Hospital San Pedro

Rioja Salud
Departamento de Enfermedades Infecciosas

CIBIR
Centro de Investigación Biomédica de La Rioja

Microbioma, VIH y fármacos antirretrovirales

Dr. José A. Oteo Revuelta

A Coruña, 5 de febrero de 2016

Agenda

Conceptos básicos sobre el microbioma y la microbiota intestinal

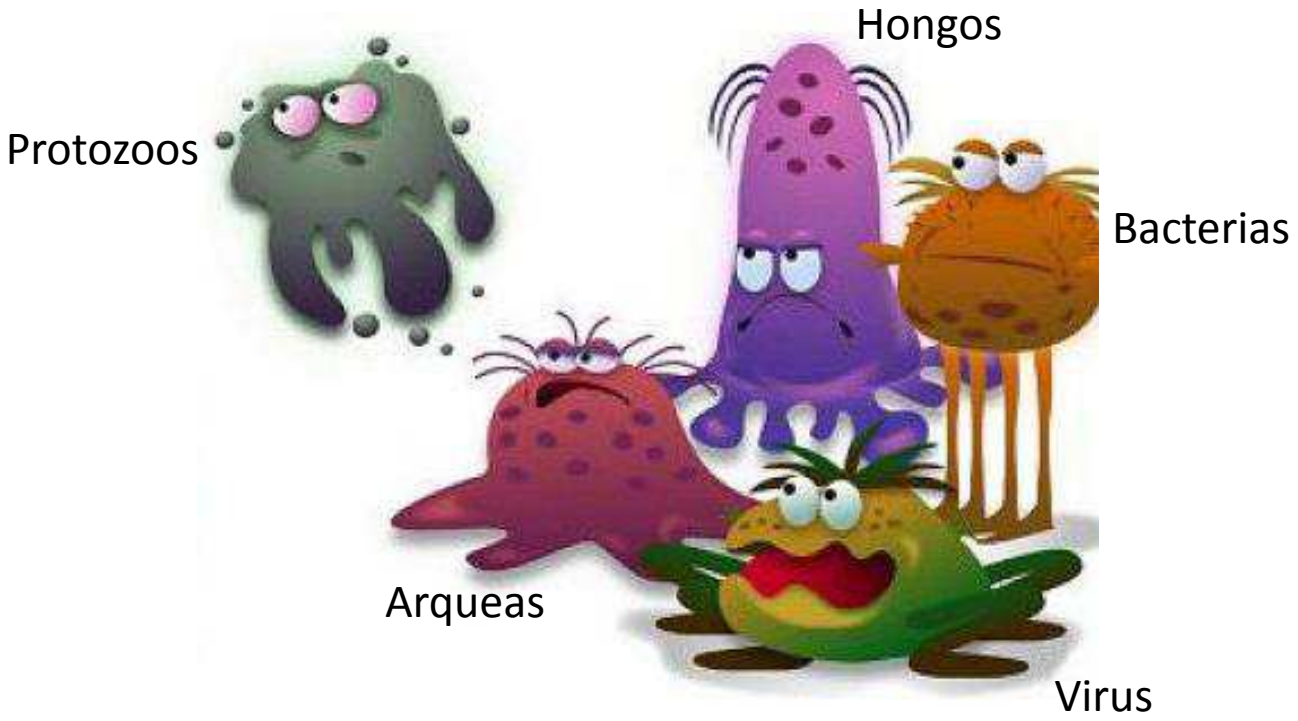
Translocación bacteriana y sus consecuencias

Infección por VIH
alteración de la microbiota y translocación

Acción del TAR sobre la microbiota

¿Restablece el TAR la microbiota intestinal?

¿Qué es el microbioma humano?



Conjunto de microorganismos estructurados en comunidades que viven e interactúan en nuestro organismo

Se calcula que en el cuerpo humano residen más de 10^{14} microorganismos

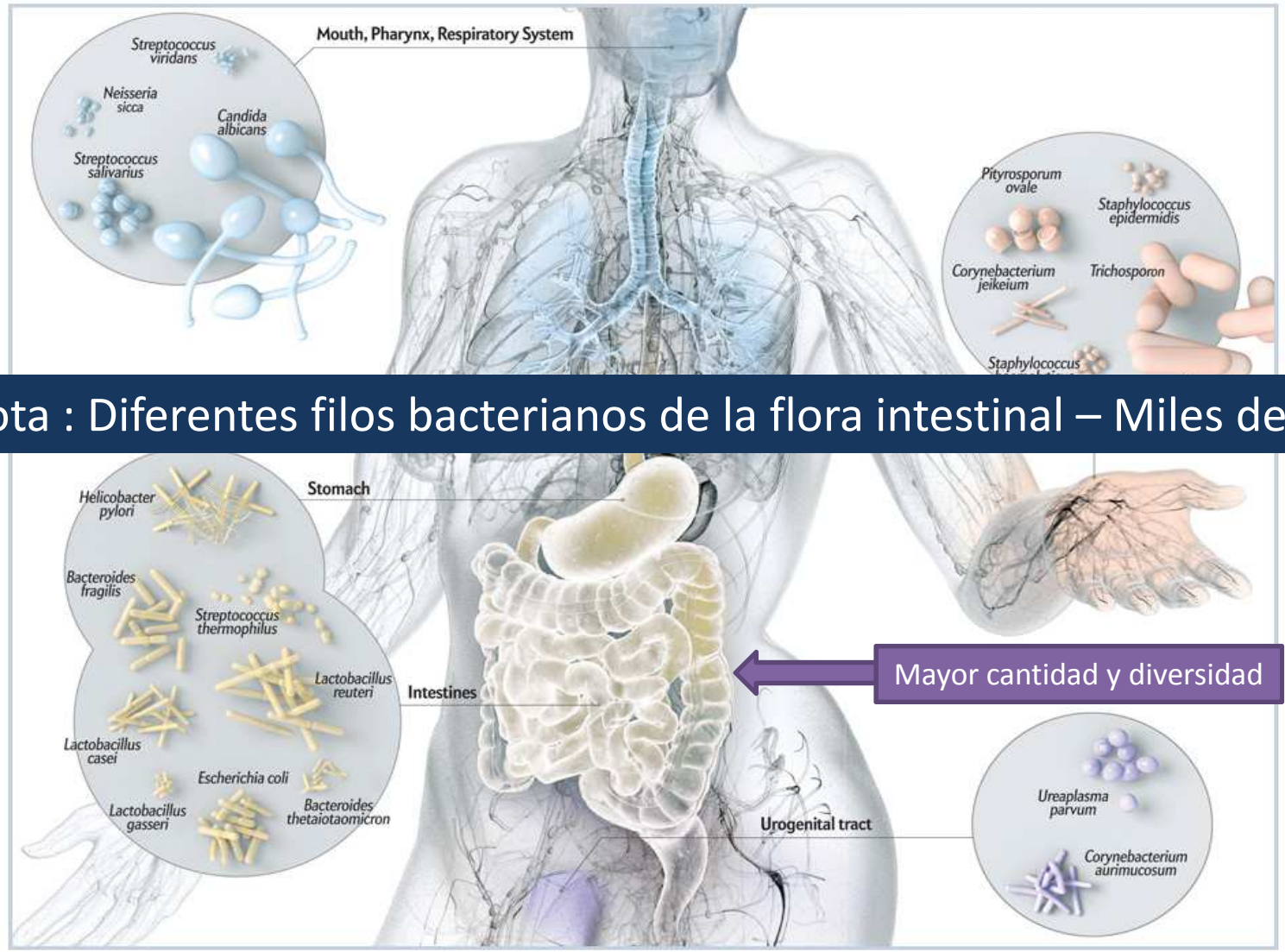
La mayor parte de los mismos no están cultivados

Alta diversidad

Composición diferente en función de la parte del cuerpo que colonizan

Xochitl *et al.* *Trends in Genetics* 2013

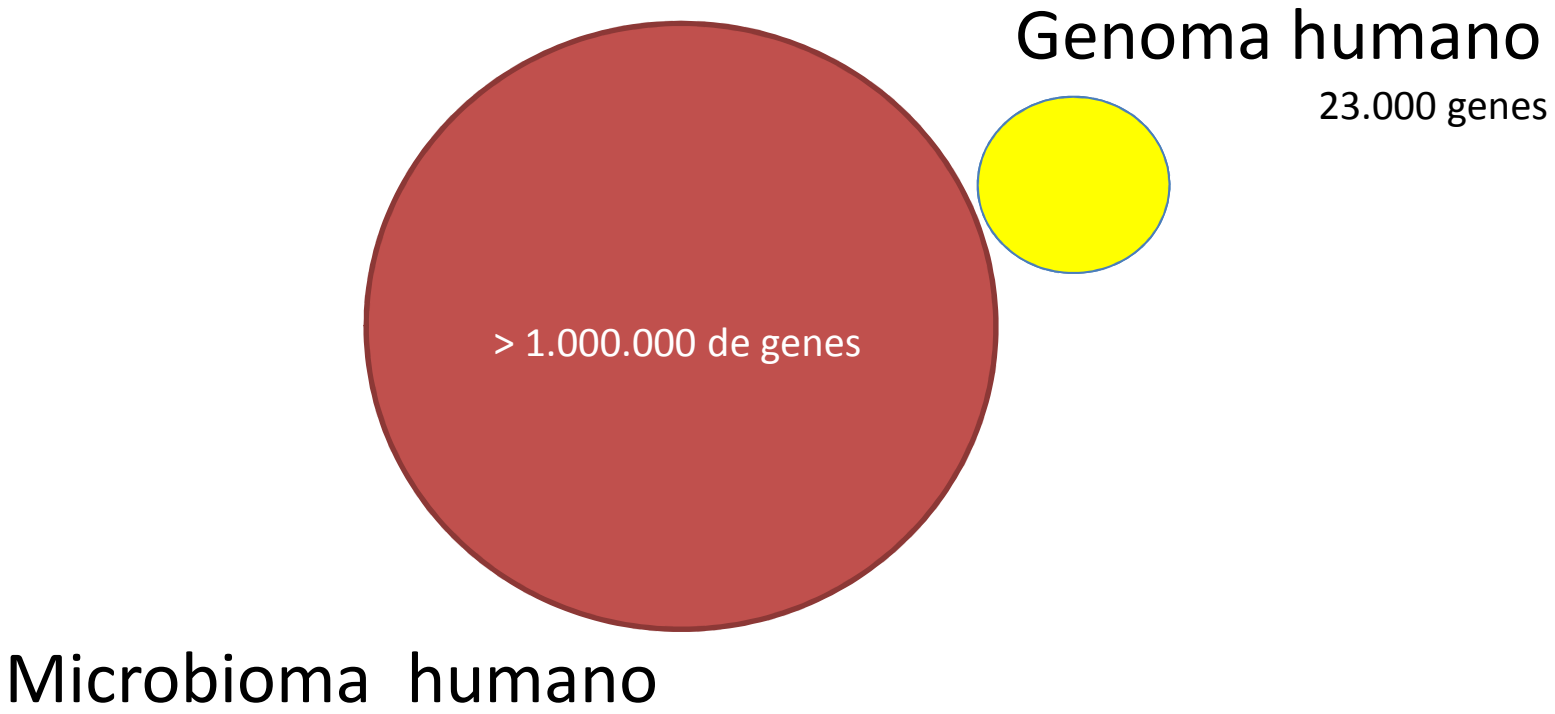
Especies bacterianas que componen el microbioma humano



Microbiota : Diferentes filos bacterianos de la flora intestinal – Miles de clones

Mayor cantidad y diversidad

Funciones del Microbioma Humano



Desconocemos todas las funciones
¿Qué significan 1 millón más de genes que forman parte de nuestro organismo?

Equilibrio de la microbiota y disbiosis

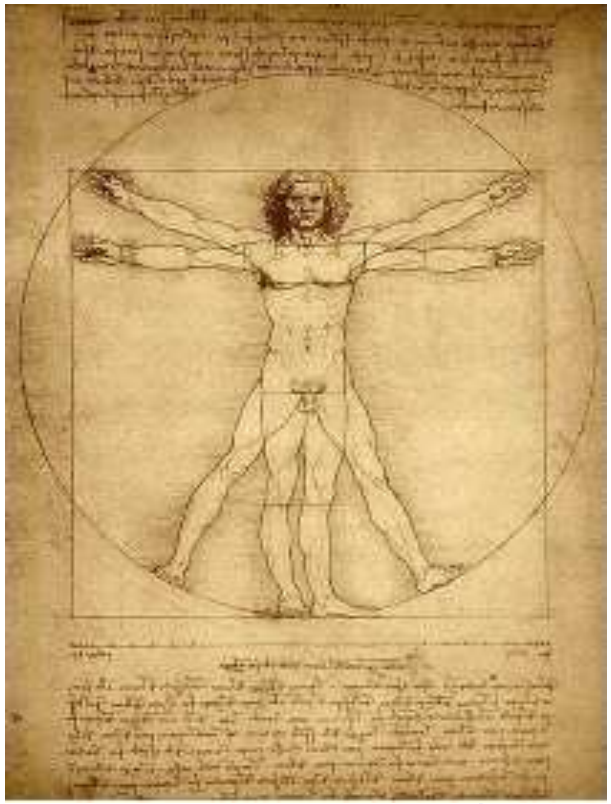
- En condiciones normales la flora intestinal se mantiene en equilibrio.
- Cuando se altera, existen mecanismos que logran que se restablezca su composición (resilencia).
- Si los mecanismos de resilencia no son capaces de lograr la restauración del equilibrio se produce la denominada **disbiosis**.

