Il MICROBIOMA UMANO

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La metagenomica: un nuovo approccio allo studio degli “sconosciuti” ospiti del nostro organismo e al loro ruolo sulla nostra salute

Lo studio del “microbiota umano” (cioè dei microorganismi presenti nell’uomo) e della sua relazione con varie patologie risale al 1683 quando Antonie van Leeuwenhoek raschiò materiale granuloso tra i suoi denti e visualizzò con un rudimentale microscopio i batteri della placca dentale. Tra i diversi microrganismi che compongono il microbiota umano, i batteri sono il gruppo più rappresentato, ma anche virus e funghi, sono ben rappresentati. I distretti più interessati sono l’intestino, la cavità orale, la pelle, il tratto urogenitale e quello nasofaringeo.

ttp://www.fivehundredwords.it/post/it-la-metagenomica-un-nuovo-approccio-allo-studio-degli-sconosciuti-ospiti-del-nostro-organismo-e-al-loro-ruo…

Nuovi approcci

Le scienze omiche a supporto degli studi, sempre più numerosi, sul microbioma

Con 8.085 pubblicazioni scientifiche negli ultimi due anni risulta chiara l'importanza che sta acquisendo sempre più il microbiota intestinale: alterazioni della sua composizione, comunemente conosciute come disbiosi, sono ritenute responsabili di disordini metabolici, come l'obesità, o di malattie cronico degenerative quali diabete e malattie infiammatorie intestinali. Lo scenario però si sposta decisamente "lontano" dalla sede intestinale se si pensa che sono molte le evidenze che indicano la depressione come una "malattia intestinale".

A supporto della ricerca scientifica in questo campo arrivano le scienze omiche, perché lo studio del microbiota intestinale non è affatto semplice. Molte delle specie batteriche presenti nel microbiota non sono coltivabili e quindi difficilmente isolabili con tecniche di microbiologia tradizionali, per esempio essenziali alla sua crescita e a fenomeni di *quorum-sensing*, cioè meccanismi fisiologici che impediscono a una colonia di batteri della stessa specie di proliferare ulteriormente quando si è raggiunto una determinata densità di batteri. Il fatto che non tutti i microrganismi possano essere isolati in laboratorio significa che gli studi che si basano sulla sola analisi della microflora coltivabile sono poco veritieri. Dal punto di vista prettamente tecnico la differenza tra analisi di ceppi puri e di intere commità è che nel caso di batteri coltivabili la Per, quindi l'amplificazione e l'analisi del suo genoma, avviene dopo la separazione, mentre nel caso delle specie incoltivabili prima si amplifica il genoma, poi si provvedere con clonaggio o a separare su gel e ad analizzare.

Sequenziamenti di nuova generazione

Negli ultimi quindici anni l'incidenza di

nuti tramite trapianto fecale del microbiota in pazienti altamente recidivanti o refrattari alla terapia. Fino a pochi anni fa le sole tecniche di analisi microbiologica fornivano risposte molto limitate, mentre la metagenomica ha portato un nuovo metodo di analisi in grado di fornire molte delle risposte mancanti. La metagenomica produce un profilo tassonomico del campione e permette di determinare la biodiversità del microbiota dell'ospite attraverso il sequenziamento di una specifica regione ribosomiale del gene 16S rRNA. Questo è un gene lungo circa 1.500-1.600 nucleotidi, che dopo la trascrizione non è tradotto in proteina ma assume una particolare struttura secondaria che serve per la costruzione del ribosoma e poiché è essenziale per la vita è presente nei genomi in multicopia (anche quindici copie) e per que-

si estrae Dna batterico partendo da un campione fecale e grazie all'amplificazione mediante primer specifici si identificano le diverse specie batteriche. La bioinformatica fa il resto nel determinare il completo profilo batterico presente nel campione fecale. Presso l'Università di Parma hanno utilizzato proprio questa tecnica in pazienti anziani ricoverati classificati in base alla

poverimento di alcuni commensali, come *Alistipes*, ma non una riduzione della ricchezza di specie. E sempre presso l'università di Parma, la profilatura ITS dei bifidobatteri associata all'analisi metagenomica dei campioni fecali ha permesso l'identificazione di bifidobatteri dal profilo comune nelle coppie madre-bambino e ha rivelato la presenza di ceppi identici condivisi da entrambi gli intestini. La trasmissione verticale dei batteri intestinali dalle madri alla loro prole è infatti considerata un percorso fondamentale per istituzione del microbiota nei neonati, ma lo studio di questa relazione senza l'ausilio di queste tecni-

ziare, determinando così la specie batterica o fungina in maniera simile al 16S. Questa ulteriore tecnica permette di identificare sottospecie. Questo approccio rappresenta sicuramente uno strumento pratico perché l'approccio si presta a divenire un test non invasivo poiché viene fatto su materiale fecale e permette in un solo atto di diagnosticare eventuali disbiosi intestinali e allo stesso tempo stabilire e regolare gli interventi terapeutici con prebiotici e o probiotici.

Non solo metagenomica

Mentre la metagenomica aiuta a rispondere alla domanda "Qual è la composizione di una comunità microbica in condizioni diverse?", la metatrascrittomica spiega quali geni siano collettivamente espressi in condizioni diverse, aiutandoci a ottenere un profilo funzionale. Gli studi di trascrittomica e proteomica permettono di capire

Michael C. Toh and Emma Allen-Vercoe

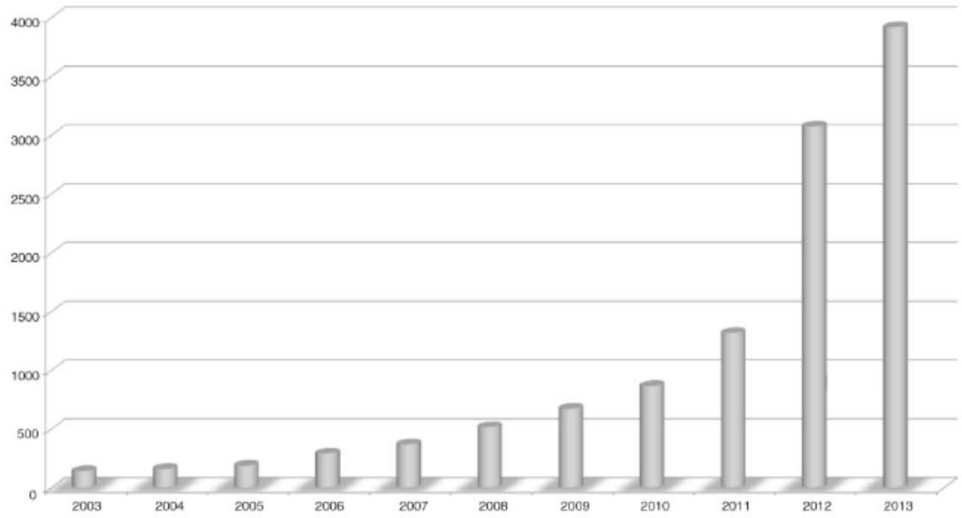
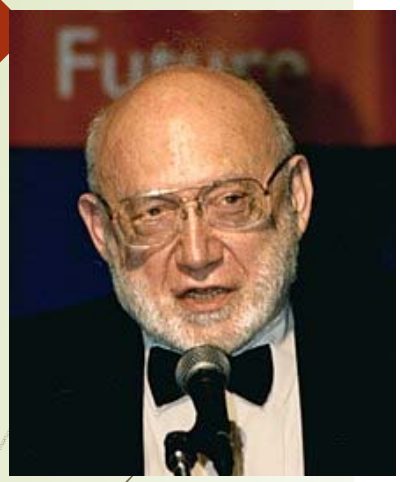


Fig. 1. Trends in human microbiome research over the last decade: PubMed Citations by year using search term 'Human microbiome'. Y-axis: number of publications.

In recent years, research into the human microbiome has captured the imagination of the general public, much in the same way that human genome research permeated public consciousness at the start of the new millennium. As a field of study, human microbiome research has exploded in the last decade (Fig. 1), which has led to a new awareness of the importance of these associated microbes to our overall health. This came as somewhat of a shock to those of us who were raised to think of all microbes as 'germs' to be eradicated; instead, we are beginning to see ourselves as microbe managers, tending to the needs of our microbial 'employees' for mutual benefit. This short review discusses how human-associated

IL CONCETTO DI MICROBIOMA



A VIEW OF GENETICS.

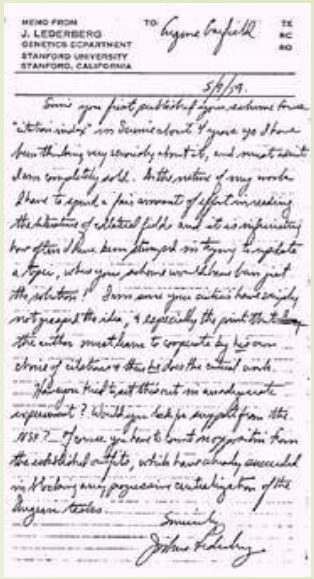
By

JOSHUA LEDERBERG.

Nobel Lecture, May 29, 1959.

The Nobel Statutes of 1900 charge each prize-winner to give a public lecture in Stockholm within six months of Commemoration Day. That I have fully used this margin is not altogether ingenious, since it furnishes a pleasant occasion to revisit my many friends and colleagues in your beautiful city during its best season.

The charge might call for a historical account of past "studies on genetic recombination and organization of the genetic material in bacteria", studies in which I have enjoyed the companionship of many colleagues, above all my wife. However, this subject has been reviewed regularly (36, 37, 38, 41, 42, 45, 49, 54, 55, 58) and I hope you will share my own inclination to assume a more speculative task, to look at the context of contemporary science in which bacterial genetics can be better understood, and to scrutinize the future prospects of experimental genetics.



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Clinical and Experimental Immunology

STELLAR REVIEW

The 'hygiene hypothesis' for autoimmune and allergic diseases: an update

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Summary

According to the 'hygiene hypothesis', the decreasing incidence of infections in western countries and more recently in developing countries is at the origin of the increasing incidence of both autoimmune and allergic diseases. The hygiene hypothesis is based upon epidemiological data, particularly migration studies, showing that subjects migrating from a low-incidence to a high-incidence country acquire the immune disorders with a high incidence at the first generation. However, these data and others showing a correlation between high disease incidence and high socio-economic level do not prove a causal link between infections and immune disorders. Proof of principle of the hygiene hypothesis is brought by animal models and to a lesser degree by intervention trials in humans. Underlying mechanisms are multiple and complex. They include decreased consumption of homeostatic factors and immunoregulation, involving various regulatory T cell subsets and Toll-like receptor stimulation. These mechanisms could originate, to some extent, from changes in microbiota caused by changes in lifestyle, particularly in inflammatory bowel diseases. Taken together, these data open new therapeutic perspectives in the prevention of autoimmune and allergic diseases.

