MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

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UNIVERSIDAD DE LOS ANDES

NO TENGO CONFLICTOS DE INTERÉS
NO TENGO VÍNCULOS LABORALES CON INDUSTRIA FARMACÉUTICA

PORQUE MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

- SOY PATÓLOGA
- ESCLEROSIS MÚLTIPLE
- TRASPLANTE FECAL (REPORTE DE CASO)
- FAN DEL COMPLEMENTO

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

- QUÉ ES LA MICROBIOTA:
- FLORA “BACTERIANA, VIRAL Y FUNGICA” Y OTROS: TRACTO GASTROINTESTINAL (BOCA), GENITAL, PIEL, RESPIRATORIO
  - TRILLONES DE BACTERIAS (MEGA-ORGANO)
  - 100 VECES MAS EL GENOMA HUMANO
  - CONVIVENCIA REGULADA

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO: ESCENARIO

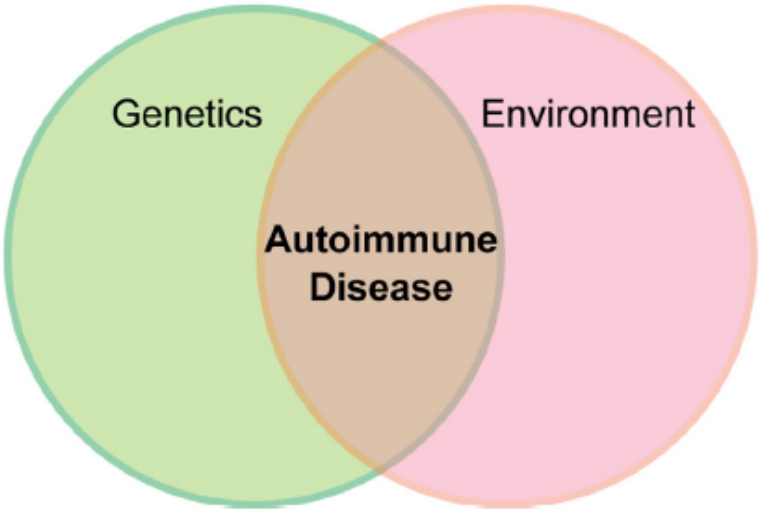
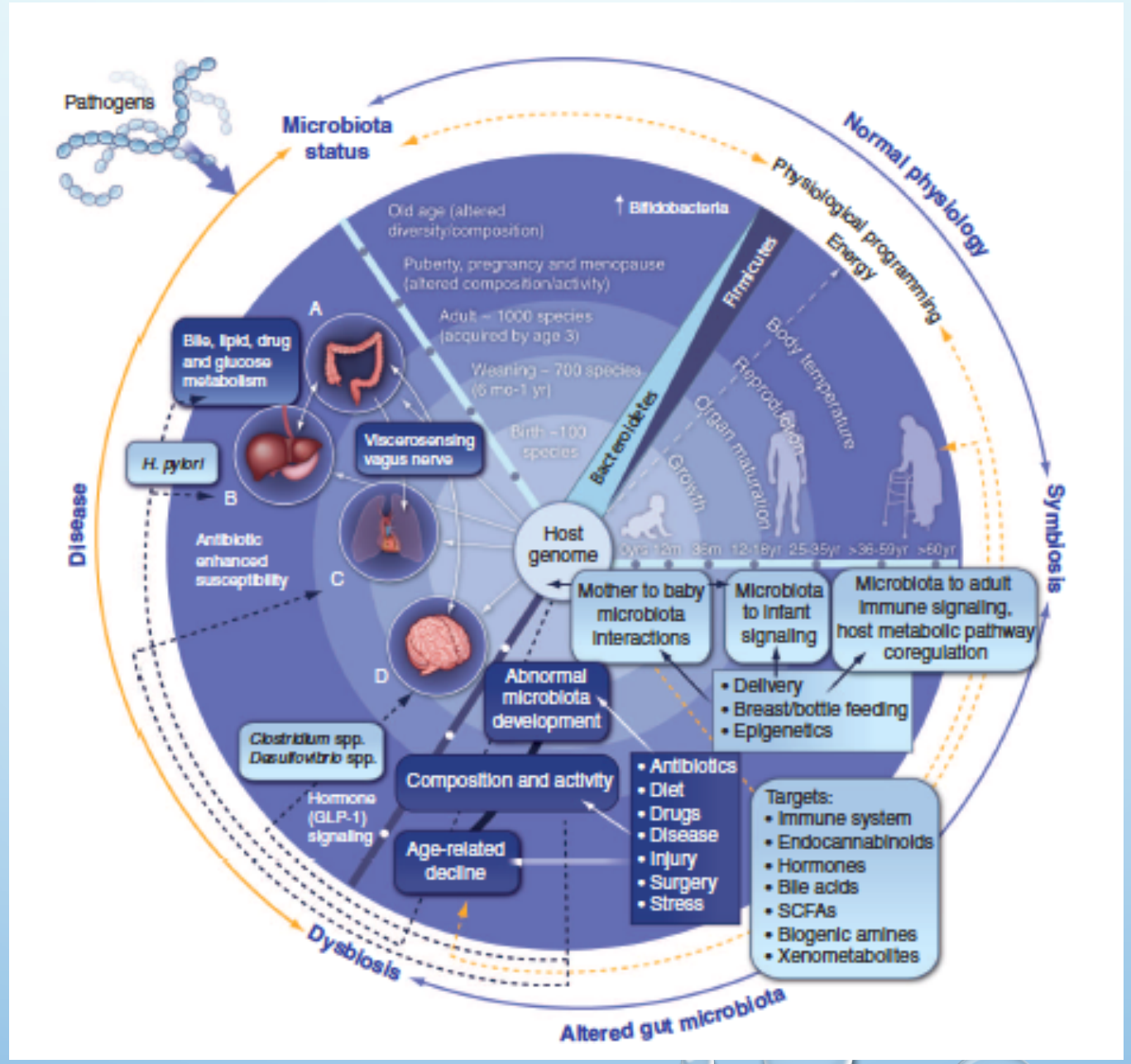