Funciones de la Microbiota intestinal

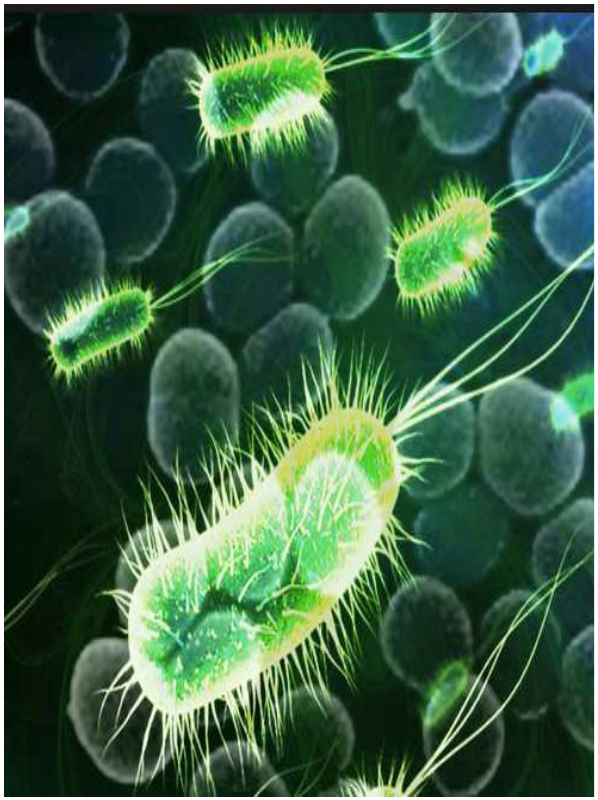
Relación simbiótica con el huésped

- Procesar componentes digeribles e indigeribles de la dieta
  polisacáridos de las plantas.
- Mantenimiento de la barrera epitelial
  (además producción de ácido láctico, ácid
  IgA, que protegen de la colonización d
- Competencia con
- Sínte
  ción del sistema inmune innato.
- Metabolismo de las sales biliares.
- Metabolismo de sustancias tóxicas potencialmente carcinogénicas
  (pirolisatos)

Funciones del Microbioma-Microbiota Humana



HOMEOSTASIS



Su alteración provoca problemas que van desde caries a desarrollo de cáncer

13780–13785 | PNAS | August 21, 2007 | vol. 104 | no. 34

Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases

Daniel N. Frank*, Allison L. St. Amand*, Robert A. Feldman†, Edgar C. Boedeker‡, Noam Harpaz§, and Norman R. Pace*¶

*Department of Molecular, Cellular, and Developmental Biology, University of Colorado, Boulder, CO 80309-0347; †SymBio Corporation, Menlo Park, CA 94025; ‡Department of Medicine, University of New Mexico, Albuquerque, NM 87131; and §Department of Pathology, Mount Sinai School of Medicine, New York, NY 10029

Gut 2015; *64:1553-1561*

Gut microbiota

OPEN ACCESS

ORIGINAL ARTICLE

Spatial variation of the colonic microbiota in patients with ulcerative colitis and control volunteers

A Lavelle,[1,2] G Lennon,[1,2] O O'Sullivan,[3] N Docherty,[4] A Balfe,[1] A Maguire,[2] H E Mulcahy,[2] G Doherty,[2] D O'Donoghue,[2] J Hyland,[2] R P Ross,[3,5] J C Coffey,[6] K Sheahan,[2] P D Cotter,[3,5] F Shanahan,[5] D C Winter,[1,2] P R O'Connell[1,2]

Alteraciones de la microbiota asociadas a enfermedad

J Physiol Biochem
DOI 10.1007/s13105-015-0390-3

Published online: 08 March 2015

ORIGINAL PAPER

Gut microbiota: a key player in health and disease. A review focused on obesity

M. J. Villanueva-Millán · P. Pérez-Matute · J. A. Oteo

Eur. J. Immunol. 2015. 45: 17–31 DOI: 10.1002/eji.201444972 REVIEWS

European Journal of Immunology

The role of the microbiota in inflammation, carcinogenesis, and cancer therapy

Amiran Dzutsev[1,2], Romina S. Goldszmid[1], Sophie Viaud[3,4], Laurence Zitvogel[3,4] and Giorgio Trinchieri[1]

[1] Cancer and Inflammation Program, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Frederick, MD, USA
[2] Leidos Biomedical Research, Inc., Frederick, MD, USA

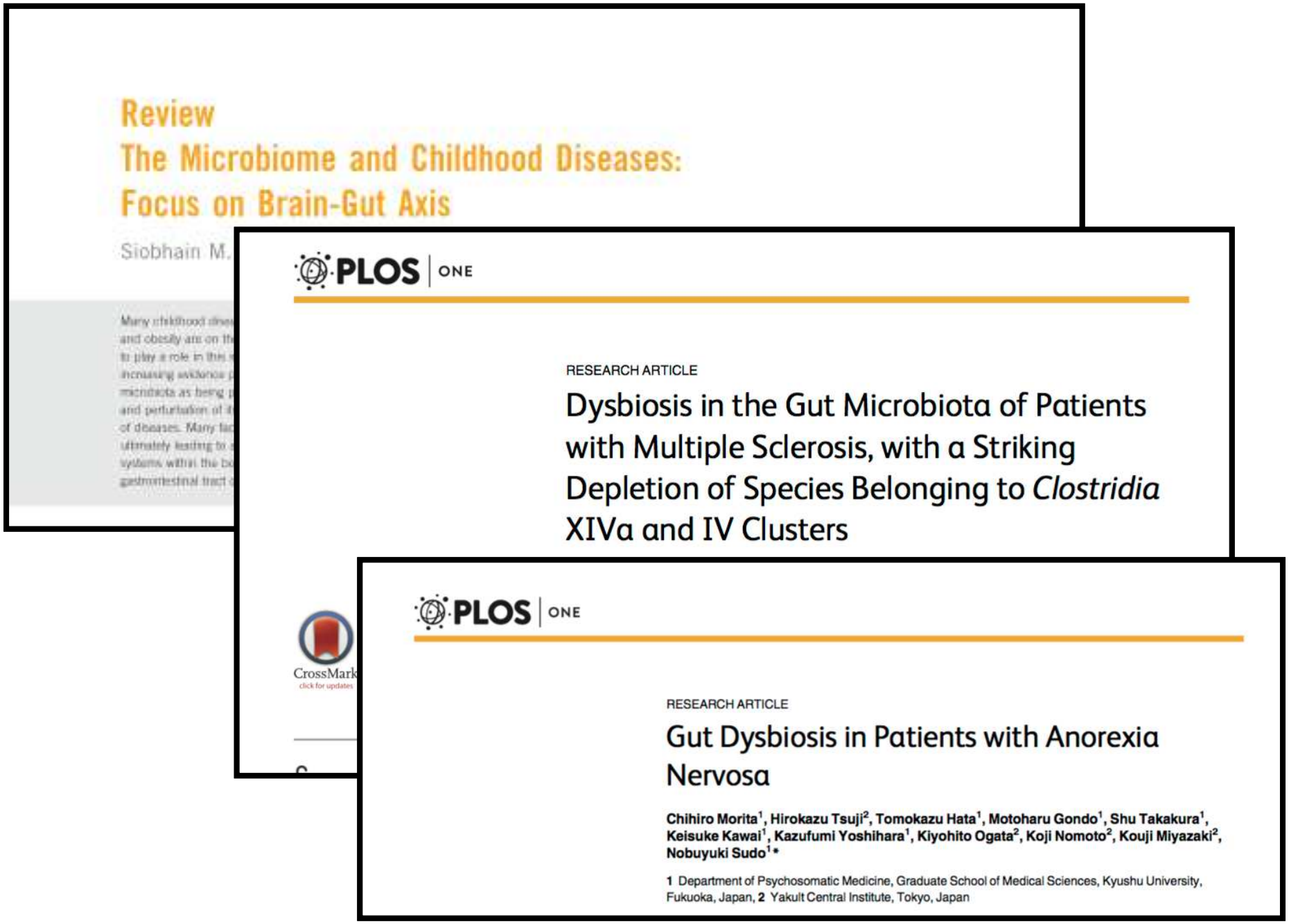
REVIEW

Gut Microbes 5:4, 441–445; July/August 2014; © 2014 Landes Bioscience

The role of the gut microbiome in the development and progression of liver cirrhosis and hepatocellular carcinoma

Christoph Roderburg* and Tom Luedde

Department of Medicine III; University of Aachen (RWTH); Aachen, Germany



Review

The Microbiome and Childhood Diseases: Focus on Brain-Gut Axis

Siobhain M.

PLOS ONE

RESEARCH ARTICLE

Dysbiosis in the Gut Microbiota of Patients with Multiple Sclerosis, with a Striking Depletion of Species Belonging to *Clostridia* XIVa and IV Clusters

PLOS ONE

RESEARCH ARTICLE

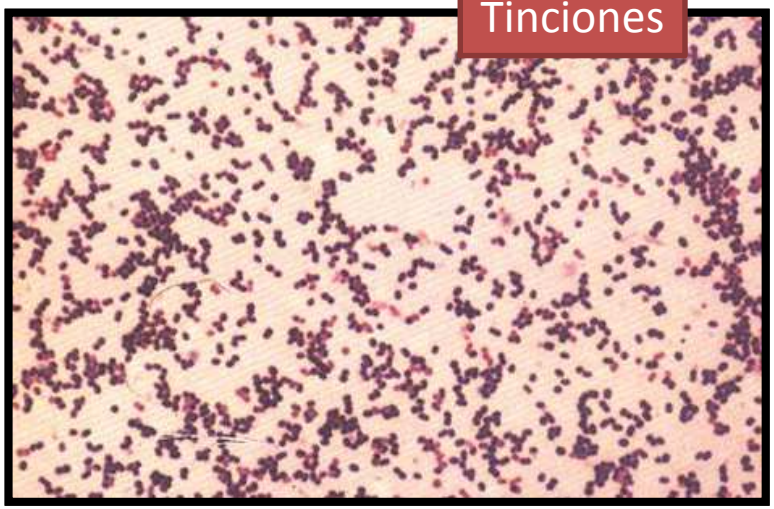
Gut Dysbiosis in Patients with Anorexia Nervosa

Chihiro Morita[1], Hirokazu Tsuji[2], Tomokazu Hata[1], Motoharu Gondo[1], Shu Takakura[1], Keisuke Kawai[1], Kazufumi Yoshihara[1], Kiyohito Ogata[2], Koji Nomoto[2], Kouji Miyazaki[2], Nobuyuki Sudo[1]*

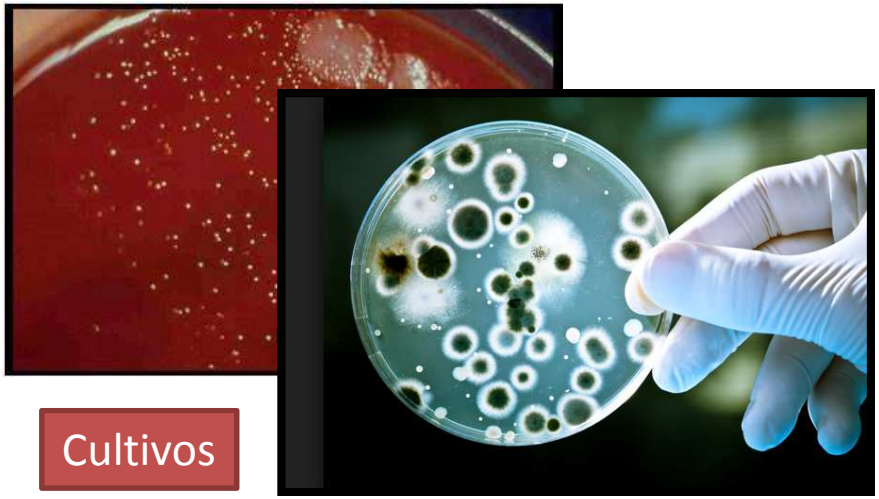
1 Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, **2** Yakult Central Institute, Tokyo, Japan

¿Cómo se estudia el Microbioma?

Tinciones



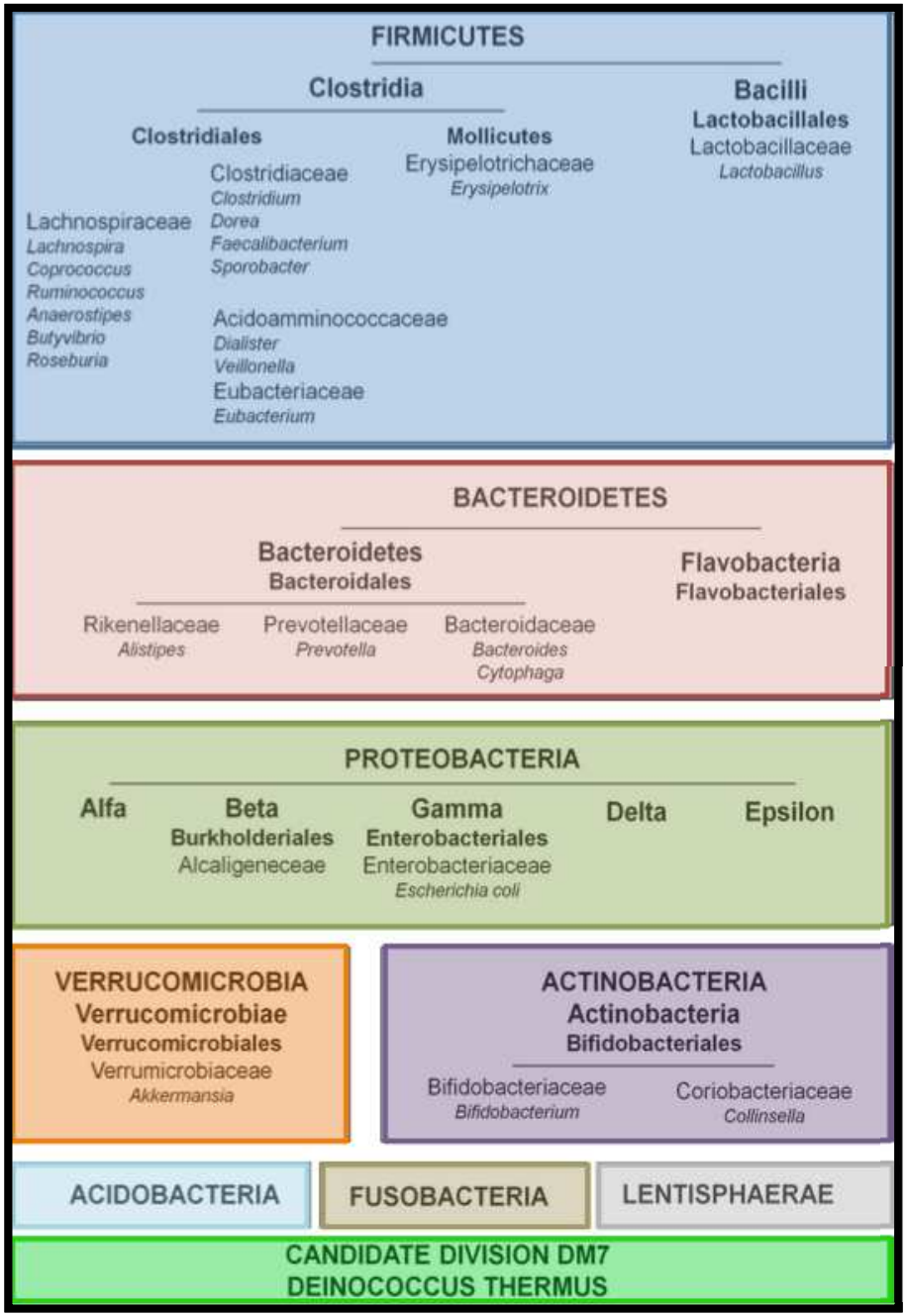
Microscopía electrónica



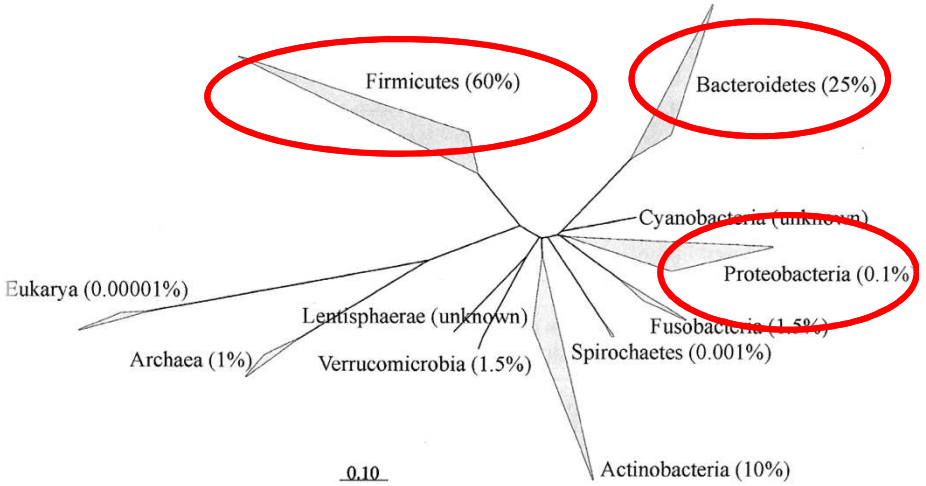
Cultivos

Técnicas de PCR

METAGENÓMICA: estudio directo del conjunto de genomas de un determinado entorno (metagenoma) a partir de muestras de ese ambiente, sin necesidad de su aislamiento y cultivo