Keywords: allergy, autoimmunity, regulatory T cells

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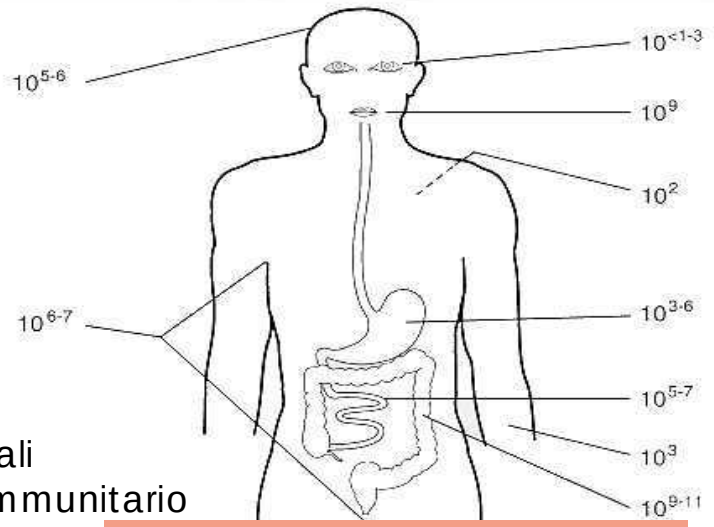
La popolazione microbica residente/ flora normale
IL MICROBIOMA UMANO

(SIMBIOSI MUTUALISTICA)

Il corpo umano è sterile prima della nascita e va incontro a colonizzazione al momento del parto.

- **distretti sterili**: vie sanguigne e linfatiche, organi interni, sistema nervoso
- **distretti colonizzati:** tutte le parti comunicanti con l'esterno: cute e mucose (cavità orale, prime vie respiratorie, apparato intestinale, uro-genitale, congiuntiva, canale uditivo esterno)

Quantità di microrganismi presenti in ufc/ml, ufc/g, ufc/cm2



Il numero totale di batteri (oltre 10^{14}= 100.000 miliardi) che normalmente colonizza alcuni distretti del corpo umano (tratto intestinale) supera di un ordine di grandezza il numero di cellule che lo costituiscono (10^{13}).

Vantaggi per l'ospite

- ❖ produzione di vitamine e fattori nutrizionali
- ❖stimolazione e maturazione del sistema immunitario
- ❖ competizione con patogeni

Vantaggi per il microbiota

- ❖ Disponibilità di nutrienti
- ❖ Condizioni ambientali ottimali (temp., pH, O2, aw)

Il Microbioma umano

MUTUALISTI/PROBIOTICI

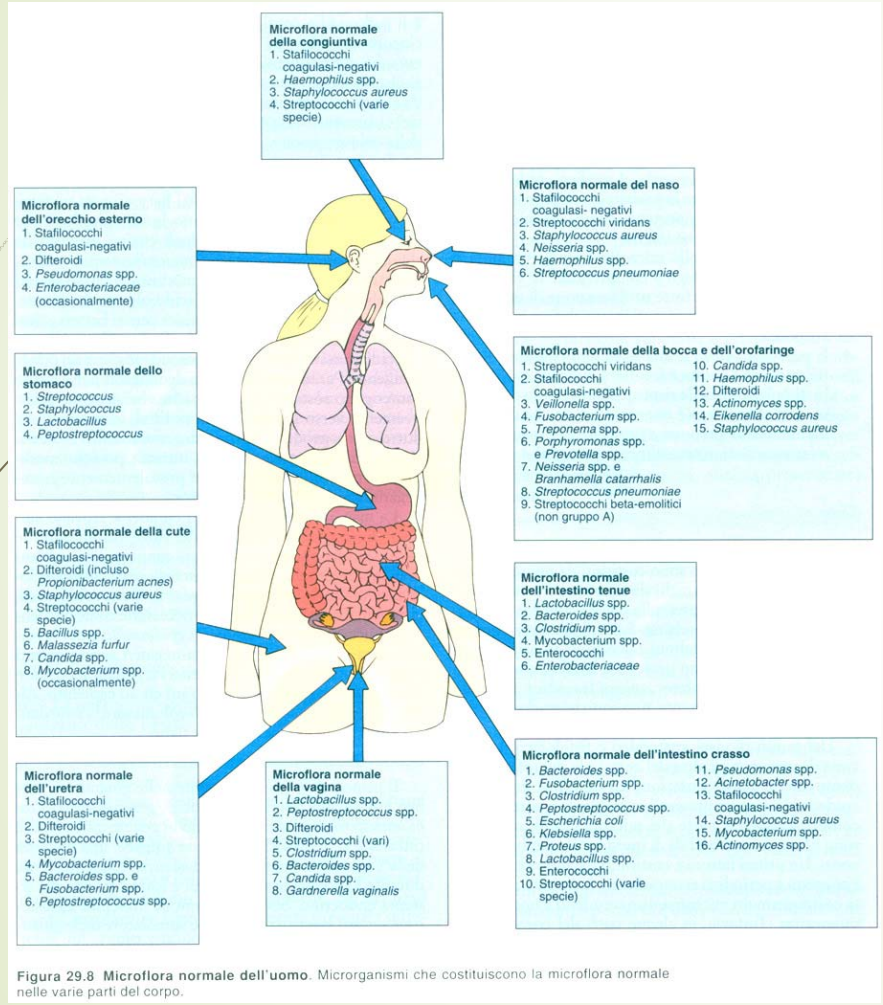


Figura 29.8 **Microflora normale dell'uomo**. Microrganismi che costituiscono la microflora normale nelle varie parti del corpo.

MICROBIOMA UMANO:
oltre 10000 specie diverse
di batteri, virus e funghi, microrganismi con cui conviviamo quotidianamente, che costituiscono circa il 3% totale del corpo umano.

Uno strumento al servizio della prevenzione e di cure future. "Contribuiscono al benessere e alla salute generale"

La composizione di queste comunità di microrganismi è sorprendentemente **varia e abbondante**.

Human Microbiome Project, iniziativa del *National Istitute of Health*

Characterization of the microbiomes of healthy human subjects at five major body sites, using 16S and metagenomic shotgun sequencing.

Enter HMP1

Characterization of microbiome and human host from three cohorts of microbiome-associated conditions, using multiple 'omics technologies.

Enter iHMP

OPEN ACCESS Freely available online

PLOS | BIOLOGY

Community Page

The Human Microbiome Project: A Community Resource for the Healthy Human Microbiome

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Identifying personal microbiomes using metagenomic codes

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Edited by Ralph R. Isberg, Howard Hughes Medical Institute, Tufts University School of Medicine, Boston, MA, and approv December 15, 2014)

Community composition within the human microbiome varies across individuals, but it remains unknown if this variation is sufficient to uniquely identify individuals within large populations or stable enough to identify them over time. We investigated this by developing a hitting set-based coding algorithm and applying it to the Human Microbiome Project population. Our approach defined body site-specific metagenomic codes: sets of microbial taxa or genes prioritized to uniquely and stably identify individuals. Codes capturing strain variation in clade-specific marker genes were able to distinguish among 100s of individuals at an initial sampling time point. In comparisons with follow-up samples collected 30–300 d later, ∼30% of individuals could still be uniquely pinpointed using metagenomic codes from a typical body site; coincidental (false positive) matches were rare. Codes based on the gut microbiome were exceptionally stable and pinpointed >80% of individuals. The failure of a code to match its owner at a later time point was largely explained by the loss of specific microbial strains (at current limits of detection) and was only weakly associated with the length of the sampling interval. In addition to highlighting patterns of temporal variation in the ecology of the human microbiome, this work demonstrates the feasibility of microbiome-based identifiability—a result with important ethical implications for microbiome study design. The datasets and code used in this work are available for download from huttenhower.sph.harvard.edu/idability.

over a century, beginning with the
ABO blood types (6). In more rec
higher-resolution genetic variants–
(STRs)—has substantially booste
man genetic information. These t
plied in forensics to link suspects t
victims, and establish familial rela
stances, identifying codes based
expected to be unique among billi
practical concerns (e.g., sample
among individuals) can reduce thi

Like STRs, SNPs in the humar
ing power, with an estimated 30–
to uniquely pinpoint each person
readily inferred from a variety of
commonly applied in modern bi
advancements, coupled with a dri
wider audience, have led to incre
vacy in genomics research (11, 12). These privacy concerns extend beyond subject identification: human SNPs are increasingly powerful for subject characterization, including prediction of physical traits, disease risk, demography, and family history (10, 11). In part due to these privacy concerns, human DNA sequences are routinely removed from microbiome datasets (where

8/11/2017 Dna dei microbi può svelare il colpevole di un delitto - Repubblica.it

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GENETICA

Dna dei microbi può svelare il colpevole di un delitto

Ogni persona ha sulla pelle batteri unici, con un codice genetico diverso per ciascun individuo. La scoperta aiuterà gli esperti della 'scientifica' in assenza di altre tracce organiche

ROMA - Gli appassionati di telefilm come Csi o Ris lo sanno bene: spesso il criminale lascia sul luogo del delitto non solo le famigerate impronte digitali, ma anche tracce biologiche fondamentali come saliva, sangue, altri liquidi o capelli. Ma ora uno studio potrebbe fornire agli esperti della 'scientifica' un'altra arma: i batteri.

Secondo uno studio diretto da Noah Fierer dell'Università del Colorado a Boulder le tracce del Dna di batteri che vivono sulla pelle delle mani possono rivelare l'identità di una persona perché ognuno di noi ha sulle proprie palme un differente e unico assortimento di microbi, riconoscibili analizzandone il profilo genetico. Ad esempio su mouse e tastiera, spiega la rivista scientifica *Proceedings of the National Academy of Sciences*, meglio conosciuta come *Pnas*, resta traccia di questa famiglia unica di batteri anche per due settimane, quindi il test può funzionare più a lungo e anche in assenza di tracce biologiche dirette del colpevole.

Oggi sono molte le modalità che permettono di identificare un individuo e quindi di inchiodare un colpevole: naturalmente il test del Dna, ognuno di noi ce l'ha diverso, solo i gemelli identici hanno lo stesso codice genetico. Invece l'impronta digitale e anche l'iride, una membrana muscolare dell'occhio con la funzione di diaframma, è diversa da individuo a individuo sia per la disposizione delle fibre muscolari sia per le pigmentazioni.

Ma gli esperti hanno visto che c'è un'altra cosa che distingue ciascuno di noi: i batteri che vivono sulla nostra pelle. In genere si tratta di un assortimento di 150 specie diverse, di cui il 13% è unico per ciascun individuo. Anche i gemelli identici, dunque, pur avendo lo stesso Dna, hanno una colonia di batteri cutanei diversa tra loro. I ricercatori hanno visto che quando posiamo la mano sulla tastiera o sul mouse questi batteri vi rimangono sopra. Andando ad analizzare il Dna della colonia di microbi che si è depositata su queste superfici, le specie batteriche presenti sono riconducibili sempre ad un'unica persona.