Fig. 1. Development of autoimmune disease is dependent upon a complex interplay between genetic and environmental factors. Although the exact aetiopathogenesis of autoimmune disease remains unknown, it is hypothesized that a combination of both genetic and environmental factors are needed for disease development. The relative importance of genetics versus environmental factors in the development of autoimmunity is yet to be understood, although it is currently under active investigation. Although several environmental factors have been linked to disease development in genetically predisposed individuals, recent research has suggested that changes in the composition of the gut microbiota may play an important role.

Simbiosis:
Metabolismo de elementos de la dieta no digeribles
Obtención de Vitaminas
Activación del sistema Inmune

Microbiota
Presencia de otras bacterias
Antibioticos
Tipo de Dieta
Otros….

Rosser, EC., Mauri C. A Clinical Update of the Significance of the Gut Microbiota in Systemic Autoimmunity. Journal of Autoimmunity 2016. http://dx.doi.org/10.1016/j.jaut.2016.16.009



Nicholson, JK et al. Host-Gut Microbiota Metabolic Interactions. Science 336 1262 (2012)

Disbiosis y asociaciones con múltiples patologías

Alergias
Metabólicas
Intestinales (Neo y no Neo)

Renales
Hepáticas
Neurológicas
Articulares

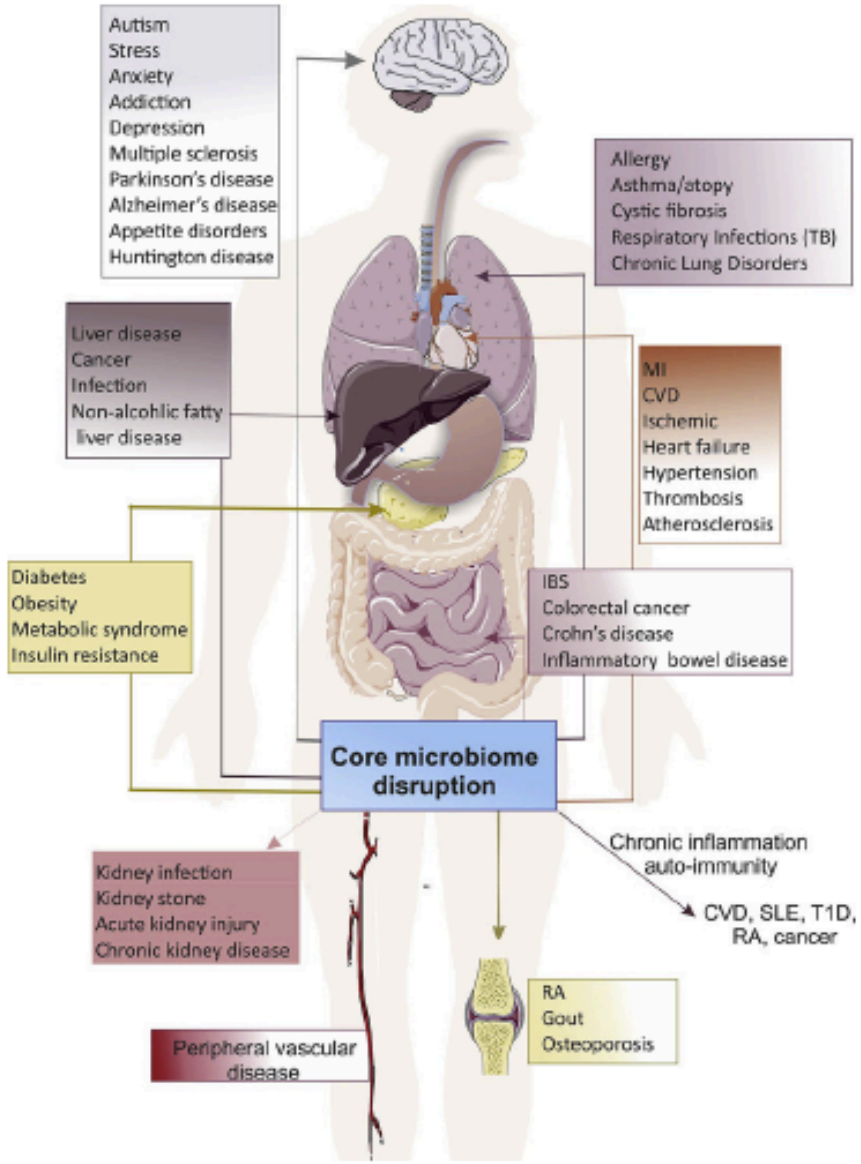


Fig. 2. Disruption of gut microbiota may prone the individuals to develop a range of pathological processes. CVD: Cardiovascular diseases, IBD: Inflammatory bowel diseases, MI: Myocardial infarction, RA: Rheumatoid arthritis, SLE: Systemic lupus erythematosus, T1D: Type 1 diabetes, TB: Tuberculosis.

Rahbar Saadat, Y. Et al. The Role of Microbiota in the Pathogenesis of lupus: Does it impact lupus nephritis?Pharmacological Research 139 (2019) 191-198

