.4236/aim.2013.32032 Published Online June 2013 (http://www.scirp.org/journal/aim)
Scientific Research

Clinical Studies Evaluating Effects of Probiotics on Parameters of Intestinal Barrier Function

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ABSTRACT

The intestinal barrier is important in preventing translocation of bacteria, toxins and antigens from the lumen of the gut into the body. Enhanced permeability, or gut leakiness, has been associated with different diseases. Probiotics can, strain-specifically, improve the epithelial barrier function. However, so far most researches have used cell lines or animal models due to the difficulty of measuring the effects of products on the epithelial barrier function *in vivo* in humans. Here a systematic literature search was performed to find articles addressing the effects of probiotics on the barrier function in human trials. The Pubmed database was searched (January 2013) to identify human *in vivo* studies with probiotic products in which parameters for epithelial barrier function were measured. In total 29 studies were identified, but patients, bacterial characteristics and methods to measure intestinal barrier function caused large heterogeneity among these studies. About half of the studies showed positive results of probiotics on the epithelial barrier function, indicating a clear potential of probiotics in this field. In a case series of 14 patients using Ecologic®825, a probiotic food supplement with known effect on epithelial barrier function, different markers of intestinal integrity improved significantly. Further studies in this field should consider strain(s), dose and duration of the probiotic supplementation as well as the markers used to measure epithelial barrier function. Besides the lactulose/mannitol test, zonulin and α1-antitrypsin might be valuable markers to measure epithelial barrier function in future experiments.

Keywords: Bacteria; Epithelial Barrier; Gut Permeability; Intestinal Barrier Function; Intestinal Integrity; Probiotics; Review; Vivo Studies

- kevés az adat: de VAN!! az intestentinalis barrier funkció javítására
- A súlyos diverzitás-csökkenést (<15p) nem fogja helyreállítani (több ezer faj pusztult ki), **de az invazív fajok túlszaporodását megakadályozza**

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Az app ami összeköt

- Nem „B2C" eszköz: nem hiszünk abban, hogy a gép megmondja…
- Kommunikációs és logisztikai platform a beteg, az orvos(ok), a dietetikus és a személyi edző, gyógytornász között
- „okos tányér" alapú megközelítés, a betegeknek adagokat es elkészítési technológiákat kell (újra) tanulniuk
- Egy adatbázis, ahol orvosi leletek (változása), diétás információ és mozgás/sportra vonatkozó adatok egymás mellett vannak.
- és ez összekapcsolódik a beteg triage-al, az ananaesis felvétellel, az SGT lelet kiadással/véleményezéssel, a számlázással és beteg-behívással

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DE EZ REVERTÁLHATÓ

doi:10.1038/nature12820

Diet rapidly and reproducibly alters the human gut microbiome

Nature 2014 Jan 23;505(7484):559-63

Lawrence A. David[1,2]†, Corinne F. Maurice[1], Rachel N. Carmody[1], David B. Gootenberg[1], Julie E. Button[1], Benjamin E. Wolfe[1], Alisha V. Ling[3], A. Sloan Devlin[4], Yug Varma[4], Michael A. Fischbach[4], Sudha B. Biddinger[3], Rachel J. Dutton[1] & Peter J. Turnbaugh[1]

- **Diéta**
- **Mozgás**
- **Alkohol absztinencia**
- **alvás higiénia**
- **probiotikumok**

Long-term dietary intake influences the structure and activity of the trillions of microorganisms residing in the human gut[1-5], 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[2], 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[6]. In concert, these results demonstrate that the gut microbiome can rapidly respond to altered diet, potentially facilitating the diversity of human dietary lifestyles.

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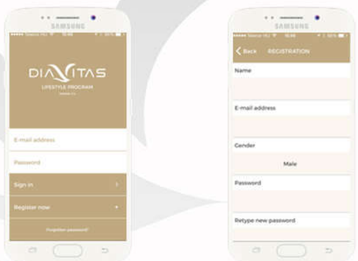
Diavitas Okostelefon App



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