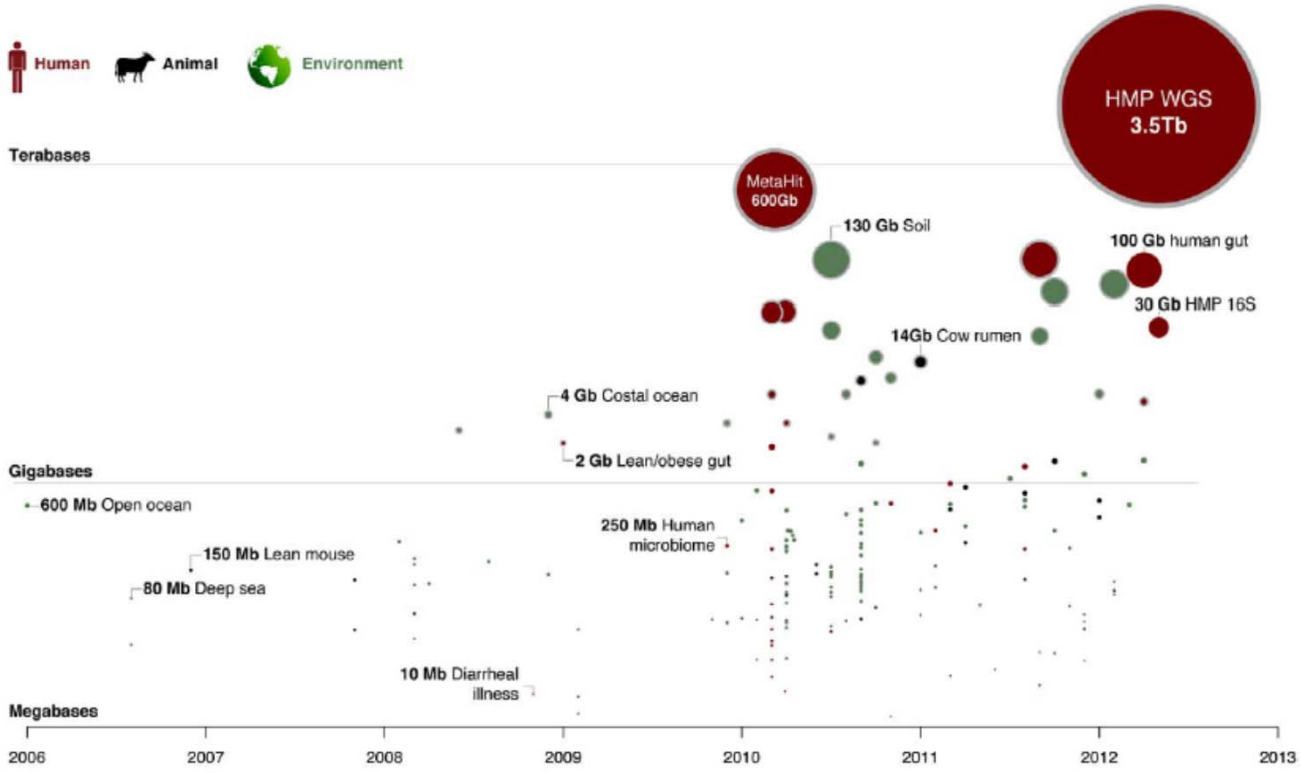

Figure 1. Timeline of microbial community studies using high-throughput sequencing. Each circle represents a high-throughput sequence-based 16S or shotgun metagenomic bioproject in NCBI (May 2012), indicating the amount of sequence data produced for each project (circle area and *y*-coordinate) at the time of publication/registration (*x*-coordinate). Projects are grouped by human-associated (red), other animal (black), or environmental (green) communities, and shotgun metagenomic projects are marked with a grey band. Selected representative projects are labeled: open ocean [68], deep sea [69], lean mouse [70], diarrheal illness [71], costal ocean [72], lean/obese gut [53], human microbiome [56], MetaHIT (gut) [58], cow rumen [73], soil (NCBI BioProject PRJNA50473), and human gut [74]. Note that HMP has deposited a total of 7.44 terabases of shotgun data in SRA, of which 49% is host DNA derived data that was filtered and only available through protected access in dbGaP project phs000228.

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The Human Microbiome: at the interface of health and disease

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Abstract

Interest in the role of the microbiome in human health has burgeoned over the past decade with the advent of new technologies for interrogating complex microbial communities. The large-scale dynamics of the microbiome can be described by many of the tools and observations used in the study of population ecology. Deciphering the metagenome and its aggregate genetic information also can be used to understand the functional properties of the microbial community. Both the microbiome and metagenome probably have important functions in health and disease; their exploration is a frontier in human genetics.

Until recently, the properties of the MICROBIOTA of humans (formerly called 'the normal flora') were largely a black box. Cultivation *in vitro*, which has been the cornerstone of microbiology since the 19th century, cannot be applied to many of the most densely populated microbial communities[1]. However, DNA-based analyses have expanded our horizon, by generating enormous new data sets that can be mined for information on the composition and functional properties of vastly greater numbers of microbial communities. For example, the Human Microbiome Project (HMP) by the NIH has produced a 2.3 terabyte 16S rRNA METAGENOMIC dataset of over 35 billion reads taken from 690 samples from 300 U.S. subjects, across 15 body sites. Large-scale endeavors (e.g. the HMP[2] and also the European project, Metahit[3]) provide a preliminary understanding of the biology and medical significance of the human MICROBIOME and its collective genes (the metagenome).

The aim of these projects, particularly the HMP, is to characterize the compositional range

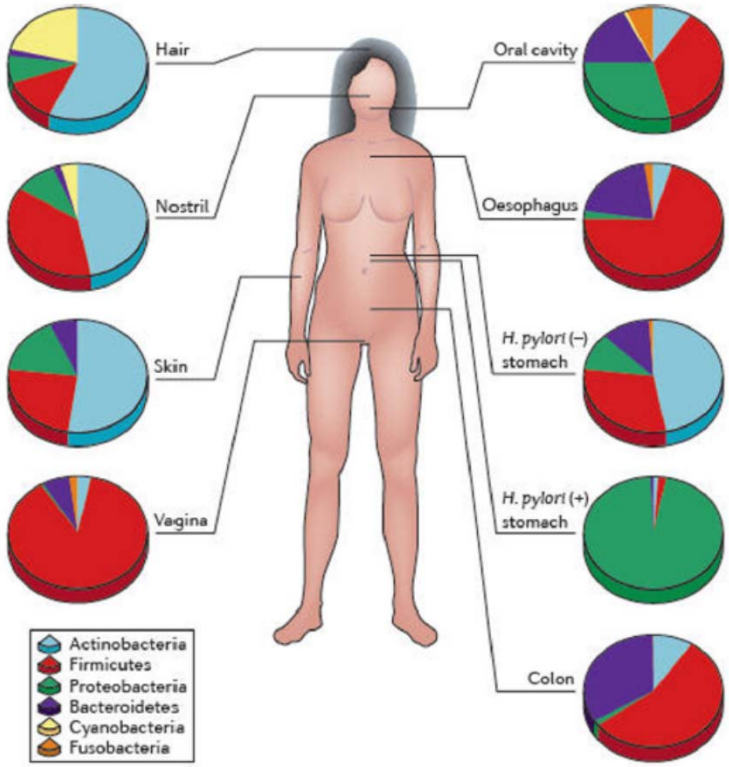

Figure 1. Compositional differences in the microbiome by anatomic site
High-throughput sequencing has revealed substantial intra-individual microbiome variation at different anatomical sites, and inter-individually for the same anatomical sites [4,5,25,52,89,93]. However, higher level (e.g. phylum) taxonomic features display temporal (longitudinal) stability in individuals at specific anatomical sites. Such site-specific differences as well as observed conservation between human hosts provide an important framework to determine the biological and pathological significance of a particular microbiome composition. The figure indicates percentages of sequences at the taxonomic phylum level from selected references. Certain features, such as the presence or absence of

Helicobacter pylori, can lead to permanent and marked perturbations in community composition[93].

The Human Microbiome: at the interface of health and disease

Ilseung Cho[1,2] and Martin J. Blaser[1,2,3,4]

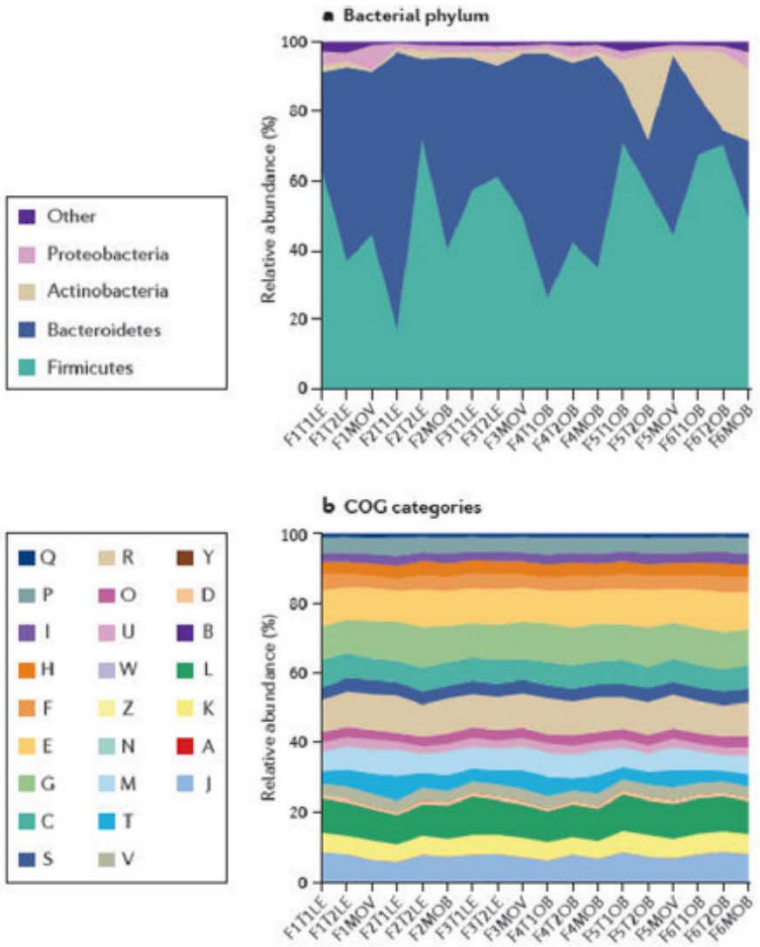

Figure 2. Conservation of bacterial genes despite taxonomic variation

A) Turnbaugh et al. studied the distal gut microbiome in lean and obese twins and their mothers[37]. There were substantial and significant taxonomic variations amongst the individuals, although Firmicutes and Bacteroidetes still constituted the majority of the taxa. B) Through metagenomic analyses, the functional characteristics of the microbiomeas identified by COG pathways are largely conserved, despite the taxonomic variation[37]. COG pathways are denoted by: S – Unknown; R – General function; L – DNA; G – Carbohydrates; E – Amino acids; M – Envelope; K – Transcription; J – Translation; C – Energy; T – Signal transduction; P – Inorganic; V – Defense; H – Coenzymes; O – Protein turnover; F – Nucleotides; U – Secretion; I – Lipids; D – Cell cycle; B – Chromatin; Q – Second metabolites; N – Cell motility; W – Extracellular; Z – Cytoskeleton; A – RNA.