“Microbiota normal”



Gran dificultad para establecer cuál es la microbiota normal

Establecimiento dinámico de la microbiota

Recién nacido

- Edad gestacional de la madre
- Condiciones sanitarias
- Exposición a antibióticos
- Modo de alumbramiento
  - Parto vaginal → Microbiota similar a la vagina de la madre
  - Cesárea → Microbiota similar a la piel

Neonato

- Dieta
  - Leche materna → > Actinobacteria y Proteobacteria
  - Leche de fórmula → > Actinobacteria y Firmicutes

6 meses

(Introducción de alimentos sólidos y colonización completa)

2,5 años

(Similar a la microbiota del adulto)

Adulto

Anciano

(Variación más grande entre individuos)

- Edad
- Dieta
- Salud
- Localización geográfica
- Exposición a antibióticos, probióticos, prebióticos
- Estrés

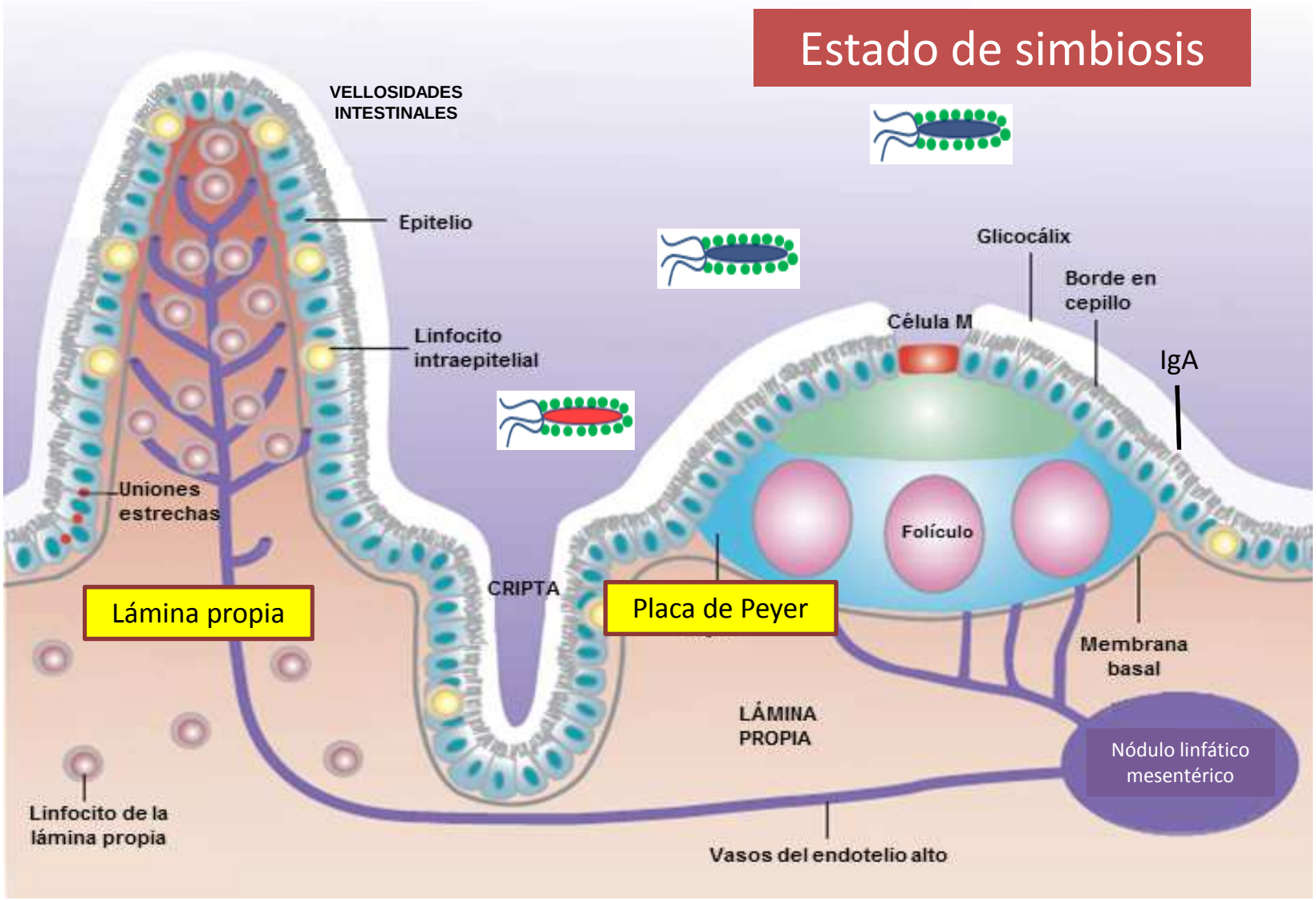
> Firmicutes y Bacteroidetes

> Diversidad y > Estabilidad → <Diversidad

Villanueva-Millán MJ *et al*. 2015

¿Qué es la translocación bacteriana?

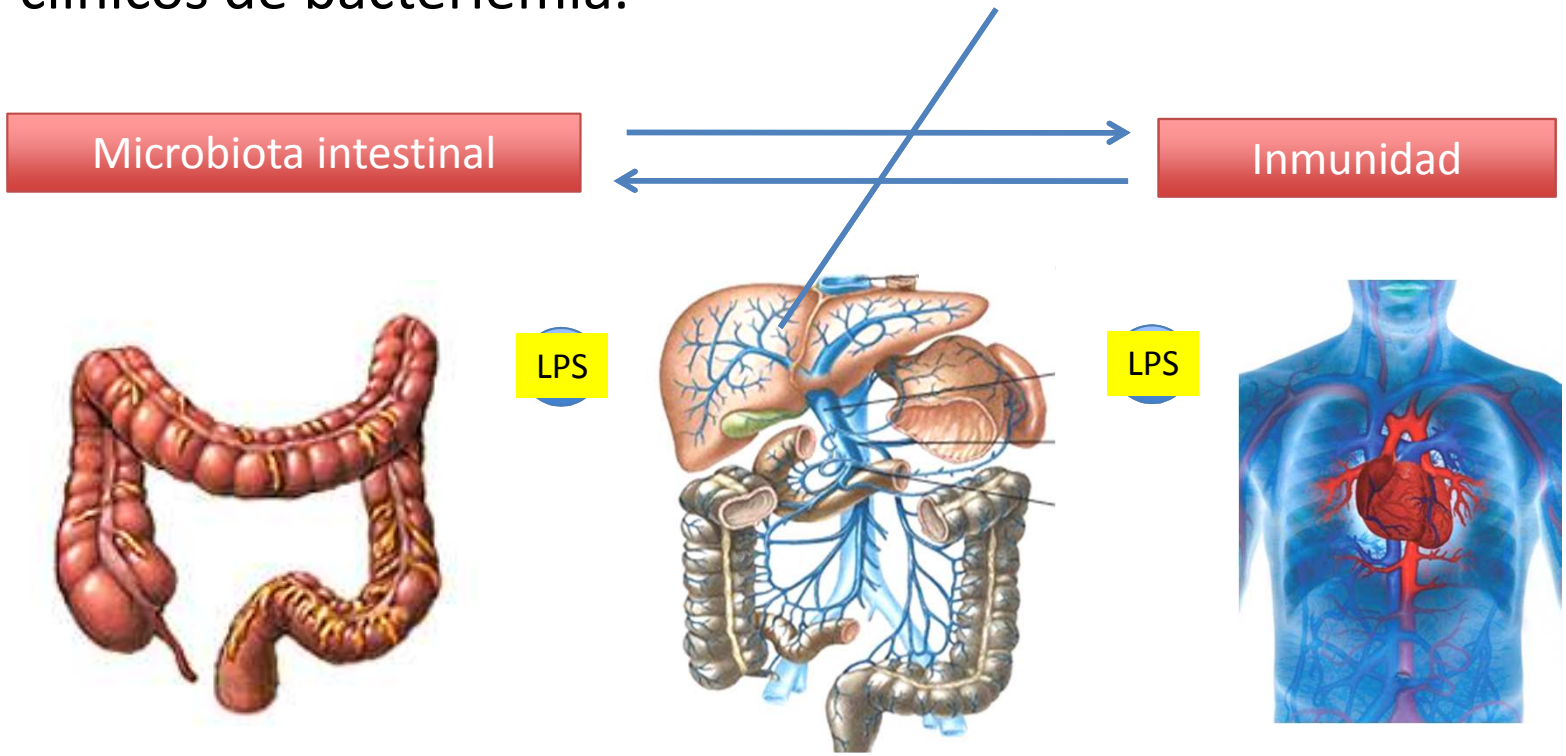
Estructura de la superficie intestinal



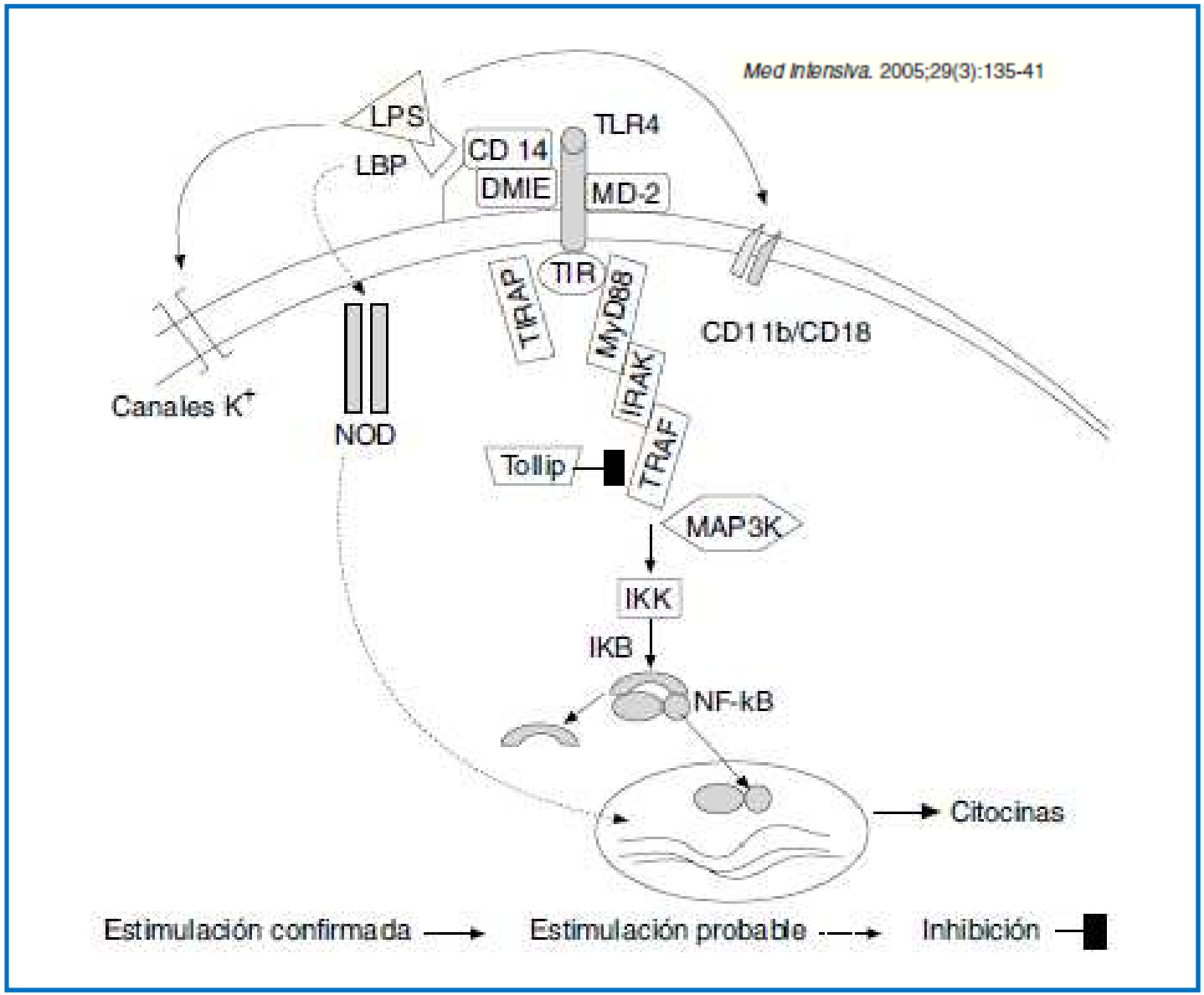
Adaptado de Cheroutre H, Madakamutil L. Acquired and natural model T cells join forces at the mucosal front line. Nat Rev Immunol 2004; 4(4):290-300 y Mehandru S. The gastrointestinal tract in HIV-1 infection: questions, answers, and more questions. The PRN Notebook 2007; 12:1-10.

Translocación bacteriana

Proceso mediante el que microorganismos o algunos componentes de los mismos (LPS bacteriano o ADN procedente de la microbiota intestinal) pasan a la circulación portal y sistémica sin que se aprecien datos clínicos de bacteriemia.



Translocación bacteriana



Annu Rev Immunol. 2012 ; 30: 149–173. doi:10.1146/annurev-immunol-020711-075001.