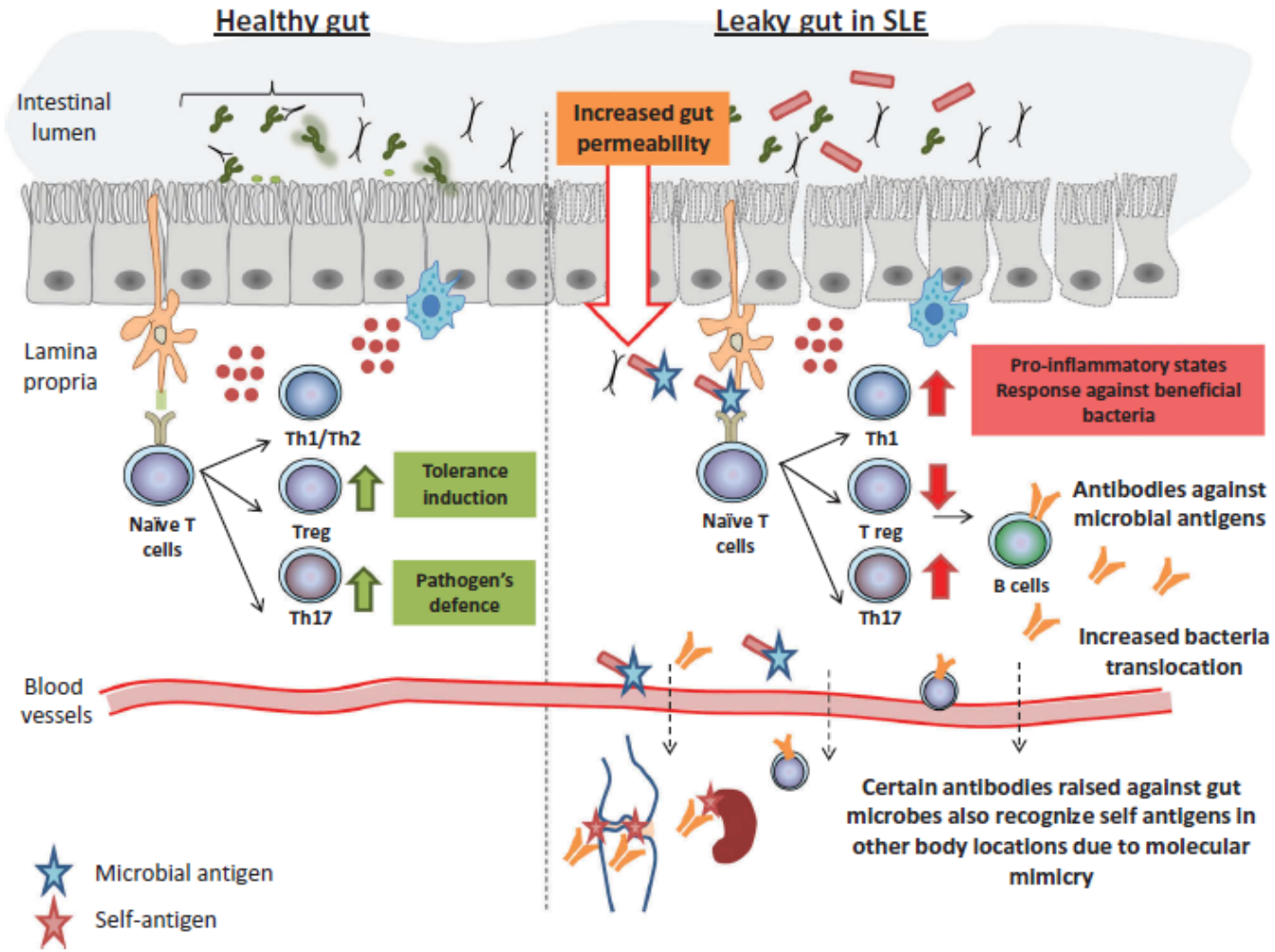