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The Human Microbiome: at the interface of health and disease

Ilseung Cho[1,2] and Martin J. Blaser[1,2,3,4]

Table 1

Examples of association of human conditions with particular microbiota characteristics

Disease	Relevant finding	Reference
Psoriasis	Increased ratio of Firmicutes to Actinobacteria	88
Reflux esophagitis	Esophageal microbiota dominated by gram-negative anaerobes Gastric microbiota with low or absent *H. pylori*	75,134
Obesity	Reduced ratio of Bacteroidetes to Firmicutes	17,31
Childhood-onset asthma	Absent gastric *Helicobacter. pylori* (especially cytotoxin-associated gene (*cagA*) genotype)	96,135
IBD (colitis)	Increased *Enterobacteriaceae*	113
Functional bowel diseases	Increased *Veillonella* and *Lactobacillus*	136
Colorectal carcinoma	Increased *Fusobacterium spp.*	101,102
Cardiovascular disease	Gut microbiota-dependent metabolism of phosphatidylcholine	137

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Diversity, stability and resilience of the human gut microbiota

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Preface

The gut microbiota, the trillions of microbes inhabiting the human intestine, is a complex ecological community that through its collective metabolic activities and host interactions, influences both normal physiology and disease susceptibilities. Understanding factors underlying compositional and functional changes will aid in designing therapies that target the gut microbiota. This goal is formidable because of the immense diversity of the microbiota, interpersonal variation and temporal fluctuations in composition, especially during disease and early development. Here, we describe recent advances in understanding gut microbiota from an ecological perspective, and discuss how these insights might promote health by guiding therapeutic strategy development.

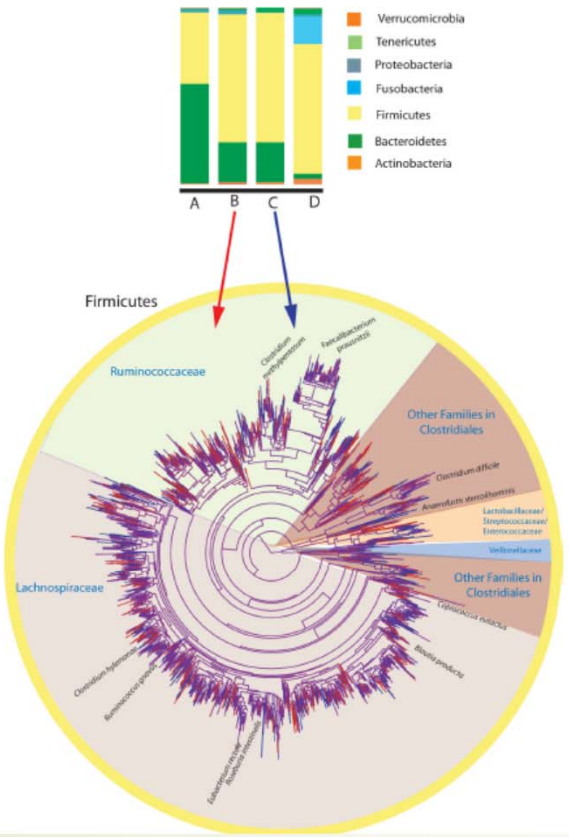

Fig. 3. Diversity of the human microbiota at different phylogenetic scales

The human microbiota displays a remarkable degree of variation within and between individuals. Although this complexity can be simplified by evaluating communities at higher taxonomic levels, such as comparing relative abundances of phyla, the many species within each phylum have different biological properties, and significant changes detected at higher taxonomic levels are likely driven by only a subset of the species in those higher taxa. Here we illustrate the high diversity and variability among individuals, and the degree to which taxonomic grouping at high levels can mask this diversity, using 16S rRNA sequence data from four of the US adults previously described in ref. [4]. We chose these four individuals to illustrate how phylum level diversity can vary dramatically even across healthy adults in the

Nature. Author manuscript; available in PMC 2013 March 13.

same population. Individual A has an unusually high proportion of Bacteroidetes, individual D unusually high Fusobacteria, and individuals B and C have more typical phylum level distributions for this cohort, dominated by Firmicutes and Bacteroidetes. However, even the apparently similar B and C differ at finer scales. The tree depicts the phylogenetic relationships between species-level phylotypes in just the Firmicutes phylum, by far the most diverse of the phyla, in individuals B and C. Branches specific to individual B are red, branches specific to individual C are blue, and shared branches are purple. Each individual has many unique phylotypes not found in the other. As described in many surveys of the human gut [14,18,40], the Ruminococcaceae and Lachnospiraceae families are particularly rich in phylotypes.

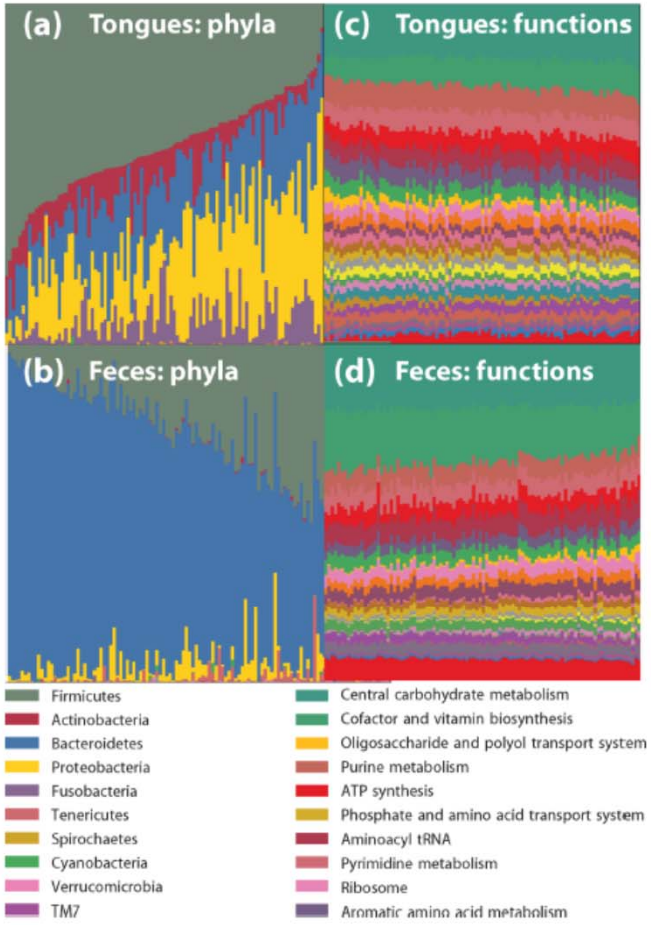

Fig. 4. Functional redundancy

Microbial ecosystems exhibit a high degree of functional redundancy in microbial ecosystems may mirror that in macroecosystems. The HMP dataset illustrates this principle: oral communities (a) and fecal communities (b) show tremendous diversity in species abundance, yet remarkable similarities to one another in functional profiles obtained by shotgun metagenomics from the same samples (c) and (d) respectively.

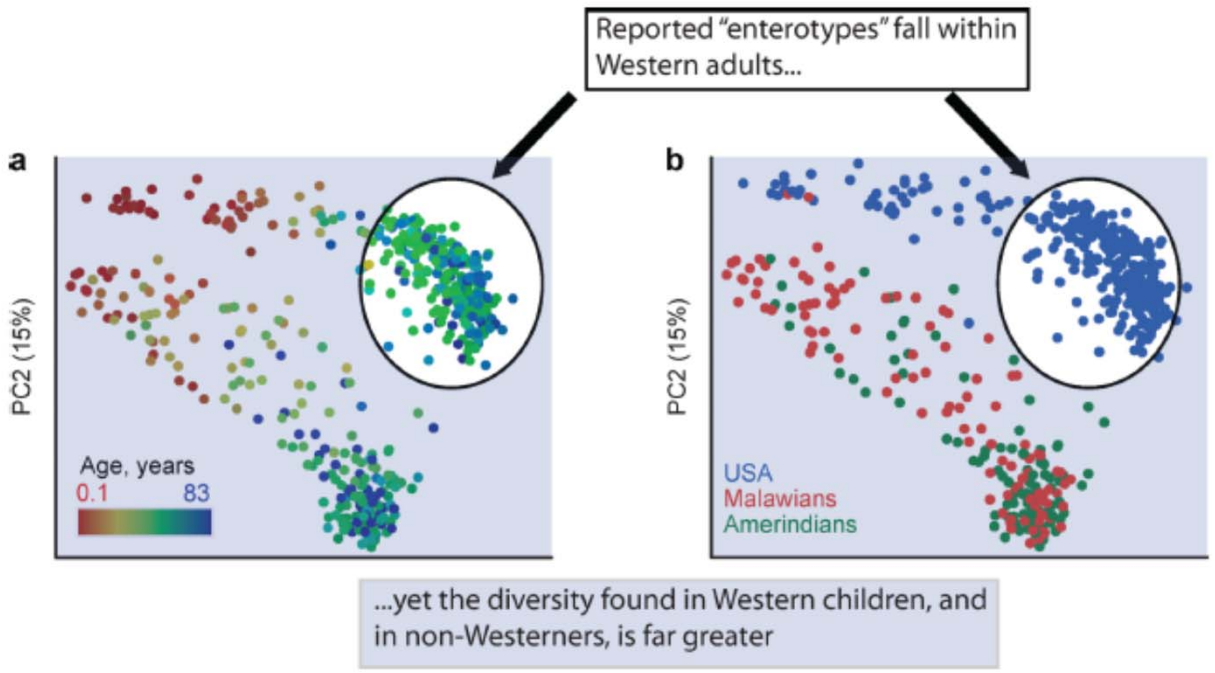

Fig. 5. Human microbial diversity and "enterotypes"

The reported "enterotypes"[31] were determined when evaluating only individuals from the US and Europe, yet including children from the US and children and adults from developing countries greatly expands the picture of human-associated microbiota diversity. We illustrate this here by showing the relationship between the microbiota of 531 healthy infants, children, and adults from Malawi, Venezuelan Amerindians, and the US that were evaluated using sequences from the 16S rRNA gene in fecal samples and a PCoA analysis of unweighted UniFrac distances (adapted from ref. [4] Fig. S2). Microbiota diversity is explained primarily by age (with infants differentiating strongly from adults) and next by culture (with adults from the US having distinct composition compared to adults from Malawi and Venezuelan Amerindians). The points from Western adults are circled in white, and the rest are shaded in blue.