Microbial Translocation Across the GI Tract*

Jason M. Brenchley[1] and **Daniel C. Douek**[2]

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[1]Program in Barrier Immunity and Repair and Immunopathogenesis Unit, Lab of Molecular Microbiology, NIAID, NIH, Bethesda, Maryland [2]Human Immunology Section, Vaccine Research Center, NIAID, NIH, Bethesda, Maryland

Abstract

The lumen of the gastrointestinal (GI) tract is home to an enormous quantity of different bacterial species, our microbiota, that thrive in an often symbiotic relationship with the host. Given that the healthy host must regulate contact between the microbiota and its immune system to avoid overwhelming systemic immune activation, humans have evolved several mechanisms to attenuate systemic microbial translocation (MT) and its consequences. However, several diseases are associated with the failure of one or more of these mechanisms, with consequent immune activation and deleterious effects on health. Here, we discuss the mechanisms underlying MT, diseases associated with MT, and therapeutic interventions that aim to decrease it.

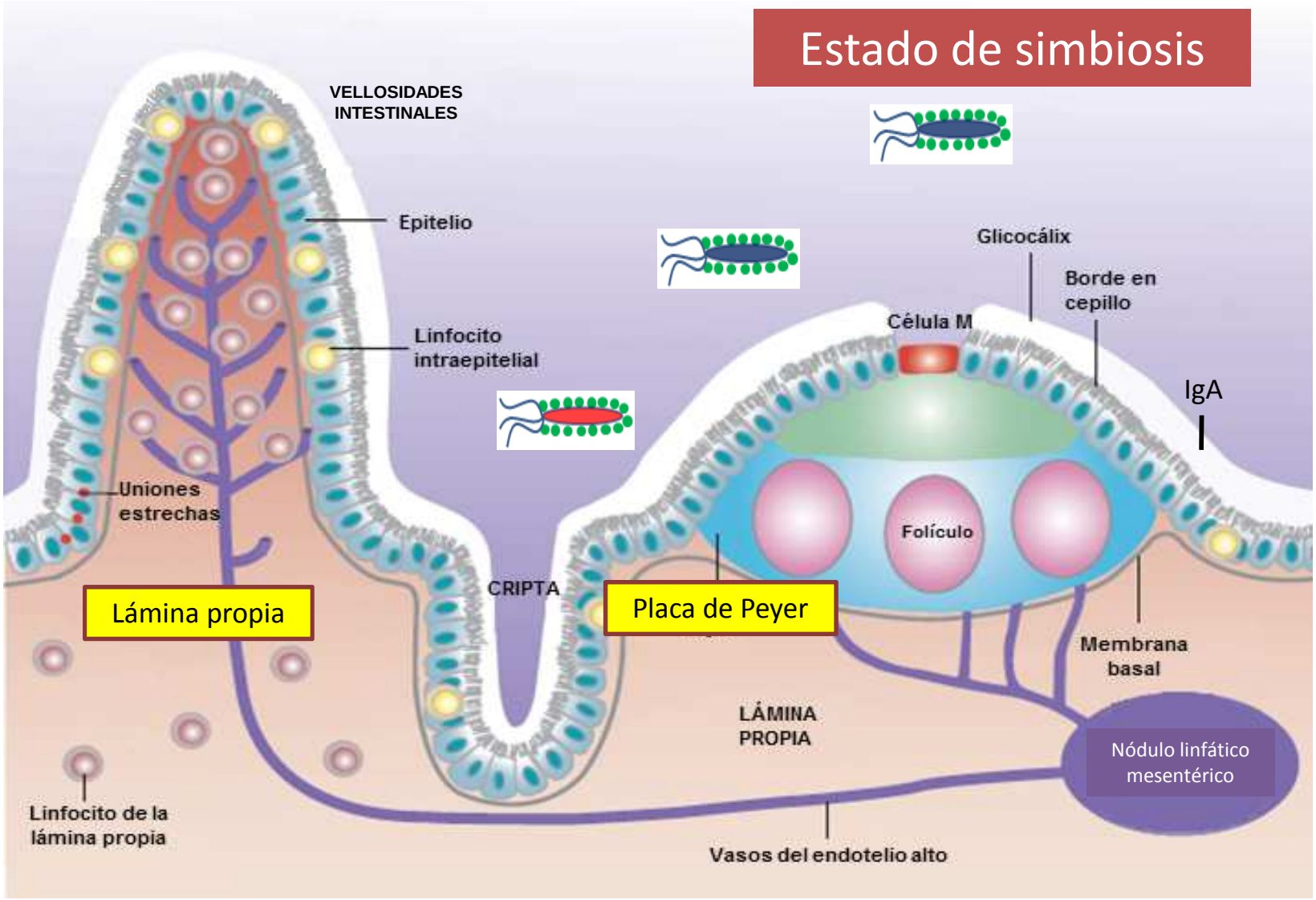
El contacto de la flora intestinal y sus componentes con el sistema inmune provoca una inmunoactivación o estado de inflamación crónica que se asocia a efectos deletéreos sobre la salud

Translocación bacteriana

- En condiciones fisiológicas hay un bajo nivel de translocación bacteriana.
- Existen múltiples procesos que pueden provocar aumentos transitorios y/o persistentes de la translocación bacteriana por alterar la integridad de la mucosa intestinal y/o los mecanismos de inmunidad intestinal.
- Ej: enfermedad inflamatoria intestinal, infecciones intestinales.
- Infecciones crónicas como el VIH, VHC, …
- Ingesta excesiva de alcohol, quimioterápicos, …
- …

Alteraciones de la microbiota y translocación bacteriana en la infección por el VIH

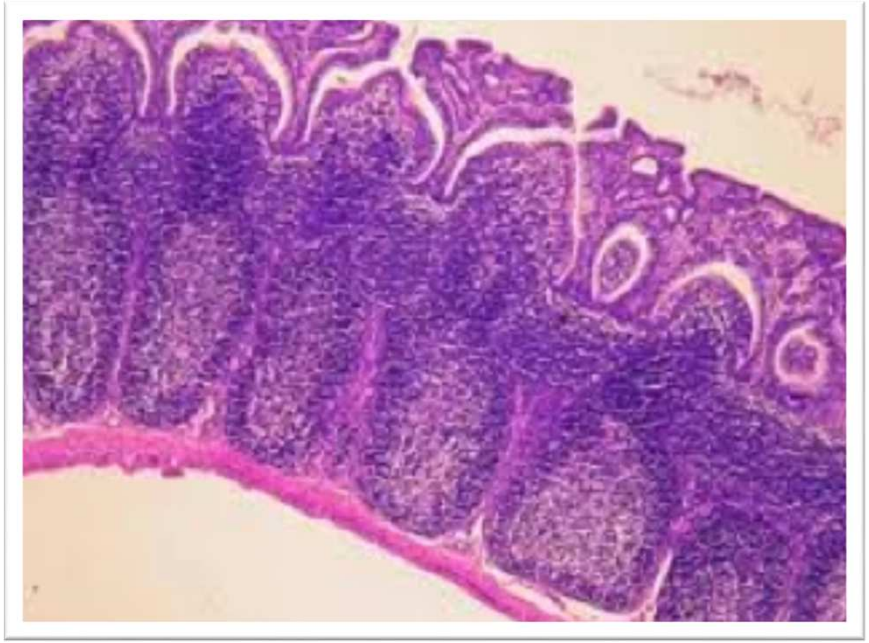
Estructura de la superficie intestinal



Adaptado de Cheroutre H, Madakamutil L. Acquired and natural model T cells join forces at the mucosal front line. Nat Rev Immunol 2004; 4(4):290-300 y Mehandru S. The gastrointestinal tract in HIV-1 infection: questions, answers, and more questions. The PRN Notebook 2007; 12:1-10.

Tejido linfoide asociado al tracto gastro-intestinal (GALT)

- El tracto gastrointestinal es la zona del organismo que más cantidad de tejido linfoide y linfocitos alberga, incluyendo los linfocitos CD4+ de memoria activados que son las dianas preferentes para el VIH.



Placas de Peyer

http://www.picstopin.com/233/placas-de-peyer-sobresaliendo-en-el-interior-la-luz/http:%7C%7Cscielo*isciii*es%7Cimg%7Crevistas%7Cnh%7Cv22s2%7Cfuncion_intestinal2_f1*gif/

Normal Human Intestinal B Lymphocytes

Increased Activation Compared with Peripheral Blood

Marion G. Peters, Heather Secrist, Kirk R. Anders, Geoffrey S. Nash, She
Washington University School of Medicine, St. Louis, Missouri 63110

J. Clin. Invest.

0021-9738/89/06/1827/07 $2.00
Volume 83, June 1989, 1827–1833

Abstract

The state of activation of normal human intestinal mononuclear cells obtained from transplant donors was studied. Compared with PBMC, freshly isolated intestinal mononuclear cells expressed significantly more cell surface activation antigens on both B and T lymphocytes. Intestinal mononuclear cells contained significant numbers of immunoglobulin secreting cells immediately after cell separation. This population included CD5-positive B cells that secreted predominantly IgA. Cells from the large bowel consistently revealed higher numbers of IgA secreting cells than cells from the small bowel. Thus, intestinal B cells are markedly activated in vivo compared with PBMC and this increased activation correlates with increased spontaneous antibody secretion. B cells from the large intestine are more highly activated and secrete more antibody than do cells from the small intestine. The intestinal lamina propria lymphoid compartment exhibits a heightened state of activation that may be important for its distinct role in mucosal defense.

transplant donor intestinal specimens, which now allows the examination of normal INT MNC from both large and small bowel.

We investigated the activation state of normal INT B cells by three methods. First, we quantitated the expression of activation markers on the plasma membrane using MAb. Second, we quantitated immunoglobulin-secreting cells (ISC) immediately after cell separation (time zero) and after various periods of time in culture. Finally, we have correlated these data with total and isotype-specific Ig secretion in culture. We find by all three criteria that normal INT B cells are more activated than PBMC. B cells from large bowel are more activated by these criteria than the equivalent cell population from small bowel. The presence of a highly activated population of lymphocytes at this intestinal mucosal surface may be an important mechanism of host defense and of normal bowel immunity.

Methods

Isolation of cells. PBMC were isolated from heparinized blood of normal healthy volunteers using Ficoll-Hypaque centrifugation (2). Nor-

A diferencia de lo que sucede en sangre periférica, la mayoría de los linfocitos de la lámina propia del intestino son linfocitosmT de memoria en un estado continuo de activación, lo que hace que sean muy susceptibles a la infección VIH

Human intestinal lamina propria lymphocytes are naturally permissive to HIV-1 infection

Caterina Lapenta[1], Monica Boirivant[2], Marco Marini[2], Stefano M. Santini[1], Mariantonia Logozzi[1], Marina Viora[2], Filippo Belardelli[1] and Stefano Fais[2]

[1] Laboratory of Virology, Istituto Superiore di Sanità, Rome, Italy
[2] Laboratory of Immunology, Istituto Superiore di Sanità, Rome, Italy

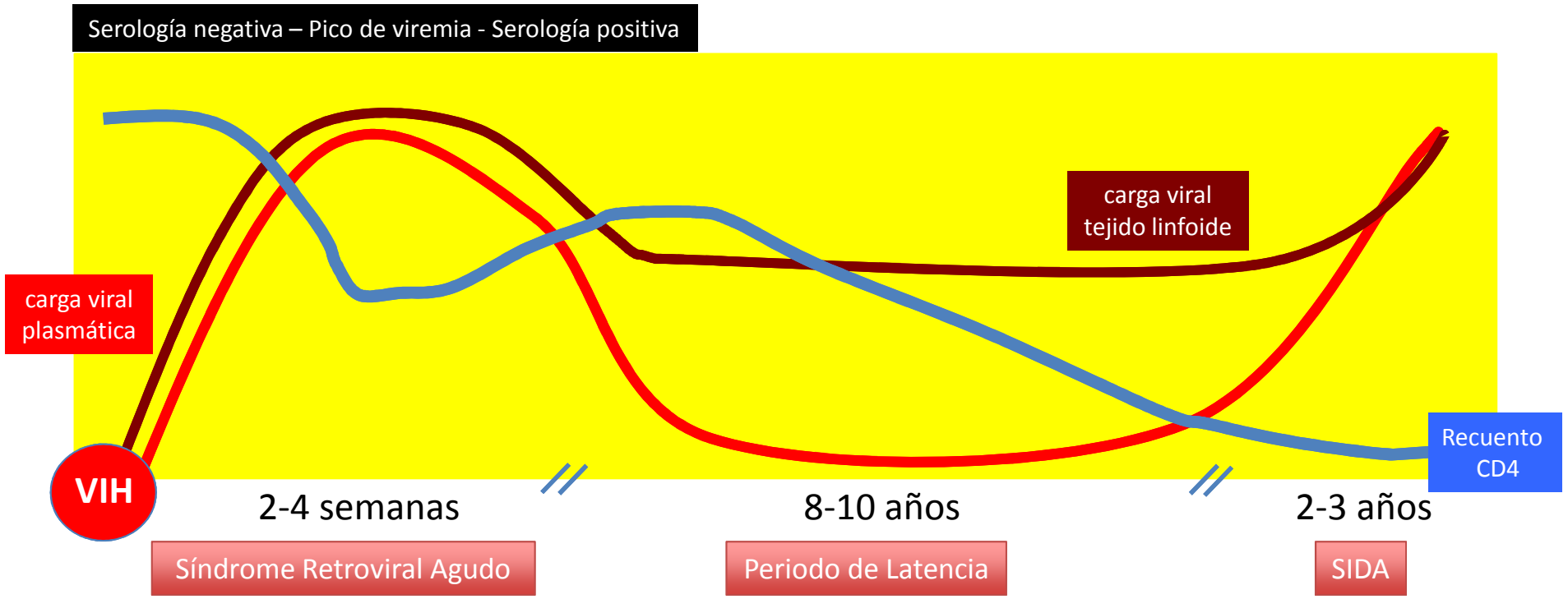
The presence of HIV-1 in the intestinal mucosa of AIDS patients has been reported and human intestinal lamina propria lymphocytes (LPL) have been proposed as important targets for HIV-1 infection. However, little information is available concerning the permissiveness of human intestinal $CD4^+$ T lymphocytes to HIV-1 infection. Here, we show that human LPL, in contrast to autologous peripheral blood lymphocytes (PBL), are permissive to both X4 T-tropic and R5 M-tropic strains of HIV-1, as well as to clinical isolates, in the absence of exogenous stimuli. Flow cytometry showed that the vast majority of T LPL were $CD45RO^+$ and $CD69^+$, and that $CD4^+$ T LPL highly expressed CC chemokine receptor 5 (CCR5) as compared to PBL, while CX chemokine receptor 4 was equally expressed on LPL and PBL. Exogenous RANTES and macrophage inflammatory protein-1α (natural CCR5 ligands) virtually abolished the entry of the R5 M-tropic strain HIV-1 into human LPL. Thus, we infer that human intestinal $CD4^+$ T lymphocytes are naturally susceptible to HIV-1 infection, due to their physiological state of activation and to marked expression of HIV-1 coreceptors, independently of the route of primary (either mucosal or parental) infection and the shifts of the virus phenotype occurring during the course of AIDS.