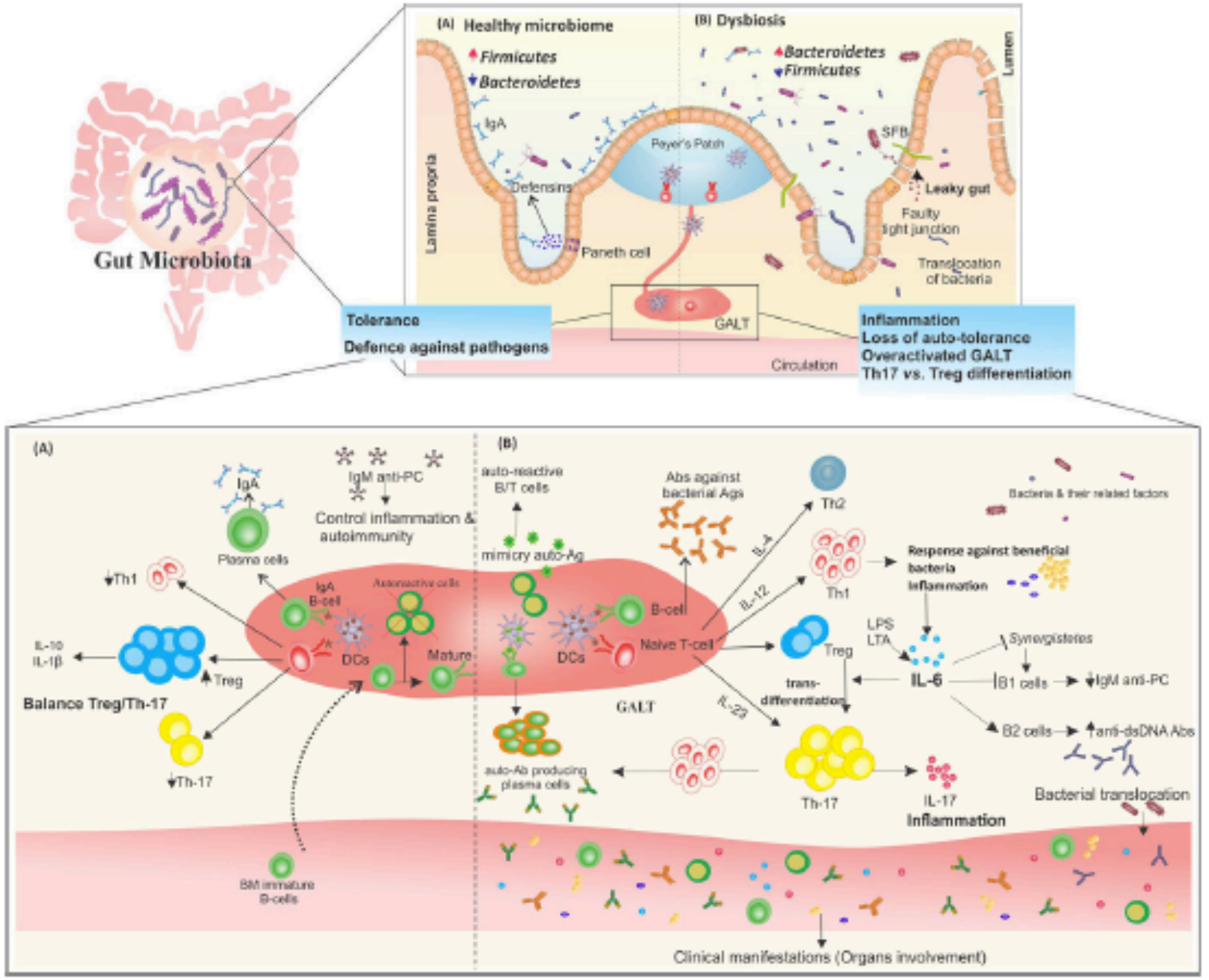