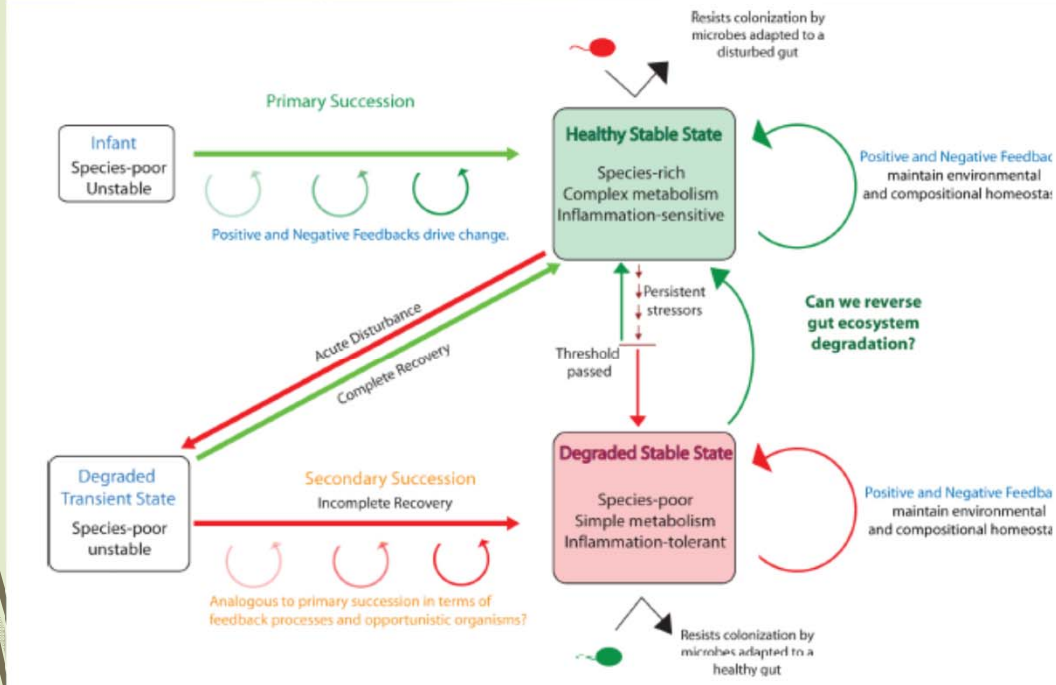

Fig. 6. Compositional transitions in the human gut microbiota

During early development, the gut microbiota undergoes a systematic turnover of species (primary succession) until a stable adult state is reached. Positive and negative feedback loops likely play a role both in driving primary succession and in conferring resilience to healthy stable equilibrium states. Acute disturbances, such as antibiotic administration, generally are followed by an unstable state that progresses to a stable state through a process of secondary succession. In some cases, the stable state that returns highly resembles the pre-disturbance state, indicating a complete recovery, but sometimes the post-recovery stable state is distinct. Post-disturbance stable states may be both degraded and resilient, for instance as suggested the persistence of post-infectious irritable bowel syndrome (i.e. IBS that forms after an initial acute disturbance of the microbiota from an enteropathogen) in some individuals for years and even decades [78]. Resilience of degraded states is likely driven by unique positive and negative feedbacks that occur both in concert with and independent of the host. Degradation to a stable state may also occur as a result of persistent stressors, such as poor diet, that slowly degrade resilience of a healthy state until a threshold is passed such that new feedbacks become important in maintaining community composition and stability. Developing therapies that encourage transition from degraded to healthy stable states, or complete recovery to a healthy stable state following disturbance, may involve identifying the species (or species combinations) and processes that are key drivers of these feedbacks. One critical unresolved question is whether interventions are more effective early in succession when communities are more unstable but may be stochastic, or later in succession when convergence to the end point is more certain but the trajectory may be more difficult to change.

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The human microbiome project: exploring the microbial part of ourselves in a changing world

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Abstract

The human microbiome project (HMP) reflects the fact that we are supraorganisms composed of human and microbial components. This international effort emanates from a confluence of ongoing technical and computational advances in the genome sciences, an evolving focus of microbiology on the properties and operations of microbial communities, and the notion that rapid, and marked, transformations in human lifestyles are not only affecting the health of the biosphere, but possibly our own health as a result of changes in our microbial ecology. HMP is designed to understand the microbial components of our genetic and metabolic landscape, and how they contribute to our normal physiology and disease predisposition. It is a global and interdisciplinary project that promises to break down the artificial barriers between medical and environmental microbiology. Here, we discuss some the challenges that HMP faces and options for addressing them.

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The human microbiome project: exploring the microbial part of ourselves in a changing world

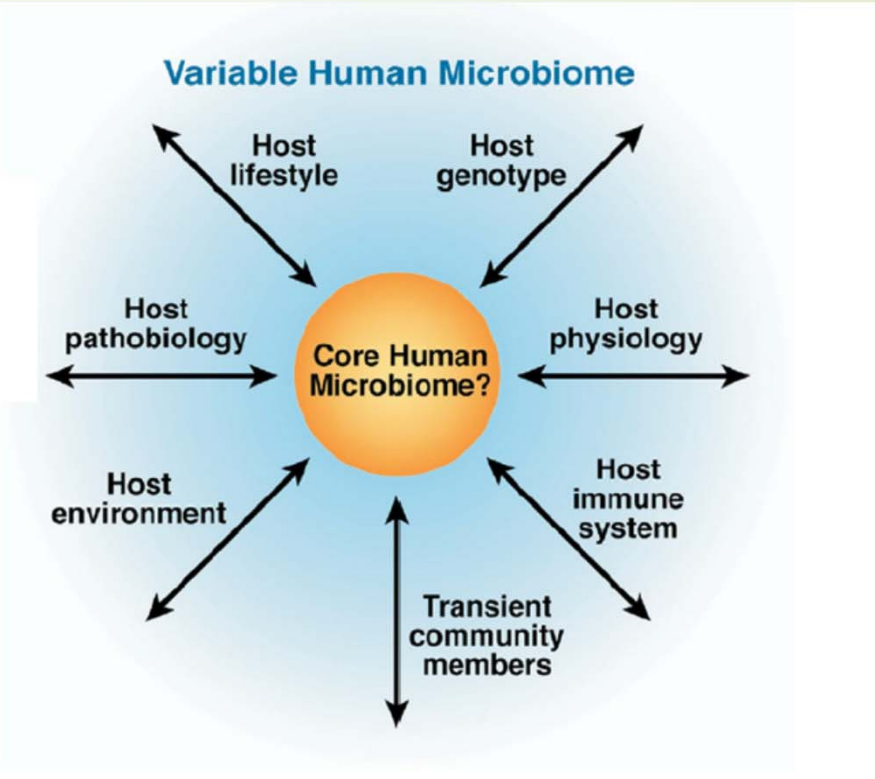

Figure 2.
A super-organismal view of the human microbiome. Core and variable components of the human microbiome could have important implications for human health, including nutrient responsiveness, innate and adaptive immunity, and development. As the microbiome affects multiple aspects of human health and disease, host biology influences the composition and function of the commensal microbiota. A subset of microbial genes may be found in most healthy human beings (core microbiome), whereas variable components are present only in specific ethnic groups, age groups, geographic locations, or associated with specific dietary patterns or disease states. Manipulation of either the core or the variable parts of the human microbiome can affect human physiology, overall health status, and disease susceptibilities. Adapted with permission from Macmillan Publishers Ltd: Nature,[1] copyright 2007. http://www.nature.com/nature/.

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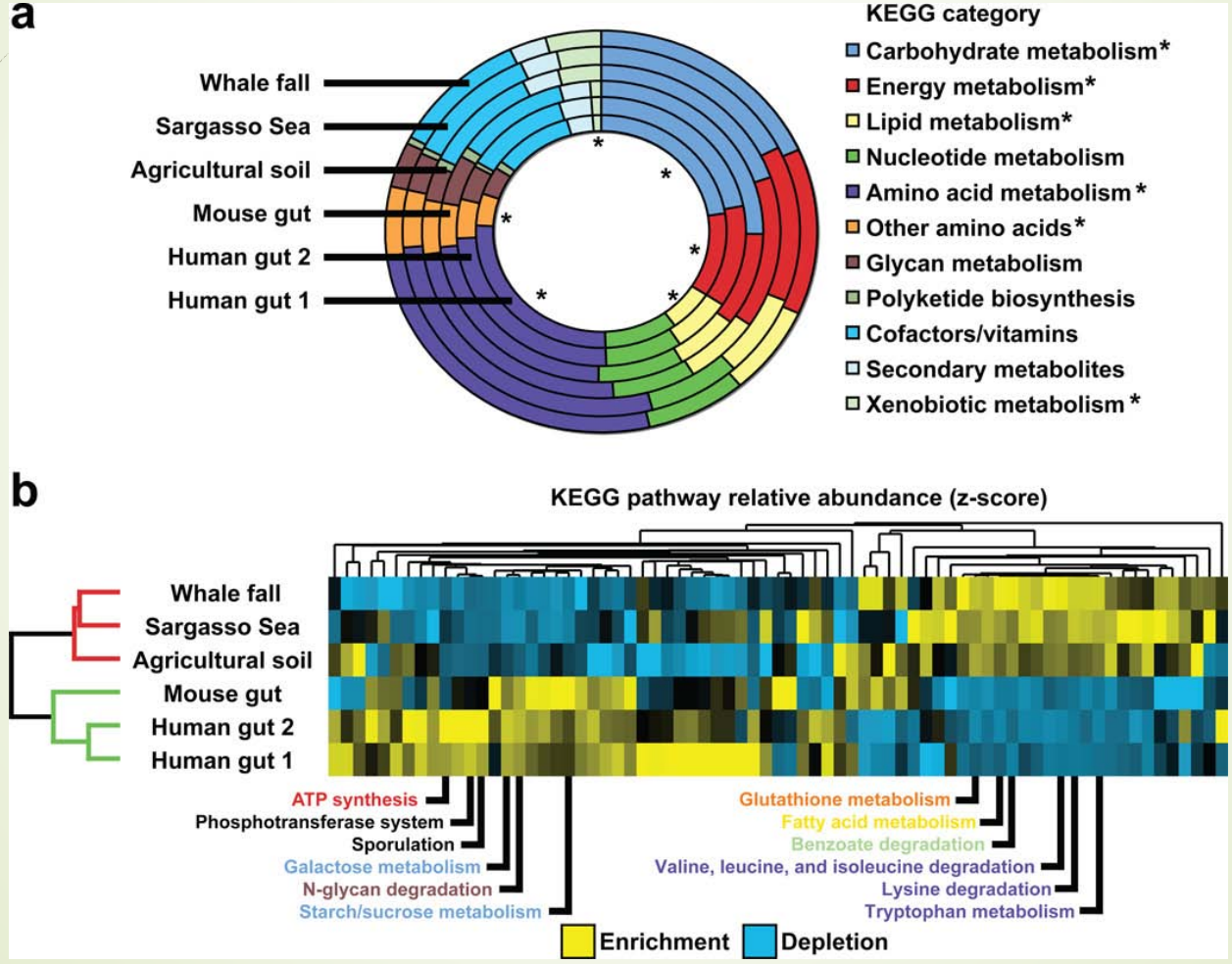
The human microbiome project: exploring the microbial part of ourselves in a changing world



Host Demise as a Beneficial Function of Indigenous Microbiota in Human Hosts

Martin J. Blaser,[a,b,c] Glenn F. Webb[d]

Departments of Medicine and Microbiology, New York University Langone Medical Center, New York, New York, USA[a]; VA Medical Center, New York, New York, USA[b]; Department of Biology, New York University, New York, New York, USA[c]; Department of Mathematics, Vanderbilt University, Nashville, Tennessee, USA[d]

ABSTRACT The age structure of human populations is exceptional among animal species. Unlike with most species, human juvenility is extremely extended, and death is not coincident with the end of the reproductive period. We examine the age structure of early humans with models that reveal an extraordinary balance of human fertility and mortality. We hypothesize that the age structure of early humans was maintained by mechanisms incorporating the programmed death of senescent individuals, including by means of interactions with their indigenous microorganisms. First, before and during reproductive life, there was selection for microbes that preserve host function through regulation of energy homeostasis, promotion of fecundity, and defense against competing high-grade pathogens. Second, we hypothesize that after reproductive life, there was selection for organisms that contribute to host demise. While deleterious to the individual, the presence of such interplay may be salutary for the overall host population in terms of resource utilization, resistance to periodic diminutions in the food supply, and epidemics due to high-grade pathogens. We provide deterministic mathematical models based on age-structured populations that illustrate the dynamics of such relationships and explore the relevant parameter values within which population viability is maintained. We argue that the age structure of early humans was robust in its balance of the juvenile, reproductive-age, and senescent classes. These concepts are relevant to issues in modern human longevity, including inflammation-induced neoplasia and degenerative diseases of the elderly, which are a legacy of human evolution.