Key words: Intestinal lymphocyte / Chemokine receptor / HIV-1 / $CD4^+$ memory T cell / CCR5

Received	30/10/98
Revised	30/12/98
Accepted	7/1/99

Los linfocitos CD4 de la lámina propia intestinal expresan en mayor número que los CD4 de sangre periférica CXR4 y CCR5 facilitando la infección por el VIH

Dinámica de la CV y respuesta inmune en la infección por el VIH



Modificada de: Harari & Pantaleo. In: Cohen ID- 3ed 2010

The Journal of Experimental Medicine • Volume 200, Number 6, September 20, 2004 749–759

CD4+ T Cell Depletion during all Stages of HIV Disease Occurs Predominantly in the Gastrointestinal Tract

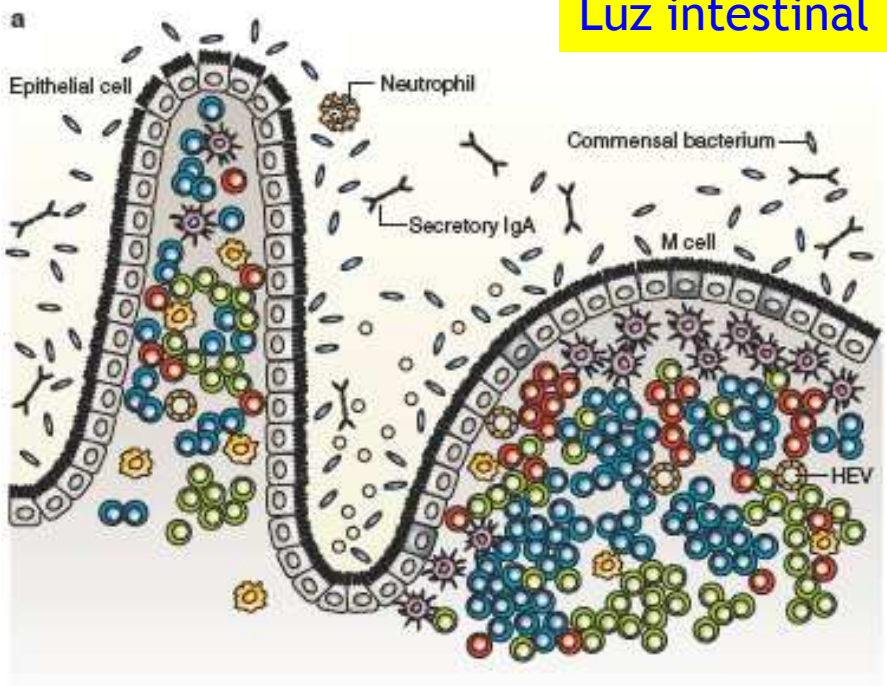
Jason M. Brenchley,[1] Timothy W. Schacker,[2] Laura E. Ruff,[1] David A. Price,[1] Jodie H. Taylor,[3] Gregory J. Beilman,[3] Phuong L. Nguyen,[5] Alexander Khoruts,[2] Matthew Larson,[2] Ashley T. Haase,[4] and Daniel C. Douek[1]

[1]*Human Immunology Section, Vaccine Research Center, National Institute of Allergy and Infectious Diseases, National Institutes of Health (NIH), Bethesda, MD 20892*
[2]*Department of Medicine,* [3]*Department of Surgery, Division of Surgical Critical Care, and* [4]*Department of Microbiology, University of Minnesota, Minneapolis, MN 55455*
[5]*Division of Hematopathology, Mayo Clinic, Rochester, MN 55905*

La infección por VIH provoca depleción rápida y consistente de los linfocitos CD4+ en la lámina propia intestinal durante todos los estadios de la enfermedad

VIH-

Luz intestinal

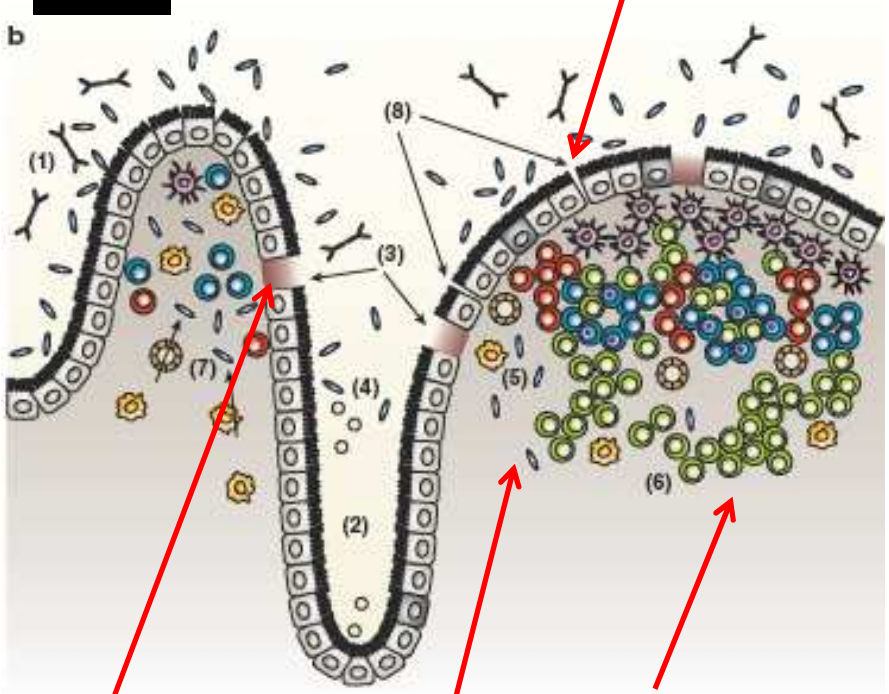


Parénquima intestinal

VIH+

Disbiosis

Pérdida de las uniones



Pérdida de CD4+

Translocación bacteriana

Apoptosis enterocitos

LPS

Modificado de Brenchley et al. Mucosal Immunol 2008

nature medicine

Article

Nature Medicine **12**, 1365 - 1371 (2006)
Published online: 19 November 2006 | doi:10.1038/nm1511

Microbial translocation is a cause of systemic immune activation in chronic HIV infection

Jason M Brenchley[1], David A Price[1], Timothy W Schacker[2], Tedi E Asher[1], Guido Silvestri[3], Srinivas Rao[4], Zachary Kazzaz[1], Ethan Bornstein[1], Olivier Lambotte[5], Daniel Altmann[6], Bruce R Blazar[7], Benigno Rodriguez[8], Leia Teixeira-Johnson[8], Alan Landay[9], Jeffrey N Martin[10], Frederick M Hecht[10], Louis J Picker[11], Michael M Lederman[8], Steven G Deeks[10] & Daniel C Douek[1]

Journal of Infectious Diseases Advance Access published October 12, 2012

MAJOR ARTICLE

Biomarkers of Microbial Translocation and Macrophage Activation: Association With Progression of Subclinical Atherosclerosis in HIV-1 Infection

Theodoros Kelesidis,[1,2] Michelle A. Kendall,[4] Otto O. Yang,[1,2] Howard N. Hodis,[3] and Judith S. Currier[1]

[1]Department of Medicine, Division of Infectious Diseases, and [2]Department of Microbiology, Immunology, and Molecular Genetics, David Geffen School of Medicine, University of California, and [3]Atherosclerosis Research Unit, Department of Medicine and Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles; and [4]Center for Biostatistics in AIDS Research

Background. The relationships between soluble CD14 (sCD14), endotoxin (lipopolysaccharide [LPS]), and progression of atherosclerosis have not been defined in human immunodeficiency virus (HIV) infection.

Methods. We retrospectively assessed serum sCD14 and LPS levels of 91 subjects in a prospective 3-year study of carotid artery intima-media thickness (CIMT) (AIDS Clinical Trials Group [ACTG] 5078), where subjects were enrolled as risk factor–controlled triads of HIV-uninfected (n = 36) and HIV-infected individuals with (n = 29) or without (n = 26) protease inhibitor (PI)–based therapy for ≥2 years. The primary end point was the yearly rate of change of CIMT (ΔCIMT).

Results. In multivariate analysis of the HIV-infected subjects, each 1 μg/mL above the mean of baseline serum sCD14 corresponded to an additional 1.52 μm/y (95% confidence interval, .07–2.98; $P = .04$) in the ΔCIMT. Every 100 pg/mL above the mean of baseline serum LPS corresponded to an additional 0.49 μm/y (95% confidence interval, .18–.81; $P = .003$) in the ΔCIMT. However, in univariate analysis in the HIV-uninfected group sCD14 ($P = .33$) and LPS ($P = .27$) levels were not associated with higher ΔCIMT. HIV infection and PI therapy were not associated with baseline serum LPS and sCD14 levels ($P > .1$).

Conclusions. Our data are among the first to suggest that serum biomarkers of microbial translocation (LPS) and macrophage activation (sCD14) predict subclinical atherosclerosis progression in HIV-infected persons.

En personas infectadas por el VIH, el incremento de LPS (marcador de translocación bacteriana) y sCD14 (marcador de activación macrofágica) se asocian a progresión subclínica de la ateroescloresis con aumento importante de la morbi-mortalidad

OPEN ACCESS Freely available online

PLoS one

Microbial Translocation Is Associated with Increased Monocyte Activation and Dementia in AIDS Patients

Petronela Ancuta[1¤], Anupa Kamat[1], Kevin J. Kunstman[2], Eun-Young Kim[2], Patrick Autissier[3], Alysse Wurcel[4], Tauheed Zaman[4], David Stone[4], Megan Mefford[1], Susan Morgello[5], Elyse J. Singer[6], Steven M. Wolinsky[2], Dana Gabuzda[1*]

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Abstract

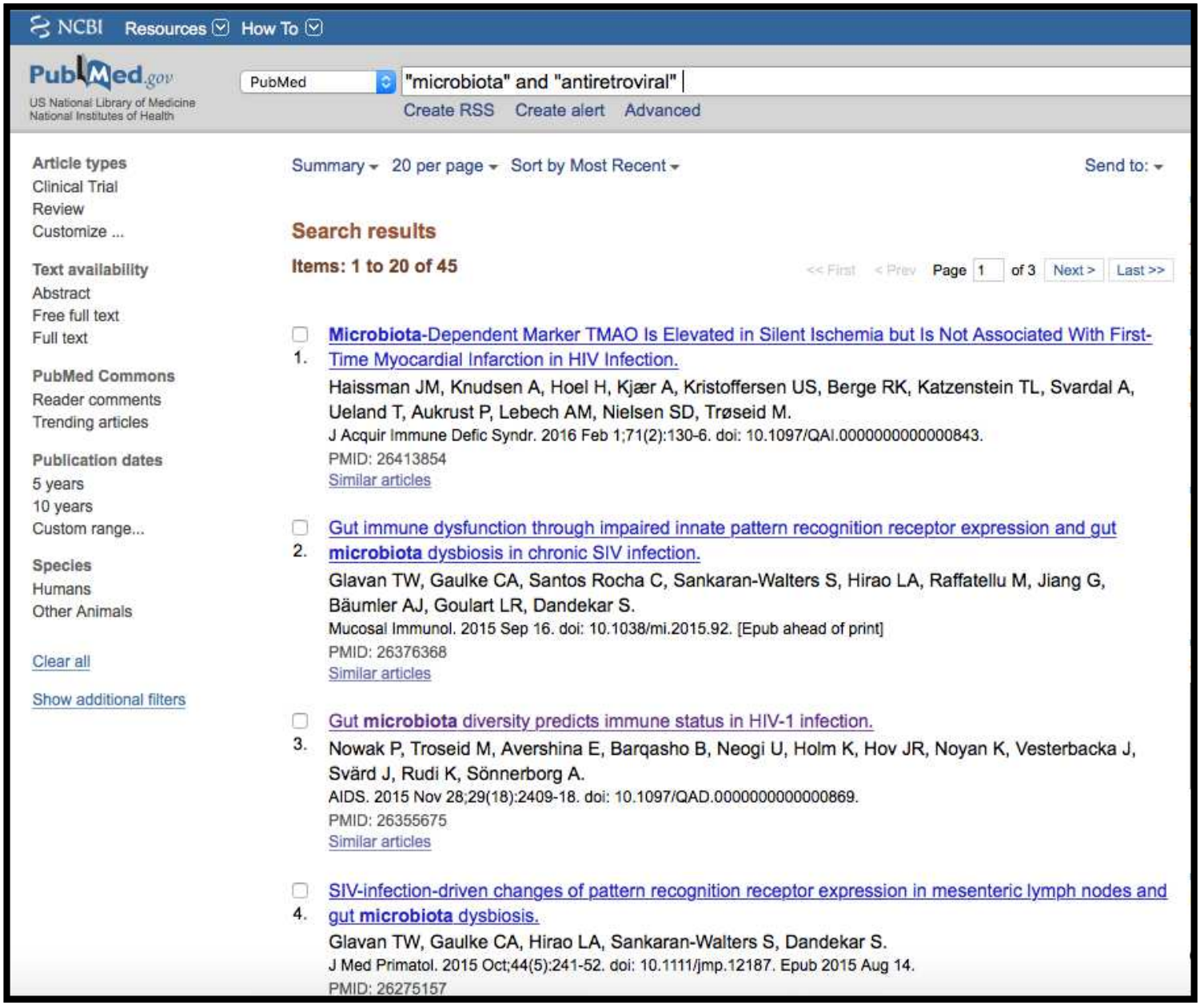
Elevated plasma lipopolysaccharide (LPS), an indicator of microbial translocation from the gut, is a likely cause of systemic immune activation in chronic HIV infection. LPS induces monocyte activation and trafficking into brain, which are key mechanisms in the pathogenesis of HIV-associated dementia (HAD). To determine whether high LPS levels are associated with increased monocyte activation and HAD, we obtained peripheral blood samples from AIDS patients and examined plasma LPS by *Limulus* amebocyte lysate (LAL) assay, peripheral blood monocytes by FACS, and soluble markers of monocyte activation by ELISA. Purified monocytes were isolated by FACS sorting, and HIV DNA and RNA levels were quantified by real time PCR. Circulating monocytes expressed high levels of the activation markers CD69 and HLA-DR, and harbored low levels of HIV compared to $CD4^+$ T-cells. High plasma LPS levels were associated with increased plasma sCD14 and LPS-binding protein (LBP) levels, and low endotoxin core antibody levels. LPS levels were higher in HAD patients compared to control groups, and were associated with HAD independently of plasma viral load and CD4 counts. LPS levels were higher in AIDS patients using intravenous heroin and/or ethanol, or with Hepatitis C virus (HCV) co-infection, compared to control groups. These results suggest a role for elevated LPS levels in driving monocyte activation in AIDS, thereby contributing to the pathogenesis of HAD, and provide evidence that cofactors linked to substance abuse and HCV co-infection influence these processes.

¿Qué efecto tienen los ARV sobre la microbiota?

¿Restablece el TAR la disbiosis intestinal?

¿Disminuye el TAR la translocación bacteriana?