Figure 1. Schematic representation of the main alterations in the gut mucosa associated immune system in SLE patients (right) as opposed to healthy individuals (left).

The gut ecosystem in SLE patients is characterized by unbalanced microbiota populations also referred to as dysbiosis states, frequently associated with changes in the Firmicutes to Bacteroidetes ratio among other changes. Besides, dysbiosis states are concomitantly related to increased permeability of the intestinal barrier and 'leaky gut' syndrome manifestations. This results in disruption of the gut homeostasis and favors translocation of gut microbiota and their products (such as LPS of Gram-positive bacteria) to systemic circulation leading to induced inflammation and tissue damage. Furthermore, the 'leaky gut' leads to increased exposure of intestinal mucosa associated lymphoid tissues to microbiota-derived antigens, including non-pathogenic commensal members of the gut microbiota. Translocation into tissues of bacterial antigens promotes TLR and NLR responsiveness that can contribute to SLE development by sensing harmful and beneficial bacteria [18]. As a result, lymphocyte over-activation and Treg-Th17 trans-differentiation take place in the gut mucosa associated lymphoid tissue, including the generation of immune responses against microbiota commensals which would not, otherwise, represent a threat of disease. The existence of cross-reactivity between antibodies generated specifically against gut microbial epitopes, and self-molecules present at distant tissues, might be the base of the increased recognition of self-tissues in autoimmune disorders such as SLE, explaining the systemic manifestations of the disease.

Ruíz, L. et al. The Role of gut microbiota in lupus: what we know in 2018?, Expert Review of Clinical Immunology, DOI: 10.1080/1744666X.2018.1519395

Y. Rahbar Saadat et al.



Incremento de la respuesta inflamatoria:

- Aumento clones Th-17
- Expresión de Citoquinas proinflamatorias

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Disbiosis

Incremento de Fretibacterium, Prevotella, Selenomonas	Cavidad Oral
Anticuerpos Generados Ro60 (RNA Binding Autoantigen) ERV gp70	Bacteroides Thetaiotaomicron Enterococcus Gallinarum (hígado)
Lachnospiraceae Incrementada Lactobacillaceae Disminuida	Mayor severidad LES

Szymula A, et al. T cell epitope mimicry between Sjögren´s síndrome Antigen A (SSA)/Ro60 and oral, gut skin and vaginal bacteria. Clin Immunol. 2014; 152:1-9