IMPORTANCE The extended longevity of modern humans is a very recent societal artifact, although it is inherent in human evolution. The age structure of early humans was balanced by fertility and mortality, with an exceptionally prolonged juvenility. We examined the role of indigenous microbes in early humans as fundamental contributors to this age structure. We hypothesize that the human microbiome evolved mechanisms specific to the mortality of senescent individuals among early humans because their mortality contributed to the stability of the general population. The hypothesis that we present provides new bases for modern medical problems, such as inflammation-induced neoplasia and degenerative diseases of the elderly. We postulate that these mechanisms evolved because they contributed to the stability of early human populations, but their legacy is now a burden on human longevity in the changed modern world.

Blaser and Webb

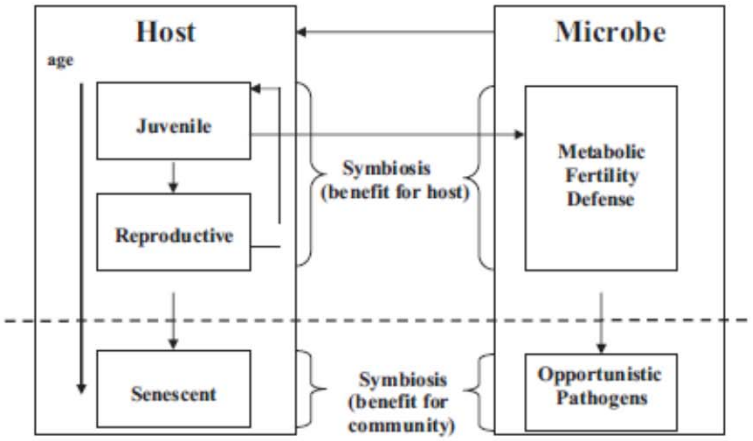
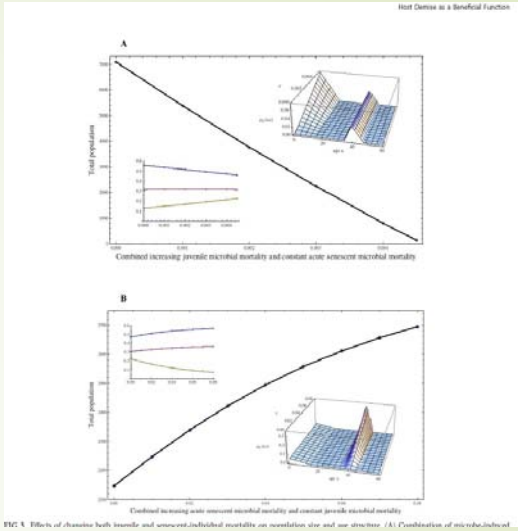


FIG 1 Schematic representation of the coevolution of host and indigenous microbes over the host's lifetime. In the senescent period, commensal and symbiotic microbes adapt to interactions that contribute to host mortality, potentially conferring benefit to the host community.



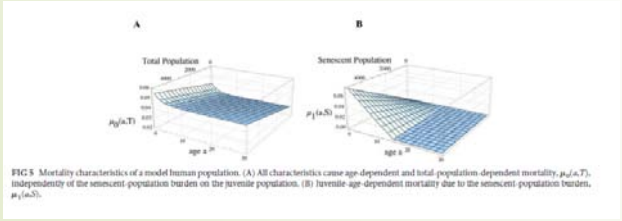


FIG 5 Mortality characteristics of a model human population. (A) All characteristics cause age-dependent and total-population-dependent mortality, $\mu_0(a,T)$, independently of the senescent-population burden on the juvenile population. (B) Juvenile-age-dependent mortality due to the senescent-population burden, $\mu_1(a,S)$.

fections manifesting during senescence (Fig. 4A and B). The idea that senescent-population mortality has a salutary effect on total-population levels is intuitive, given the assumption that the senescent population is a burden. However, the model simulations reveal that the effect is greater as the mortality of senescent individuals rises from a low level, which means that its evolutionary benefits to early human populations challenged by environmental fluctuations may have been crucial.

By varying the microbial mortality parameters (Table S3), it is evident that increased mortality among senescent individuals has a significant impact on total-population size and structure at equilibrium. While juvenile infections contract the total population and shift the population structure to the senescent class, lethal infections in senescence lead to larger total populations and to a higher juvenile fraction. The effects appear more pronounced with the acute than with persistent senescent-population mortality. The models are robust and can lead to similar solutions across a broad range of parameter values, consistent with human population demographics under human hunter-gatherer living conditions (64, 65).

DISCUSSION

Although the mathematical models proposed here are applicable to all social species, we have focused on humans because of important recent changes in human ecology and their potential impact on human society. The age structure of early human populations was intricately balanced by the fertility and mortality schedules of human existence. Modeling this balance should demonstrate that the exceptionally prolonged juvenile period of human populations, largely unchanged into modern times, was maintainable as a stable feature of early human population dynamics over evolutionary time frames. Our simulations indicate that an extended postreproductive age span was nonviable in early humans because of a resultant mortality burden on the juvenile population. Our analysis concurs with claims that the fraction of the senescent population among early humans was much smaller than in present times. Indeed, recent studies indicate that there has been a dramatic 5-fold increase in the O/Y ratio from the Middle to the Upper Paleolithic (52, 53). Changes in host population structure are predicted to select for differing microbiome populations based on altered transmission patterns.

The intrinsic fertility capacity of human females is a defining feature of human population structure. Our simulations indicate that a greatly amplified fertility capacity in early humans was not compatible with the given age structure, since with environmental fluctuations (e.g., flood, drought, epidemics, famine [66]), reset initial conditions would produce extreme population oscillations, with lower population levels resulting in extinction. Our model assigns specific mortality terms to age-compounded effects, total-population effects, and senescent-population effects. Our simula-

REVIEW SERIES: GUT MICROBIOME
Series Editor: Martin J. Blaser
The Journal of Clinical Investigation

The microbial basis of inflammatory bowel diseases

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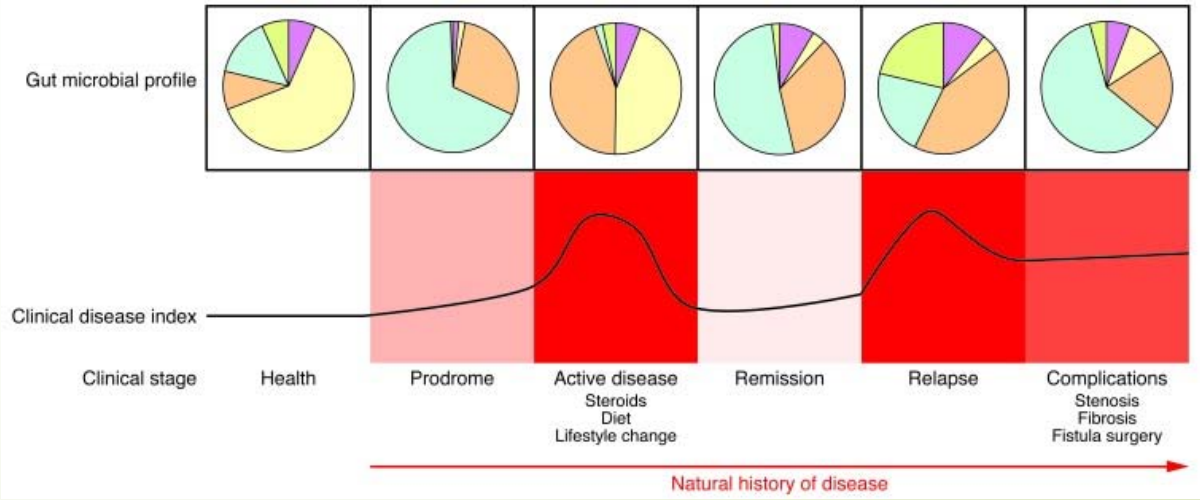
Inflammatory bowel diseases (IBD) are chronic, progressive diseases characterized by aberrant immune responses to environmental and gut microbial triggers in genetically susceptible hosts. Clinical, genetic, and experimental data support the role of gut microbes in causing and sustaining these diseases. Our understanding of IBD has changed dramatically as the result of advances in cultivation-independent approaches and computational platforms for the analysis of large data sets. However, investigations relevant to clinical observations and the natural history of the diseases will be essential for the development of microbial, genetic, and biological metrics that may be used to individualize assessment of risk and improve clinical outcomes in IBD.

IBD are chronic, progressive diseases. The composition and function of the gut microbiota likely change through the course (natural history) of IBD, reflecting transitions in host-microbe relationships that arise from disease-intrinsic and confounding factors. Microbial factors that trigger the onset of disease may be quite different from those that sustain the inflammatory process or result from the consequences of long-term complications and interventions. The interpretation of gut microbial data in the absence of this contextual information can be limited and potentially misleading. The pie charts in this figure illustrate the concept of general shifts in microbial composition and/or function over time and are not meant to indicate any quantifiable information.