¿Es igual la acción de los diferentes TAR?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1. Microbiota-Dependent Marker TMAO Is Elevated in Silent Ischemia but Is Not Associated With First-Time Myocardial Infarction in HIV Infection.
Haissman JM, Knudsen A, Hoel H, Kjær A, Kristoffersen US, Berge RK, Katzenstein TL, Svardal A, Ueland T, Aukrust P, Lebech AM, Nielsen SD, Trøseid M.
J Acquir Immune Defic Syndr. 2016 Feb 1;71(2):130-6. doi: 10.1097/QAI.0000000000000843.
PMID: 26413854
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2. Gut immune dysfunction through impaired innate pattern recognition receptor expression and gut microbiota dysbiosis in chronic SIV infection.
Glavan TW, Gaulke CA, Santos Rocha C, Sankaran-Walters S, Hirao LA, Raffatellu M, Jiang G, Bäumler AJ, Goulart LR, Dandekar S.
Mucosal Immunol. 2015 Sep 16. doi: 10.1038/mi.2015.92. [Epub ahead of print]
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3. Gut microbiota diversity predicts immune status in HIV-1 infection.
Nowak P, Troseid M, Avershina E, Barqasho B, Neogi U, Holm K, Hov JR, Noyan K, Vesterbacka J, Svärd J, Rudi K, Sönnerborg A.
AIDS. 2015 Nov 28;29(18):2409-18. doi: 10.1097/QAD.0000000000000869.
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J Med Primatol. 2015 Oct;44(5):241-52. doi: 10.1111/jmp.12187. Epub 2015 Aug 14.
PMID: 26275157

¿Qué efecto tienen los diferentes ARV sobre la microbiota?

Revista da Sociedade Brasileira de Medicina Tropical 40(6): 653-656, nov-dez, 2007

ARTIGO/ARTICLE

Microbiota intestinal de indivíduos que sofreram acidente ocupacional com materiais biológicos e que realizaram profilaxia anti-retroviral

Intestinal microbiota of individuals who suffered occupational accidents with biological materials and underwent antiretroviral prophylaxis

Micheli Evangelista de Souza[1] e Paulo Câmara Marques Pereira[1]

10 pacientes con accidente ocupacional tratados con ZDV + 3TC + NEF o EFV o RTV frente 13 donantes

Reducción de los niveles de *Lactobacillus, Bifidobacterium* y *Bacteroides* spp.
No restablecimiento de la flora a los 30 días de finalizar el tratamiento

¿Qué efecto tienen los diferentes ARV sobre la microbiota?

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Activity: Abstract
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Maraviroc, a CC5 Antagonist, Alters Gut Microbiota Composition in a Mouse Model of Obesity

Author Block: Patricia Pérez-Matute[1], Laura Pérez-Martínez[1], José R. Blanco[2], Jose A. Oteo[2], [1]CIBIR, Infectious Diseases D… Department, Logron…

Abstract:
Background: Change… inflammation, could … composition arises as… Maraviroc (MVC), a… neutral or even benef… overweight/obese HI… yet. The aim of this s… model of obesity.
Methodology: A tota… Control group (chow… diet group (HFD) or … mice were euthanize… composition. We ana…
Results: As expected… tendency to decrease… significant increase i… treatment induced a s… ($p<0.001$). HFD indu… $p<0.001$ respectively… control diet ($p<0.05$)… ($p=0.05$). No direct e… decrease was observed in HFD mice. Finally, HFD significantly increased the mRNA levels of Lactobacillales ($p<0.05$) while no significant effects were observed after MVC supplementation, although a tendency to decrease the expression levels of this order was observed in HFD mice.
Conclusions: This is the first study that demonstrates the ability of MVC to modify gut microbiota composition. Whether the changes in gut microbiota induced by MVC are associated with the lower body weight gain observed, is still unknown. Our results suggest that some MVC actions seem to be dependent on diet composition and the metabolic status of animals. If these facts should be taken into account when we design antiretroviral regimens must be further investigated.

¡No hay estudios!

Rev Esp Quimioter 2015;28(4)

Original

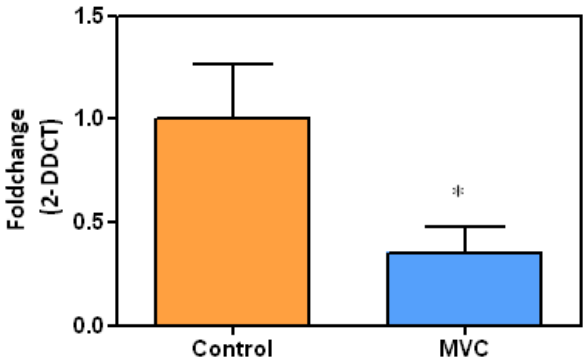
Patricia Pérez-Matute[1]
Laura Pérez-Martínez[1]
Javier Aguilera-Lizarraga[1]
José R. Blanco[1,2]
Jose A. Oteo[1,2]

Maraviroc modifies gut microbiota composition in a mouse model of obesity: a plausible therapeutic option to prevent metabolic disorders in HIV-infected patients

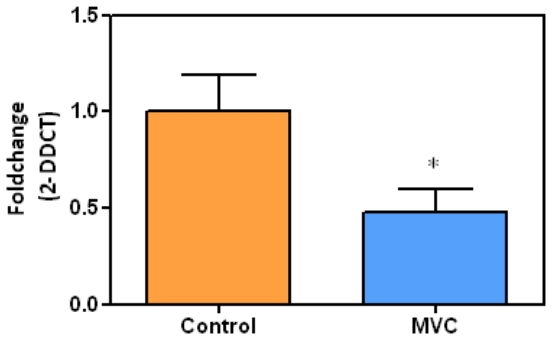
[1]HIV and Associated Metabolic Alterations Unit, Infectious Diseases Department, Center for Biomedical Research of La Rioja (CIBIR), Logroño (Spain).
[2]Infectious Diseases Department, Hospital San Pedro, Logroño (Spain).

Efecto del MVC sobre la flora intestinal en un modelo murino

ENTEROBACTERIALES
(clase γ-proteobacteria del filo proteobacteria)

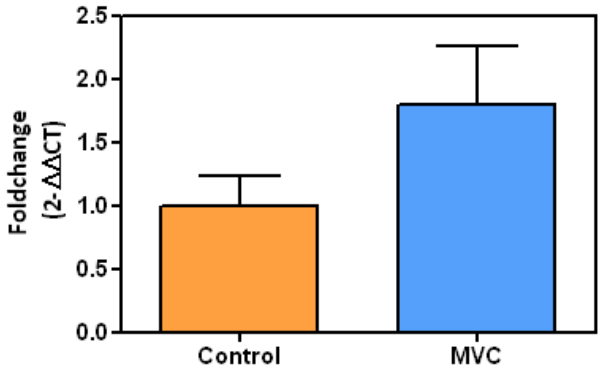


BACTEROIDALES
(clase bacteroides del filo bacteroidetes)

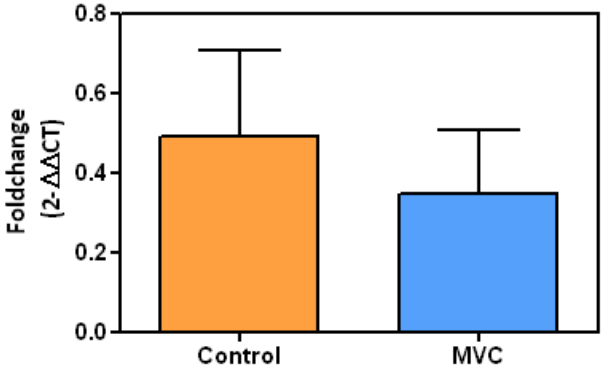


*p<0,05 vs. grupo Control

CLOSTRIDIALES
(clase clostridia del filo Firmicutes)



LACTOBACILLIALES
(clase bacilli del filo Firmicutes)



Estudios metagenómicos sobre microbiota intestinal en VIH +

Autor	Muestra	Control	VIH+ (*naive*)	VIH+ (TAR)	α-diversidad	β-diversidad	Restaura el TAR	Otros
Lozupone 2013	Heces	13	3 (diagnóstico reciente) + 11	6 (*short-term*) + 8 (*long-term*)	Aumentada en HIV+ (*naive*) vs VIH+ (TAR) y Control	Alterada	Parcialmente	Caracterización de respuestas inmunes a bacterias seleccionadas de controles y VIH+ (*naive*)
McHardy 2013	Mucosa rectal	20	20	20	Disminuida en VIH+ (*naive*) y similar en VIH+ (TAR) *vs* grupo control	Alterada	Parcialmente	Cambios metabólicos asociados a la infección por el VIH
Vujkovic-Cvijin 2013	Biopsias de recto sigmoides	9	6 (+1 no progresor a largo plazo)	18	-	Alterada	¿?	Correlación con parámetros inmunológicos Disbiosis correlacionada con el catabolismo del triptófano
Dillon 2014	Frotis rectal, aspirados fecales y biopsias de colon	14	18	-	Sin diferencias	Alterada	¿?	PCA para analizar la asociación con marcadores de inflamación, translocación bacteriana y la activación de células T sanguíneas
Mutlu 2014	Heces y biopsias de colon e íleo terminal	22	-	21	Disminuida (colon derecho e íleo terminal)	Alterada	¿?	Correlación con marcadores de inflamación y translocación

Estudios metagenómicos sobre microbiota intestinal en VIH +

Autor	Muestra	Control	VIH+ (*naive*)	VIH+ (TAR)	α-diversidad	β-diversidad	Restaura el TAR	Otros
Dinh 2015	Heces	16	-	21	Sin diferencias	Alterada	¿?	Correlación con marcadores de inflamación y translocación
Nowak 2015	Heces	9	28	19	Disminuida	Alterada (Prevotella)	Parcialmente	Correlación con cifras de CD4 bajos y marcadores de translocación

En todos los estudios resultados dispares en la α-diversidad y alteración de la β-diversidad

Diversidad alfa: riqueza de especies de una comunidad particular (ej: una persona)

Diversidad beta: análisis de los filos, clases, géneros, especies

¿Es igual la acción de los diferentes TAR?

¿Es igual la acción de los diferentes TAR?

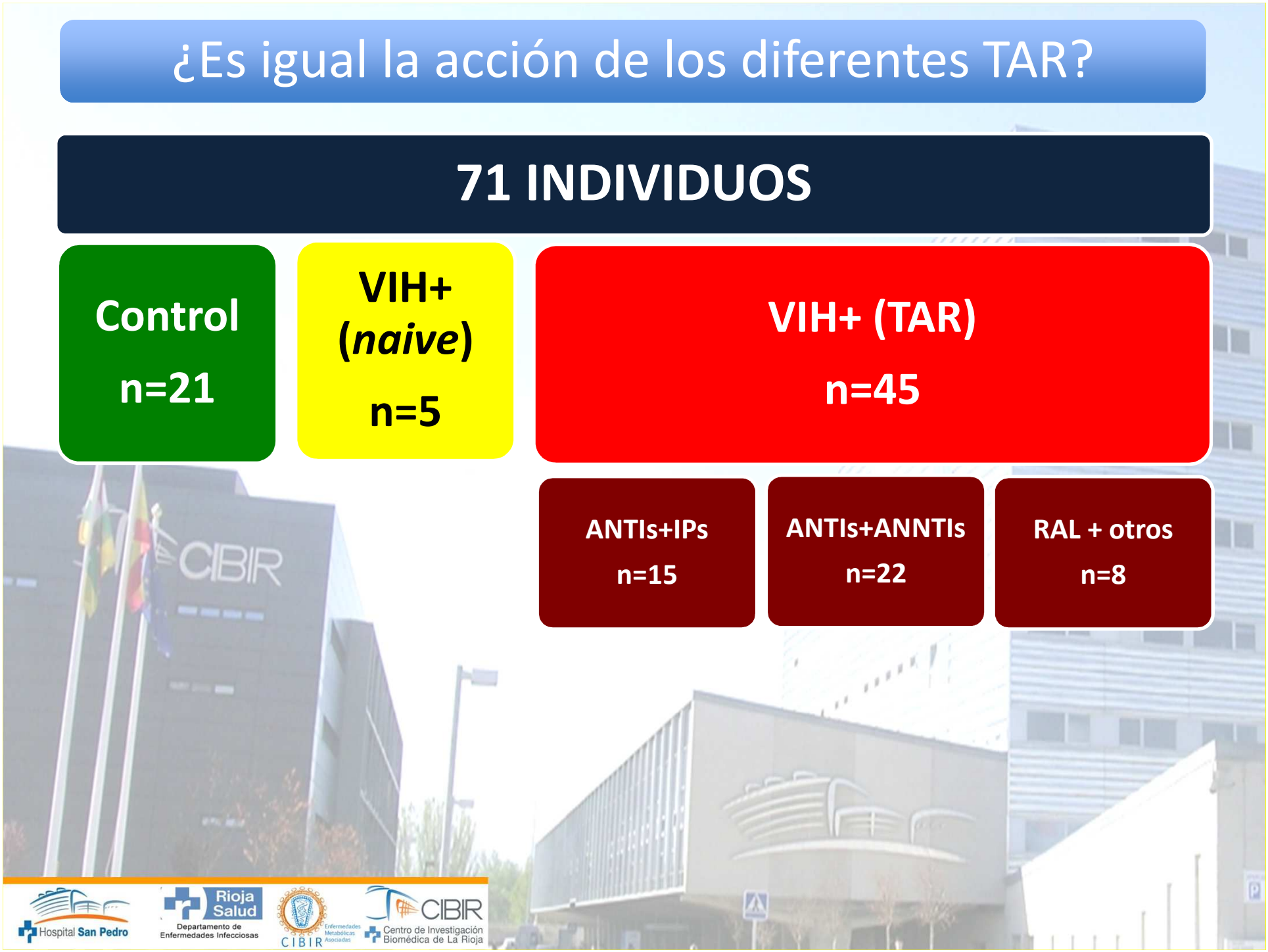
71 INDIVIDUOS

Control
n=21

VIH+ (*naive*)
n=5

VIH+ (TAR)
n=45

- **ANTIs+IPs** n=15
- **ANTIs+ANNTIs** n=22
- **RAL + otros** n=8



Hospital San Pedro
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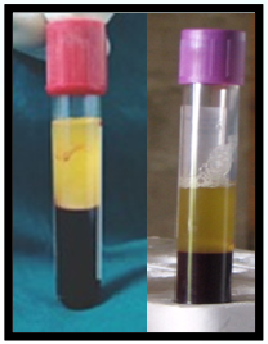
CIBIR
Centro de Investigación Biomédica de La Rioja

¿Es igual la acción de los diferentes TAR?