Manfredo Vieira s, et al. Translocation of a gut pathobiont drives autoimmunity in mice and humans. Science 2018; 359: 1156-1161

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

- MODELOS ANIMALES SUCEPTIBLES DE DESARROLLAR LES

- **EUROPEAN METAGENOMICS OF THE INTESTINAL TRACT PROJECT**
- **US GUT MICROBIOME PROJECT (16S RRNA, NGS)**
  - 90% FIRMICUTES Y BACTERIOIDES
  - OTROS: ACTINOBACTERIA, PROTEOBACTERIA, FUSOBACTERIA, VERRUCOMICROBIA

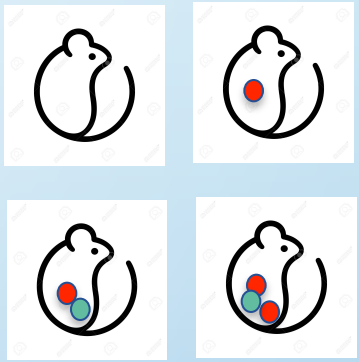
Zhang H, Liao X, Sparks JB, Luo XM. Dynamics of gut Microbiota in auto-immune lupus. *Appl Environ Microbiol* (2014) 80(24):7551–60. doi: 10.1128/ AEM.02676-14
Rosser, EC., Mauri C. A Clinical Update of the Significance of the Gut Microbiota in Systemic Autoimmunity. Journal of Autoimmunity 2016. http://dx.doi.org/10.1016/j.jaut.2016.16.009

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

Inducción del desarrollo de las Placas de Peyer
Inducción de la respuesta inmune (Linfocitos B, Thelper, Treg, Capacidad de respuesta antiviral

Disbiosis

- Lachnospiraceae Incrementada — Mayor severidad LES
- Lactobacillaceae Disminuida



Subtipos de células plasmáticas inductores de mayor cantidad de citoquinas proinflamatorias (IL6, IL9, IL17, IL22, INF α , INF β)

Otras enfermedades autoinmunes se reduce el efecto género con trasplante fecal (modelos animales)