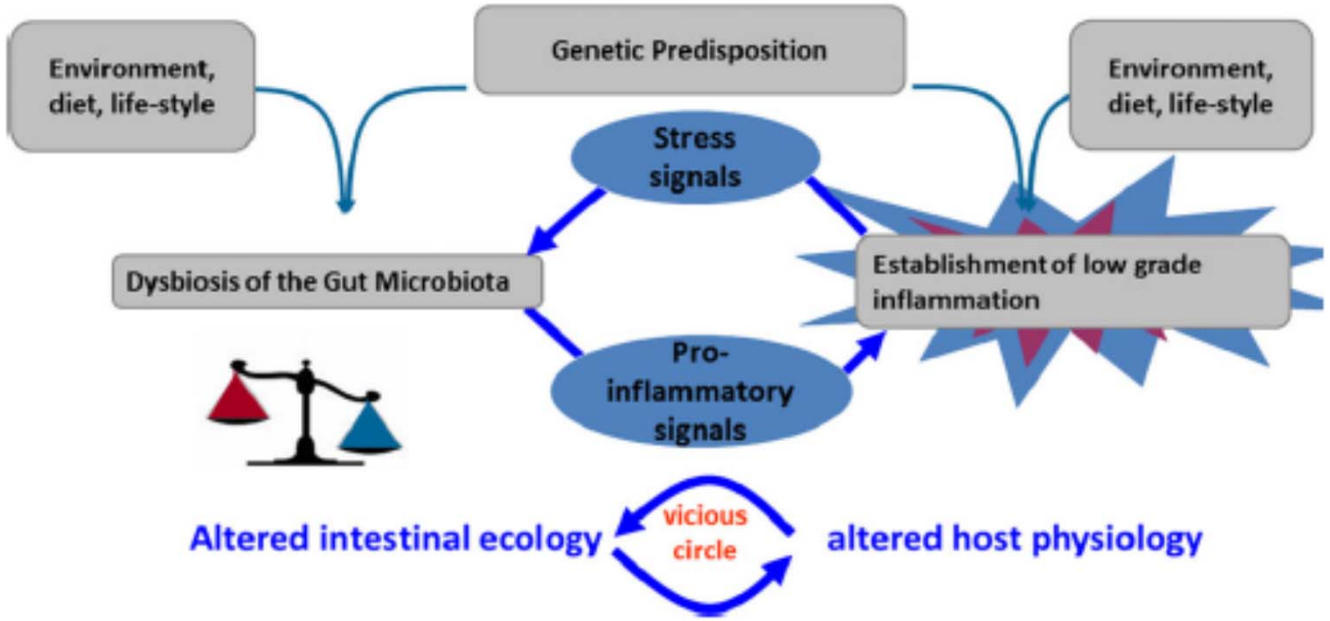


Figure 6. Alterations of the gut microbiota and low-grade inflammation may contribute to a cycle of events that induces a chronic state in immune-mediated diseases. Interventions that target the combined modulation of gut microbiota and inflammation may be the most effective way to manage such conditions.

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Probiotics, prebiotics, and the host microbiome: the science of translation

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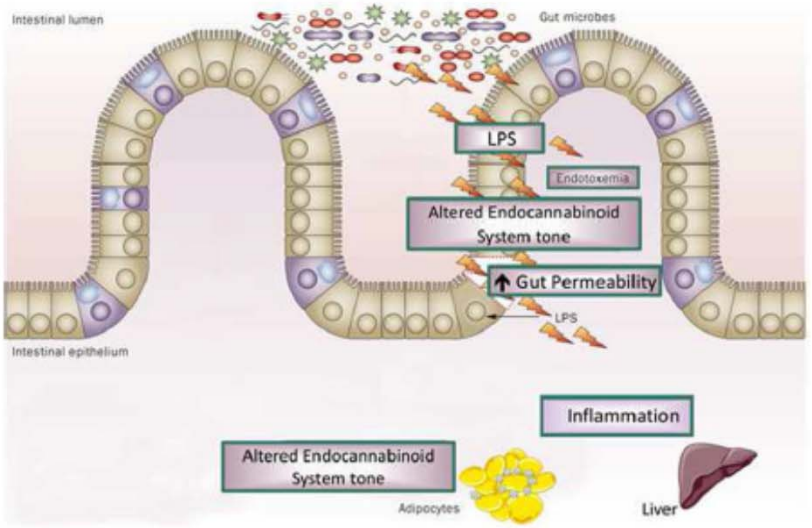

Figure 3. Interactions between gut microbiota and the endocannabinoid system: impact on gut barrier function and metabolic inflammation. Obesity (nutritional or genetic) is associated with changes in the gut microbiota composition and pathophysiological changes, whereby the endocannabinoid system tone is altered. This phenomenon is associated with the development of gut permeability, metabolic endotoxemia, metabolic inflammation, and altered adipose tissue metabolism (adipogenesis). From Delzenne NM, *et al.*[56]

MICROBIAL ECOLOGY in Health and Disease

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THE MICROBIOME IN AUTISM SPECTRUM DISORDER

The human gut microbiota with reference to autism spectrum disorder: considering the whole as more than a sum of its parts

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The human gut microbiota is a complex microbial ecosystem that contributes an important component towards the health of its host. This highly complex ecosystem has been underestimated in its importance until recently, when a realization of the enormous scope of gut microbiota function has been (and continues to be) revealed. One of the more striking of these discoveries is the finding that the gut microbiota and the brain are connected, and thus there is potential for the microbiota in the gut to influence behavior and mental health. In this short review, we outline the link between brain and gut microbiota and urge the reader to consider the gut microbiota as an ecosystem 'organ' rather than just as a collection of microbes filling a niche, using the hypothesized role of the gut microbiota in autism spectrum disorder to illustrate the concept.

Keywords: *Autism Spectrum Disorder; microbiota; human; gastrointestinal tract*

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Altered fecal microbiota composition in patients with major depressive disorder

Haiyin Jiang[a,1], Zongxin Ling[a,1], Yonghua Zhang[b,1], Hongjin Mao[c], Zhanping Ma[d], Yan Yin[c], Weihong Wang[e], Wenxin Tang[c], Zhonglin Tan[c], Jianfei Shi[c], Lanjuan Li[a,2], Bing Ruan[a,*]

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ABSTRACT

Studies using animal models have shown that depression affects the stability of the microbiota, but the actual structure and composition in patients with major depressive disorder (MDD) are not well understood. Here, we analyzed fecal samples from 46 patients with depression (29 active-MDD and 17 responded-MDD) and 30 healthy controls (HCs). High-throughput pyrosequencing showed that, according to the Shannon index, increased fecal bacterial α-diversity was found in the active-MDD (A-MDD) vs. the HC group but not in the responded-MDD (R-MDD) vs. the HC group. Bacteroidetes, Proteobacteria, and Actinobacteria strongly increased in level, whereas that of Firmicutes was significantly reduced in the A-MDD and R-MDD groups compared with the HC group. Despite profound interindividual variability, levels of several predominant genera were significantly different between the MDD and HC groups. Most notably, the MDD groups had increased levels of Enterobacteriaceae and *Alistipes* but reduced levels of *Faecalibacterium*. A negative correlation was observed between *Faecalibacterium* and the severity of depressive symptoms. These findings enable a better understanding of changes in the fecal microbiota composition in such patients, showing either a predominance of some potentially harmful bacterial groups or a reduction in beneficial bacterial genera. Further studies are warranted to elucidate the temporal and causal relationships between gut microbiota and depression and to evaluate the suitability of the microbiome as a biomarker.

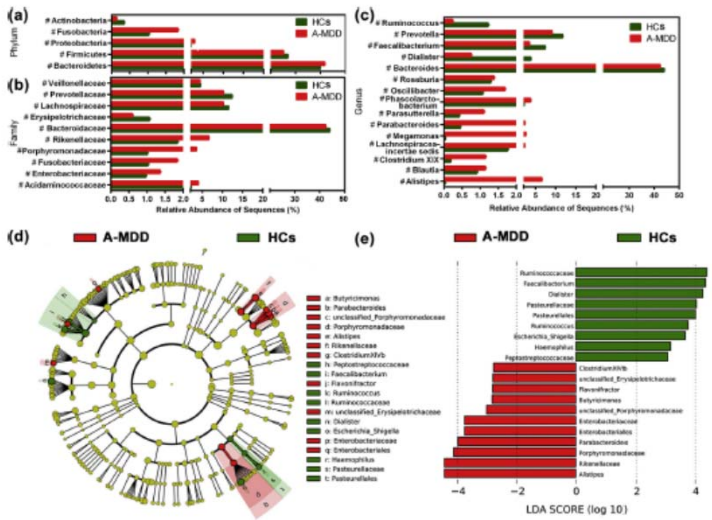

Fig. 2. Taxonomic differences of fecal microbiota between HC and A-MDD groups. Comparison of relative abundance at the bacterial phylum (a), family (b) and genus (c) levels between HC and A-MDD groups. # indicates $P < 0.05$. LEfSe identified the most differentially abundant taxons between HC and A-MDD groups. Taxonomic cladogram obtained from LEfSe analysis of 16S sequences (relative abundance >0.5%). (Red) A-MDD taxa; (Green) taxa enriched in HCs. The brightness of each dot is proportional to its effect size (d). HC-enriched taxa are indicated with a positive LDA score (green), and taxa enriched in A-MDD have a negative score (red). Only taxa meeting an LDA significant threshold > 2 are shown (e). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour.

Cryan JF[1], Dinan TG.

Author information

Abstract

Recent years have witnessed the rise of the gut microbiota as a major topic of research interest in biology. Studies are revealing how variations and changes in the composition of the gut microbiota influence normal physiology and contribute to diseases ranging from inflammation to obesity. Accumulating data now indicate that the gut microbiota also communicates with the CNS--possibly through neural, endocrine and immune pathways--and thereby influences brain function and behaviour. Studies in germ-free animals and in animals exposed to pathogenic bacterial infections, probiotic bacteria or antibiotic drugs suggest a role for the gut microbiota in the regulation of anxiety, mood, cognition and pain. Thus, the emerging concept of a microbiota-gut-brain axis suggests that modulation of the gut microbiota may be a tractable strategy for developing novel therapeutics for complex CNS disorders.

PMID: 22968153 DOI: 10.1038/nrn3346

The Placenta Harbors a Unique Microbiome

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Abstract

Humans and their microbiomes have coevolved as a physiologic community composed of distinct body site niches with metabolic and antigenic diversity. The placental microbiome has not been robustly interrogated, despite recent demonstrations of intracellular bacteria with diverse metabolic and immune regulatory functions. A population-based cohort of placental specimens collected under sterile conditions from 320 subjects with extensive clinical data was established for comparative 16*S* ribosomal DNA–based and whole-genome shotgun (WGS) metagenomic studies. Identified taxa and their gene carriage patterns were compared to other human body site niches, including the oral, skin, airway (nasal), vaginal, and gut microbiomes from nonpregnant controls. We characterized a unique placental microbiome niche, composed of nonpathogenic commensal microbiota from the Firmicutes, Tenericutes, Proteobacteria, Bacteroidetes, and Fusobacteria phyla. In aggregate, the placental microbiome profiles were most akin (Bray-Curtis dissimilarity <0.3) to the human oral microbiome. 16*S*-based operational taxonomic unit analyses revealed associations of the placental microbiome with a remote history of antenatal infection

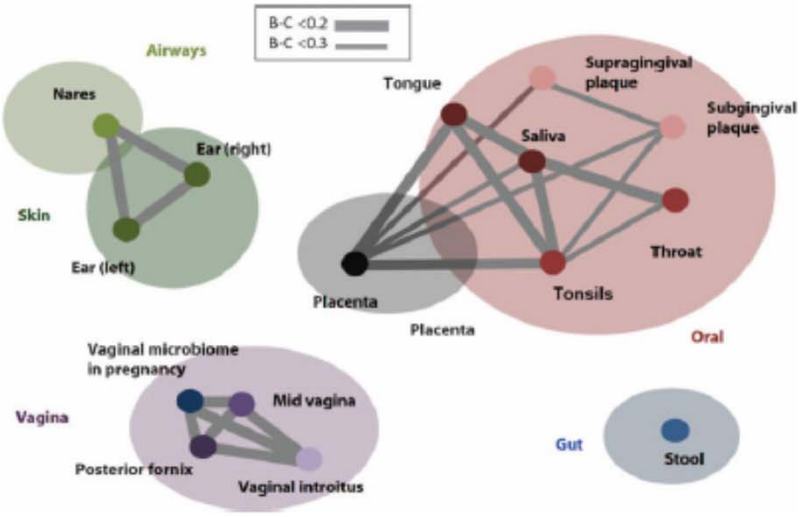

Fig. 1. The placental microbiome has a taxonomic profile that is similar to the oral microbiome
Bray-Curtis (B–C) dissimilarity was calculated using WGS-generated phylum-level abundance of bacteria from each body site, including placental data from this study; gut, vagina, posterior auricular skin, and nasal airways data from the HMP; and vaginal data from previously published gravidae (1–4). The thicker the connecting line, the greater the similarity of the taxonomic profile (Bray-Curtis <0.2). Strong phylum-level similarity was observed between the placenta and tongue, tonsils, saliva, and subgingival plaque taxonomic profiles. The colors of dots reflect the vicinity of the body sites.