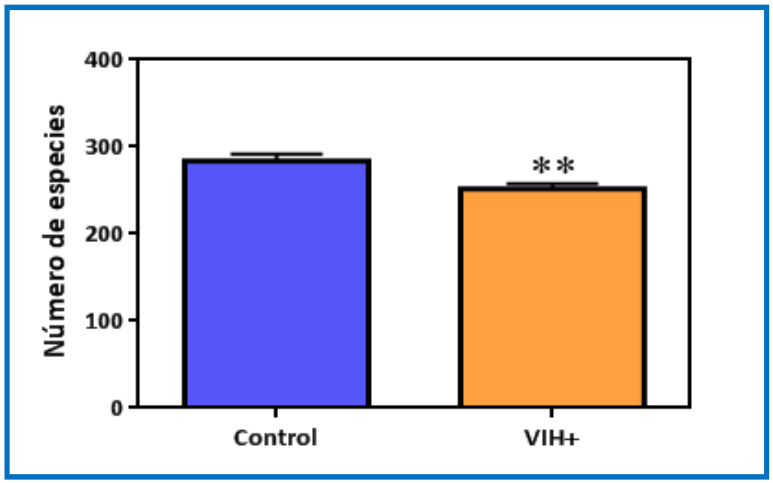
ESTUDIO DEL MICROBIOMA EN HECES

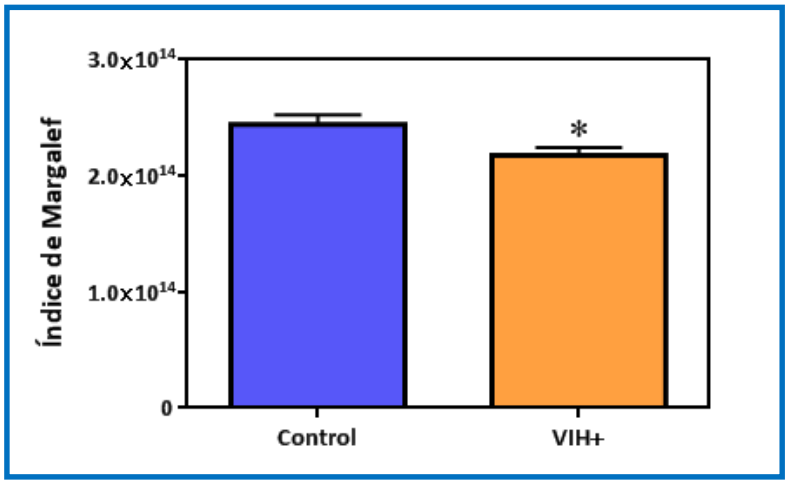
- Estudio de la alfa-diversidad
- Estudio de la beta-diversidad
- Región V4 del gen 16s del ARNr
- Secuenciador MiSeq - Ilumina

MARCADORES DE TRANSLOCACIÓN BACTERIANA

- LPS (*lipopolysaccharide*)
- LBP (*lipopolysaccharide binding protein*)
- sCD14 (*soluble CD14*)
- I-FABP (*intestinal fatty acid binding protein*)

ÍNDICES DE α-DIVERSIDAD
(*riqueza de especies bacterianas que hay en una muestra determinada*)

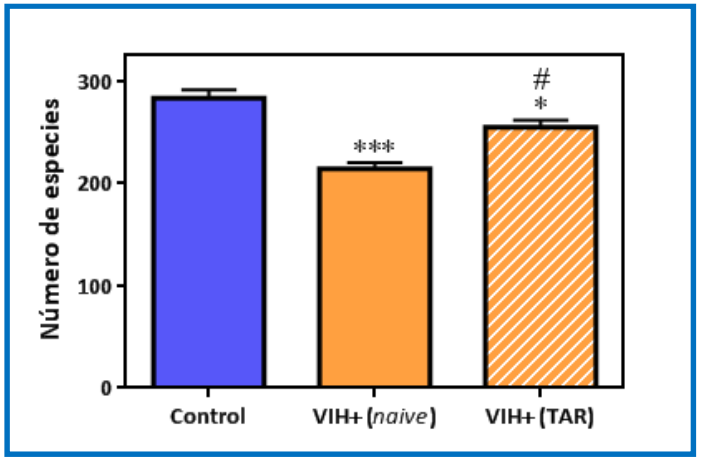


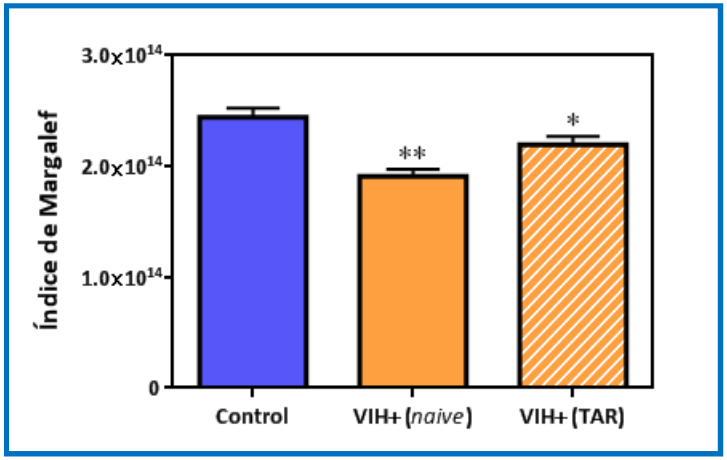


	Controles	VIH+	p
Número de especies	283.4 ± 8.19	251.5 ± 6.42	0.006
Número de individuos	99178 ± 3281	95769 ± 1910	0.148
Índice de Margalef	$2.44 \times 10^{14} \pm 8.06 \times 10^{12}$	$2.18 \times 10^{14} \pm 6.74 \times 10^{12}$	0.026
Índice Chao 1	$3.04 \times 10^{14} \pm 4.30 \times 10^{13}$	$2.13 \times 10^{14} \pm 2.87 \times 10^{13}$	0.059
Índice de Shannon	$2.91 \times 10^{14} \pm 3.77 \times 10^{12}$	$2.83 \times 10^{14} \pm 4.14 \times 10^{12}$	0.416

Los pacientes infectados por el VIH presentan menor riqueza de especies que el grupo control

ÍNDICES DE α-DIVERSIDAD
(*riqueza de especies bacterianas que hay en una muestra determinada*)



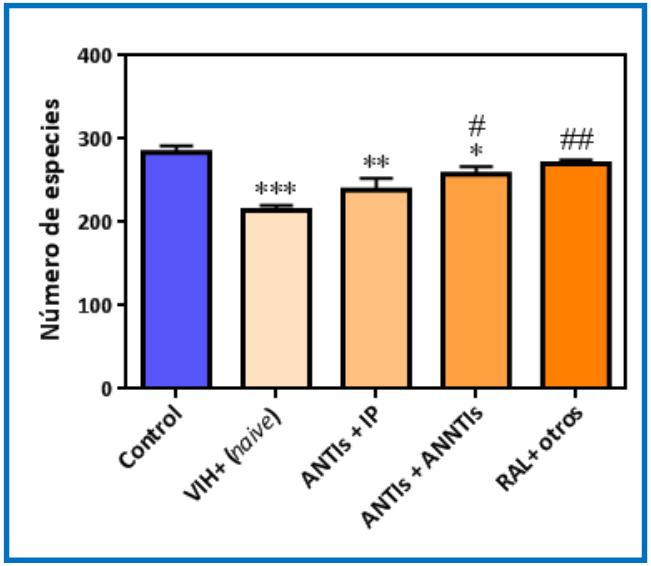


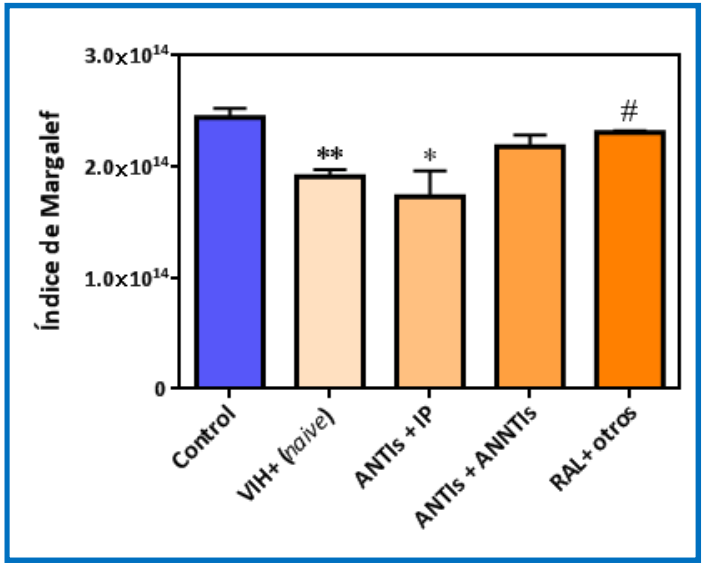
	Controles	VIH+		p
		VIH+ (*naive*)	VIH+ (TAR)	
Número de especies	283.4 ± 8.19	214.3 ± 6.07 ***	254.9 ± 6.76 *; #	0.003
Número de individuos	99178 ± 3281	91343 ± 4693	96272 ± 2061	0.212
Índice de Margalef	$2.44 \times 10^{14} \pm 8.06 \times 10^{12}$	$1.91 \times 10^{14} \pm 6.27 \times 10^{12}$ **	$2.20 \times 10^{14} \pm 7.16 \times 10^{12}$ *	0.025
Índice Chao 1	$3.04 \times 10^{14} \pm 4.30 \times 10^{13}$	$2.52 \times 10^{14} \pm 1.31 \times 10^{14}$	$2.09 \times 10^{14} \pm 2.98 \times 10^{13}$	0.168
Índice de Shannon	$2.91 \times 10^{14} \pm 3.77 \times 10^{12}$	$2.78 \times 10^{14} \pm 1.61 \times 10^{13}$	$2.84 \times 10^{14} \pm 4.26 \times 10^{12}$	0.683

*p<0.05; ** p<0.01; *** p<0.001 *vs* Control; # p<0.05 *vs* VIH+ (*naive*)

La disminución de la riqueza de especies se da tanto en pacientes naive como en TAR

ÍNDICES DE α-DIVERSIDAD
(*riqueza de especies bacterianas que hay en una muestra determinada*)





	Controles	VIH+				p
		VIH+ (*naive*)	ITRN+ IP	ITRN + ITRNN	RAL+ otros	
Número de especies	283.4 ± 8.19	214.3 ± 6.07 ***	238.7 ± 14.31 **	257.9 ± 8.63 *; #	270.3 ± 4.50 ##	0.004
Número de individuos	99178 ± 3281	91343 ± 4693	96567 ± 4449	94089 ± 2584	101451 ± 3677	0.254
Índice de Margalef	$2.44 \times 10^{14} \pm 8.06 \times 10^{12}$	$1.91 \times 10^{14} \pm 6.27 \times 10^{12}$ **	$1.73 \times 10^{14} \pm 2.37 \times 10^{13}$ *	$2.18 \times 10^{14} \pm 1.05 \times 10^{13}$	$2.31 \times 10^{14} \pm 1.92 \times 10^{12}$ #	0.021
Índice Chao 1	$3.04 \times 10^{14} \pm 4.30 \times 10^{13}$	$2.52 \times 10^{14} \pm 1.31 \times 10^{14}$	$2.11 \times 10^{14} \pm 5.61 \times 10^{13}$	$2.30 \times 10^{14} \pm 4.14 \times 10^{13}$	$1.48 \times 10^{14} \pm 6.86 \times 10^{13}$	0.407
Índice de Shannon	$2.91 \times 10^{14} \pm 3.77 \times 10^{12}$	$2.78 \times 10^{14} \pm 1.61 \times 10^{13}$	$2.03 \times 10^{14} \pm 3.38 \times 10^{13}$	$2.79 \times 10^{14} \pm 6.15 \times 10^{12}$	$2.87 \times 10^{14} \pm 7.84 \times 10^{12}$	0.604

*p<0.05; ** p<0.01; *** p<0.001 *vs* Control; # p<0.05; ## p<0.01 *vs* VIH+ (naive)

Mejora de la riqueza de especies en pacientes con ANNTI y restablecimiento con RAL

β-DIVERSIDAD
(diferencia entre comunidades)

	CONTROL	VIH+	p
Firmicutes	42.86 ± 1.56	38.86 ± 1.43	0.111
Bacteroidetes	31.25 ± 2.46	35.24 ± 1.53	0.166
Proteobacteria	2.96 ± 0.35	5.11 ± 0.51	0.020
▪ α-proteobacteria	0.43 ± 0.12	0.27 ± 0.06	0.151
▪ β-proteobacteria	0.79 ± 0.2	1.29 ± 0.18	0.254
▪ γ-proteobacteria	0.10 ± 0.02	0.11 ± 0.03	0.084
▪ δ-proteobacteria	0.49 ± 0.07	0.87 ± 0.09	0.013
Actinobacteria	0.96 ± 0.17	1.44 ± 0.20	0.172
Ratio Bacteroidetes/Firmicutes	0.76 ± 0.09	1 ± 0.07	0.062
Ratio Proteobacteria/Firmicutes	0.08 ± 0.01	0.13 ± 0.01	0.020
Ratio Actinobacteria/Firmicutes	0.02 ± 0.004	0.05 ± 0.007	0.046

Incremento del filo Proteobacteria y dentro de éste de la clase δ proteobacteria

Alteración del ratio Proteobacteria/Firmicutes y Actinobacteria/Firmicutes

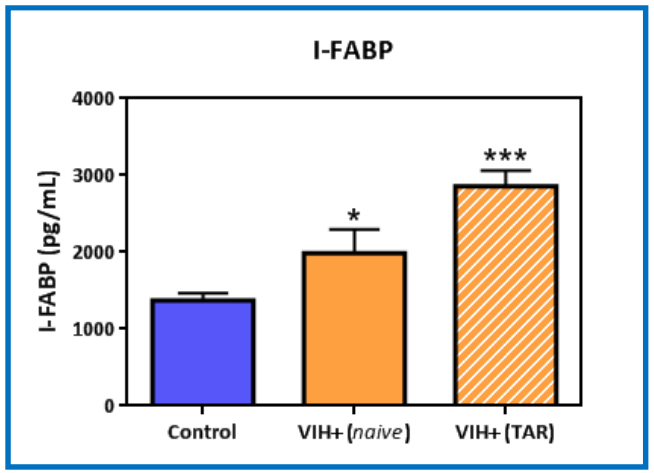
β-DIVERSIDAD
(diferencia entre comunidades)