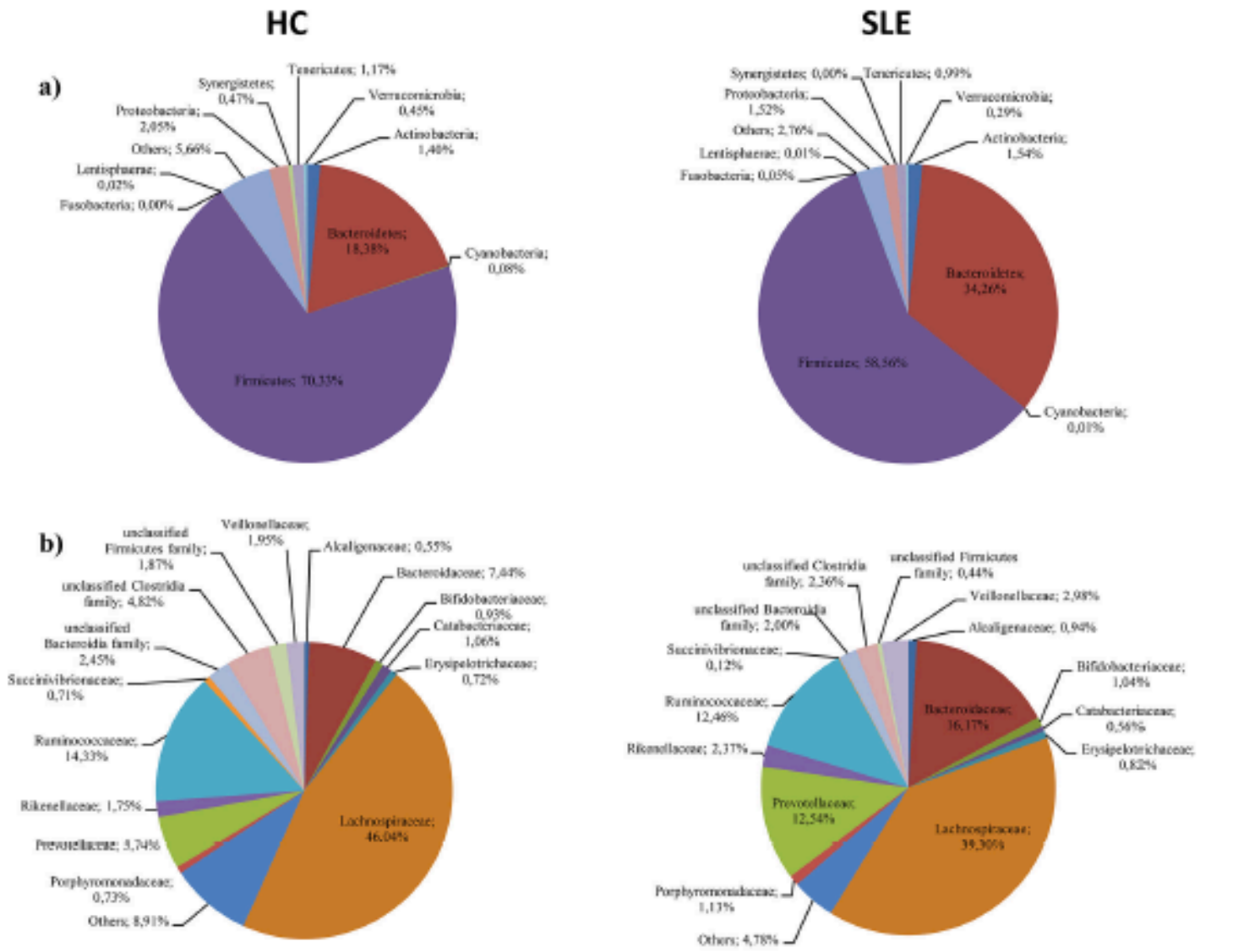


FIG 1 Aggregate microbiota composition in fecal samples from control (HC) and lupus-affected (SLE) subjects at the phylum level (a) and family level (b). In panel b, only taxonomic groups representing >0.5% are shown.

Hevia, A. Et al. Intestinal Dysbiosis Associated with Systemico Lupus Erithematosus. mBio 5(5): e01548-14. doi: 1.1128/mBio.01548-14