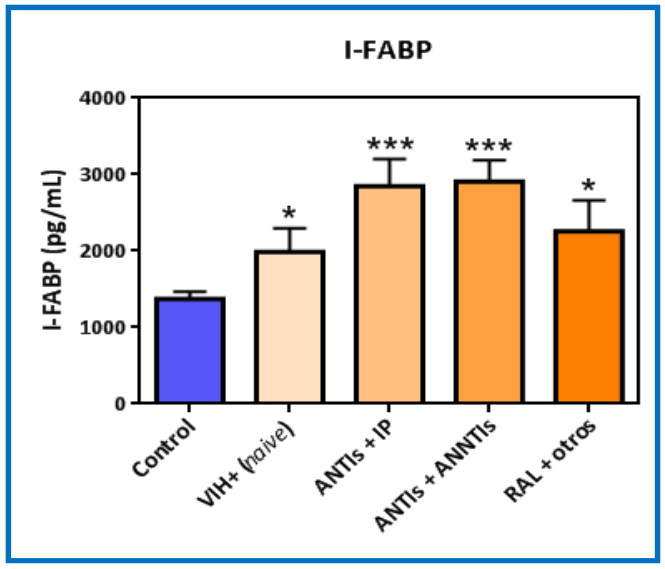
	ANTIs + IP	ANTIs+ ANNTIs	RAL+ otros	p
Firmicutes	36.72 ± 2.78	40.54 ± 2.02	40.02 ± 3.4	0.505
Bacteroidetes	37.68 ± 2.71	34.8 ± 2.49	30.69 ± 4.02	0.513
Proteobacteria	4.05 ± 0.65	5.92 ± 1.04	5.95 ± 1.11	0.386
▪ α-proteobacteria	0.34 ± 0.09	0.18 ± 0.08	1.63 ± 0.76 b	0.028
▪ β-proteobacteria	1.56 ± 0.41	1.1 ± 0.24	1.28 ± 0.49	0.837
▪ γ-proteobacteria	0.06 ± 0.02	0.34 ± 0.14	0.17 ± 0.09	0.470
▪ δ-proteobacteria	0.7 ± 0.14	0.96 ± 0.17	1.15 ± 0.14 a	0.176
Actinobacteria	3.44 ± 0.94	1.24 ± 0.21	1.11 ± 0.23	0.422
Ratio Bacteroidetes/Firmicutes	1.06 ± 0.11	0.83 ± 0.09	0.85 ± 0.16	0.268
Ratio Proteobacteria/Firmicutes	0.09 ± 0.01	0.12 ± 0.02	0.16 ± 0.04 a	0.245
Ratio Actinobacteria/Firmicutes	0.1 ± 0.02	0.04 ± 0.007	0.03 ± 0.004	0.388

Incremento de la clase alfa-Proteobacteria en los tratados con RAL

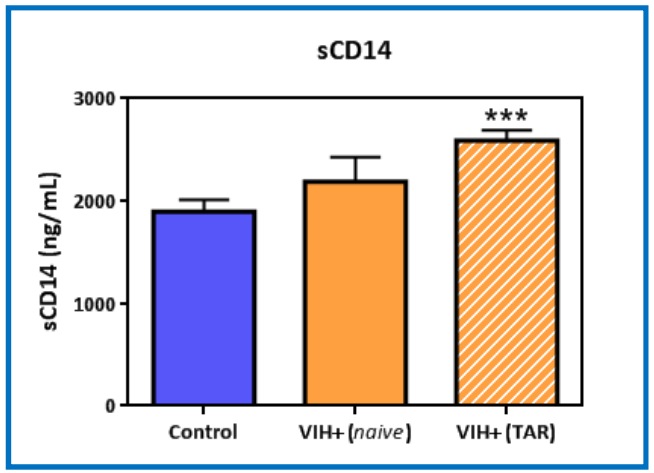
Resultados marcadores de translocación bacteriana

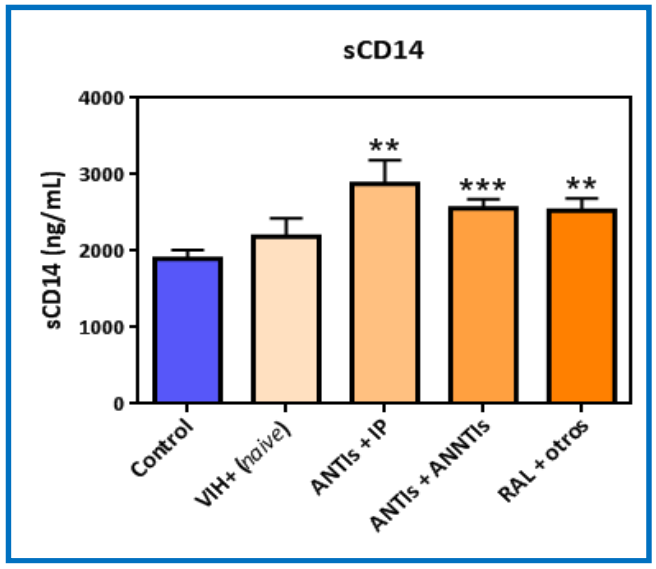
I-FABP





sCD14



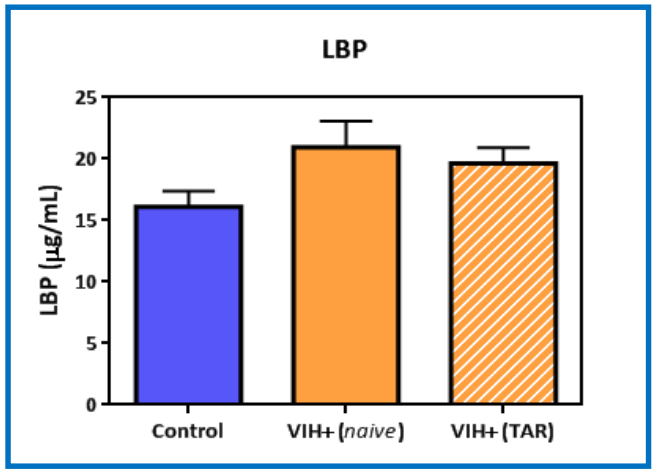


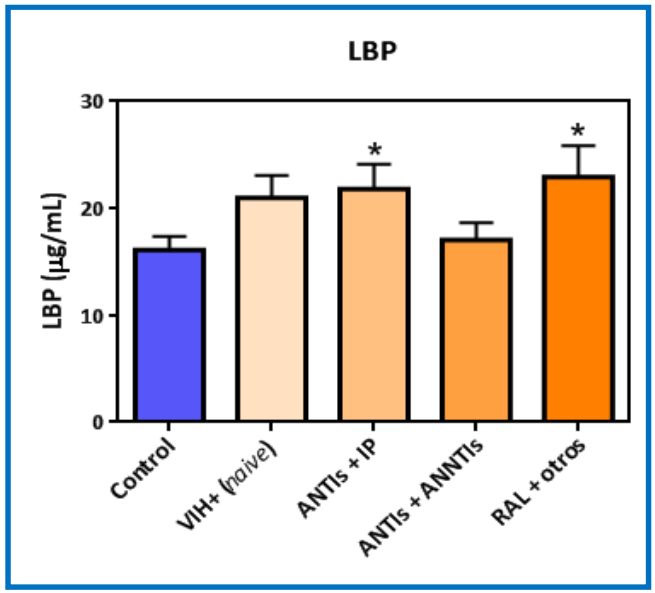
I-FABP: Proteína transportadora de ácidos grasos

*p<0,05;**p<0,01; ***p<0,001 *vs.* Control

Resultados marcadores de translocación bacteriana

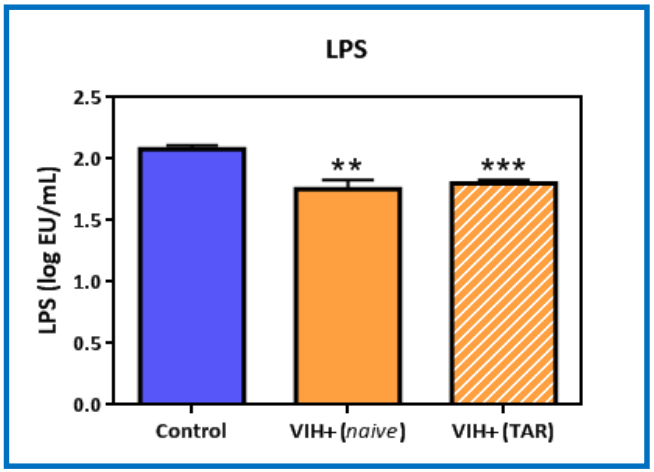
LBP

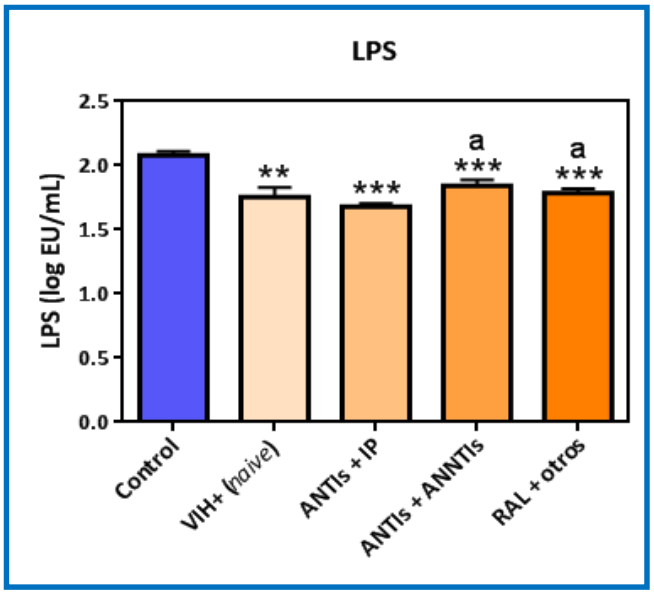




LBP: Lipoproteína transportadora de LPS

LPS





*p<0,05;**p<0,01; ***p<0,001 *vs* Control, a p<0,05 *vs* ANTIs + IP

Conclusiones

- La infección por el VIH disminuye la riqueza de especies con respecto a la población control.
- El descenso en el número de especies es mayor en los pacientes VIH sin TAR.
- El TAR recupera parcialmente la diversidad de especies en el paciente VIH.
- Los pacientes VIH en tratamiento con Inhibidores de la integrasa + otras combinaciones presentaron una riqueza de especies que se acerca a la observada en la población control.
- El filo más afectado por la infección VIH es el de las Proteobacterias (clases alfa y delta).
- Hay un aumento significativo de algunos marcadores translocación bacteriana (sCD14 y IFABP) en los pacientes VIH+ a pesar del TAR.

¿Existen implicaciones terapéuticas?

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Brief report

Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques

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HIV infection results in gastrointestinal (GI) tract damage, microbial translocation, and immune activation, which are not completely ameliorated with suppression of viremia by antiretroviral (ARV) therapy. Furthermore, increased morbidity and mortality of ARV-treated HIV-infected individuals is associated with these dysfunctions. Thus, to enhance GI tract physiology, we treated SIV-infected pigtail macaques with ARVs, probiotics, and prebiotics or with ARVs alone. This synbiotic treatment resulted in increased frequency and functionality of GI tract APCs, enhanced reconstitution and functionality of $CD4^+$ T cells, and reduced fibrosis of lymphoid follicles in the colon. Thus, ARV synbiotic supplementation in HIV-infected individuals may improve GI tract immunity and thereby mitigate inflammatory sequelae, ultimately improving prognosis.

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RESEARCH ARTICLE

Probiotics Reduce Inflammation in Antiretroviral Treated, HIV-Infected Individuals: Results of the "Probio-HIV" Clinical Trial

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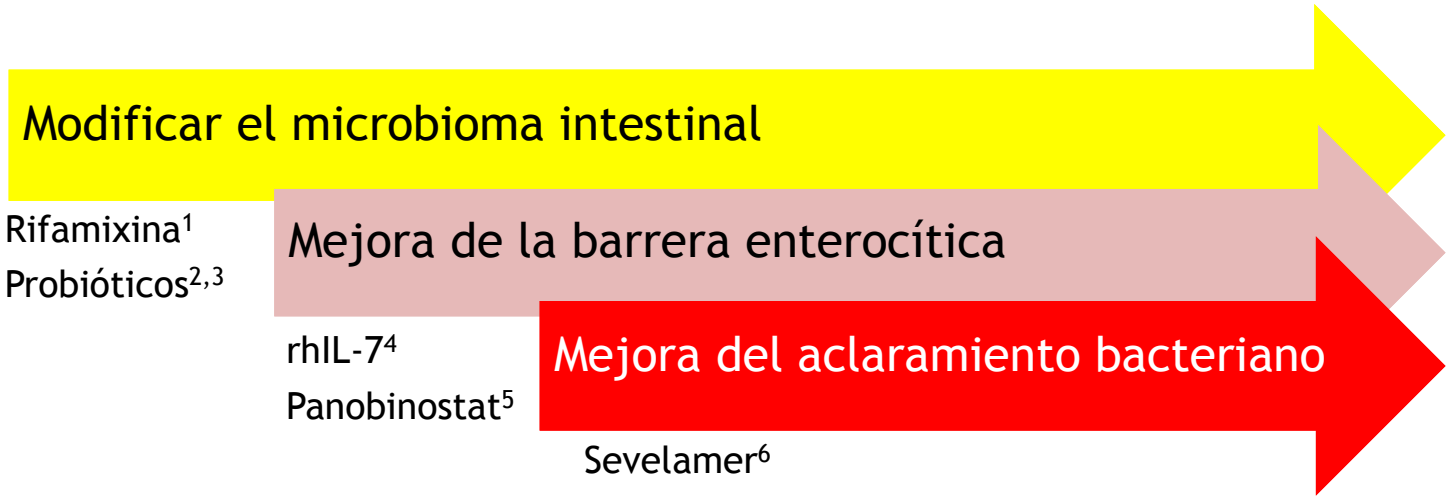
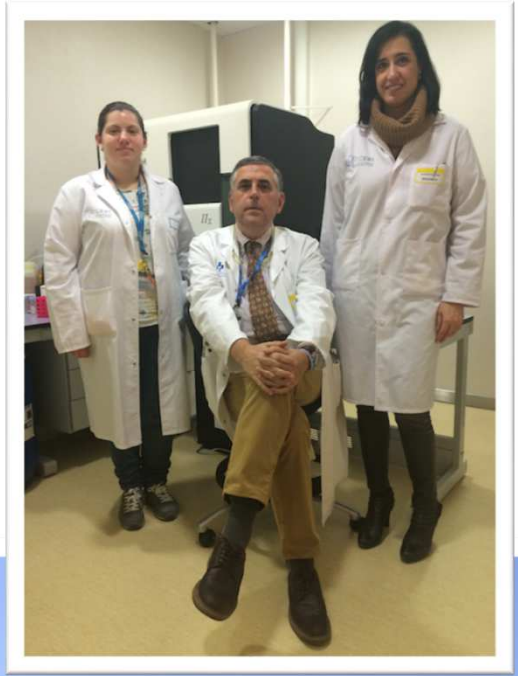
¿Qué podemos hacer?



1. Tenorio et al. JID 2015; 2. Klatt NR et al. J Clin Invest 2015; 3. d'Ettorre et al. Plos One 2015; 4. Sereti et al. Plos Pathog 2014; 5. Christensen et al. Med Inflamma 2015; 6. Hauser et al. Blood Purif 2010

Agradecimientos



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