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

- MICROBIOTA Y ACIDOS GRASOS LIBRES
  - **F/B** SCFA, FFA ACTIVACION Y "ESTADO PROINFLAMATORIO" DEL ENDOTELIO

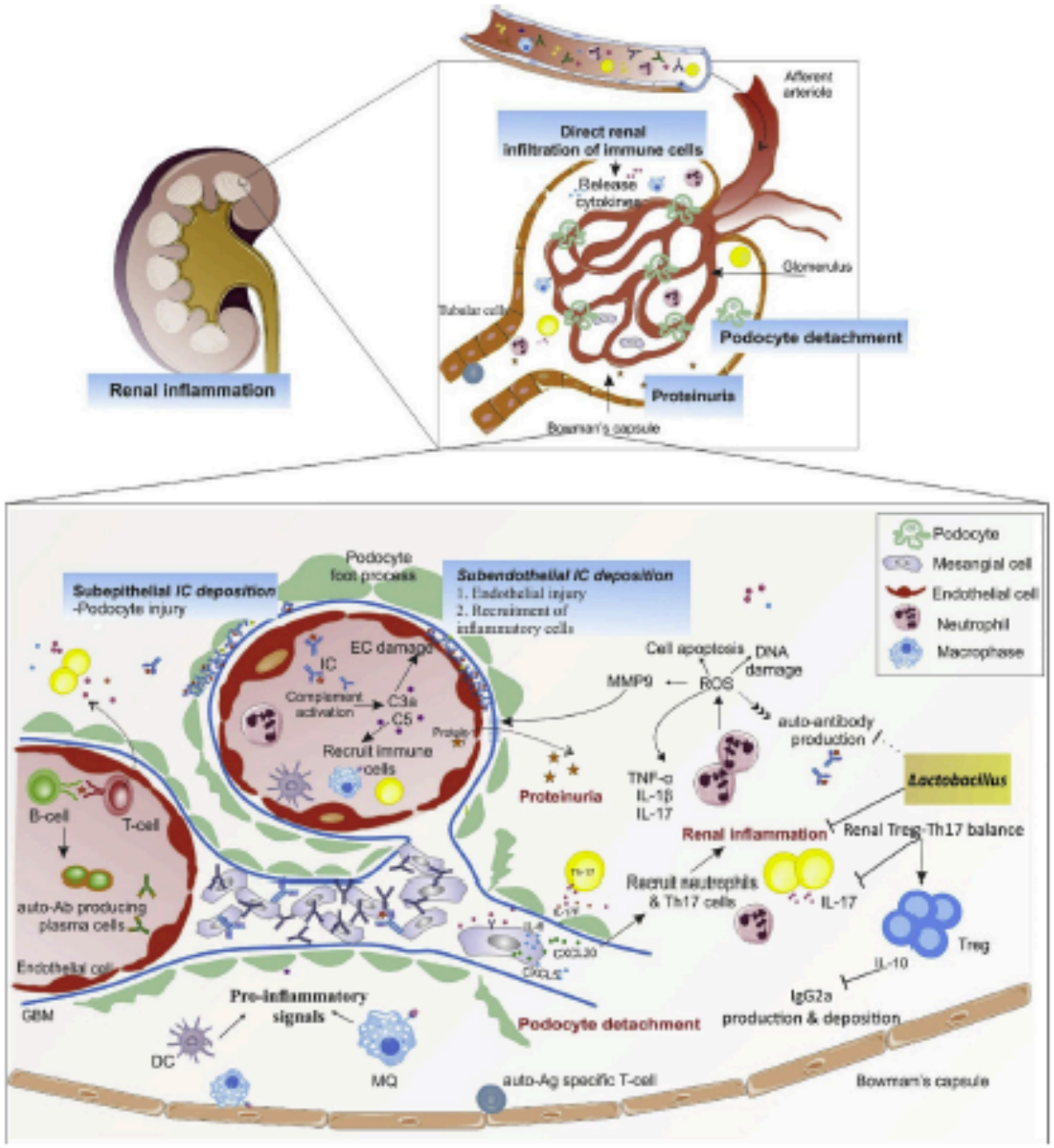
    PROPIONATO — EXPRESION DE MARCADORES DE INFLAMACION ENDOTELIAL

    BUTIRATO — DISMINUCIÓN/REGULACION DEL PROCESO INFLAMATORIO

    LACTOBACILLUS

"CONDICIÓN PREDISPONENTE SOBRE ENFERMEDAD CARDIOVASCULAR"

Rodriguez-Carrio, J, et al. Intestinal Dysbiosis is Associatesd with Altered Short-Chain Fatty Acids and Serum-Free Fatty Acids in Systemic Lupus Erythematious. Front. Immunol. 8:23. doi: 10.3389/fimmu.2017.00023



COMPROMISO RENAL EN LUPUS ERITEMATOSO SISTEMICO

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QUE DEBEMOS APRENDER? PERSPECTIVAS

CONOCER LA MICROBIOTA

MODIFICAR LA FLORA EN PACIENTES CON LUPUS ERITEMATOSO SISTEMICO

Objetivo: Incrementar la flora que induce incremento de los linfocitos Treg

Cepas de Clostridium clusters IV y XIVa

Bifidobacterium bifidum

Impedir la colonización por bacterias segmentadas filamentosas (nacimiento)

Administración de Probióticos y Prebióticos

Administración de Vitamina A

Modificación de la Dieta

Lopez P, et al. Immune response to Bifidobacterium Bifidum strains support Treg/Th17 plasticity. PloS One. 2011;6:e24776

Atarashi K, et al. Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature.2013; 500:232-236.

Goto Y, et al. Segmented filamentous bacteria antigens presented by intestinal dendritic cells drive mucosal TH17 cell differentiation. Immunity.2014; 40:594-607

Tan TG, et al. Identifying species of simbiont bacteria from the human gut taht, alone, can induce intestinal Th17 cells in mice. Proc Nath Acad Sci USA. 2016; 113:E8141-E8150.

MICROBIOTA Y LUPUS ERITEMATOSO SISTEMICO

- RETOS:
- MODIFICACIONES DE LA DIETA:
  - GASTROENTEROLOGIA
  - NUTRICION
  - OTRAS AREAS
- DISTRIBUCION DE LA COMIDA EN LAS POBLACIONES?

- ERES LO QUE COMES

GRACIAS