The Human Microbiome: at the interface of health and disease

Ilseung Cho[1,2] and Martin J. Blaser[1,2,3,4]

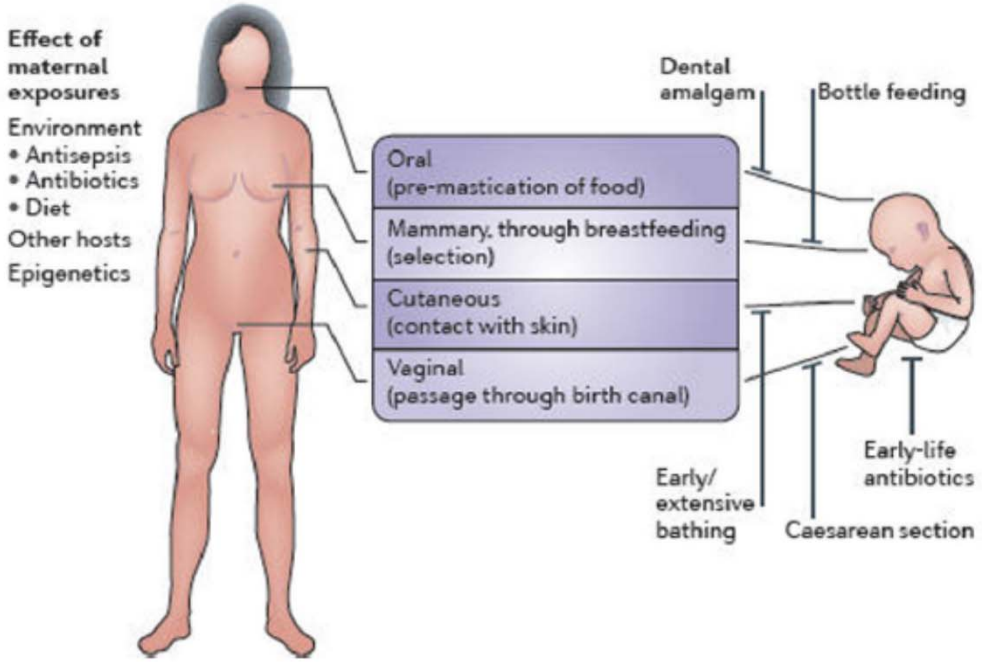

Figure 3. Acquisition of the microbiome in early life by vertical transmission and factors modifying mother-to-child microbial transmission

Through live-birth, mammals have important opportunities for mother → child microbial transmission, via direct-surface contact. However, many modern practices can reduce the organism and gene flow; several examples are illustrated. After initial introductions, there is strong selection by hosts for microbes with specific phenotypes, consistent with the extensive conservation shown in Figure 1. Acquisition is modified by offspring genetic and epigenetic differences (with respect to both maternal and paternal genes) that inform the competition for host resources by the vertically transmitted and environmentally acquired microbes. Ancestral organisms that have particular tissue- and niche-specific adaptations facilitate tissue tropisms and are selected, explaining the conserved niche-specificity compositions.

Human gut mi

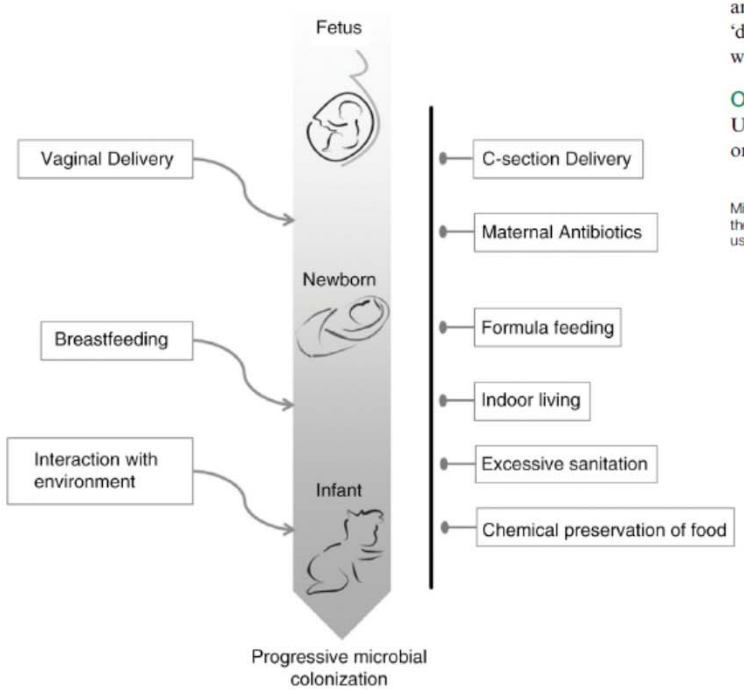

Fig. 2. Pictorial representation of the routes for, and blockages of, microbial colonization of Westernized humans during early life. On the left of the figure, routes of natural colonization are depicted, while on the right, impediments to natural colonization are shown.

much in the same way that human genome research permeated public consciousness at the start of the new millennium. As a field of study, human microbiome research has exploded in the last decade (Fig. 1), which has led to a new awareness of the importance of these associated microbes to our overall health. This came as somewhat of a shock to those of us who were raised to think of all microbes as 'germs' to be eradicated; instead, we are beginning to see ourselves as microbe managers, tending to the needs of our microbial 'employees' for mutual benefit. This short review discusses how human-associated microbes – particularly those in the gut – affect health, and how the widespread phenomenon of gut microbial 'dysbiosis' could be driving an epidemic of chronic disease, which may include autism spectrum disorder (ASD).

Origins of the human gut microbiota

Until recently, babies were believed to be born sterile and only populated by microbes on exposure to their first post-

mother and baby taking place via the placenta (2), and perhaps influenced by changes in the mother's microbiome during pregnancy (3, 4). Subsequently, the process of vaginal delivery allows for direct transfer of microbes from the birth canal and the perianal area to the baby (5–7). Finally, breastfeeding seems to provide and support specific microbes during the early phases of colonization within the infant gut (8–10). Throughout infancy and early childhood, there are changes in the gut composition that are related to microbial successions, whereby factors such as diet and host immune status appear to confer a 'permanent resident status' for some microbes but not others (8, 11–13). This process of building a gut microbiota is still poorly understood, but it is believed to be of critical importance, because there is increasing evidence that a window of time exists for the gut microbiota to develop (13). Beginning at the time of weaning, the microbiota composition stabilizes and matures (12, 14); from this point, it can be maintained with only minor

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Reduced microbial diversity and disease

Having established the importance of microbial community diversity, it is not surprising that a growing body of literature indicates that many chronic diseases are associated with less diverse gut ecosystems (35, 36). At the moment, this phenomenon is mainly associative, as it is difficult to ascertain whether reduced diversity occurs as a result of disease or *vice versa*. However, in some cases (e.g. *Clostridium difficile* infection, CDI), disease certainly results from a loss of gut microbiota diversity and robustness (36). It is undoubtedly true (both on the micro and macro scale) that ecosystems which lack functional redundancy are more prone to collapse under perturbational stress. An imbalance within the microbial ecosystem ('dysbiosis') of the human gut microbiota could result from many different scenarios (Fig. 2), including: insufficient colonization of an infant (e.g. due to Caesarean section) and/or inadequate nursing with breastmilk; exposure to antibiotics, both as short-term therapy as well as long-term pervasive exposure through the food chain; infection with pathogenic microbes; and consumption of a

Succession of microbial consortia in the developing infant gut microbiome

Jeremy E. Koenig[a], Aymé Spor[a], Nicholas Scalfone[a], Ashwana D. Fricker[a], Jesse Stombaugh[b], Rob Knight[b,c], Largus T. Angenent[d], and Ruth E. Ley[a,1]

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Edited by Todd R. Klaenhammer, North Carolina State University, Raleigh, NC, and approved June 24, 2010 (received for review March 2, 2010)

The colonization process of the infant gut microbiome has been called chaotic, but this view could reflect insufficient documentation of the factors affecting the microbiome. We performed a 2.5-y case study of the assembly of the human infant gut microbiome, to relate life events to microbiome composition and function. Sixty fecal samples were collected from a healthy infant along with a diary of diet and health status. Analysis of >300,000 16S rRNA genes indicated that the phylogenetic diversity of the microbiome increased gradually over time and that changes in community composition conformed to a smooth temporal gradient. In contrast, major taxonomic groups showed abrupt shifts in abundance corresponding to changes in diet or health. Community assembly was nonrandom: we observed discrete steps of bacterial succession punctuated by life events. Furthermore, analysis of ≈500,000 DNA metagenomic reads from 12 fecal samples revealed that the earliest microbiome was enriched in genes facilitating lactate utilization, and that functional genes involved in plant polysaccharide metabolism were present before the introduction of solid food, priming the infant gut for an adult diet. However, ingestion of table foods caused a sustained increase in the abundance of Bacteroidetes, elevated fecal short chain fatty acid levels, enrichment of genes associated with carbohydrate utilization, vitamin biosynthesis, and xenobiotic degradation, and a more stable community composition, all of which are characteristic of the adult microbiome. This study revealed that

To investigate how life events impact the developing infant gut microbiome, we performed a case study to monitor the gut microbial composition of one infant over a period of 2.5 y. We analyzed a set of more than 60 fecal samples collected concurrently with detailed information regarding diet, health status, and activities. The infant was a full-term, vaginally delivered healthy male. He was placed in a daycare facility during weekdays starting at 3 mo and then removed from group care at 1 y. His diet regimen consisted of exclusive breast-feeding for the first 134 d of life, supplemented with formula until he was no longer breast-fed at 9 mo. The first solid food introduced to the diet was rice cereal at 4 mo, followed by table foods, and the replacement of formula with cow milk at 1 y. The child suffered from several ear infections for which he was treated with antibiotics, but was otherwise healthy, and he was immunized according to the US Centers for Disease Control and Prevention's recommended schedule.

We profiled the bacterial diversity of the fecal samples with 454-pyrosequencing: First, we generated 318,620 16S rRNA gene sequences (Table S1), which we used to map the dynamics of the developing microbiota onto a timeline of changes in diet and other life events. On the basis of the patterns observed from the 16S rRNA gene analysis, we performed a metagenomic analysis of >500,000 sequences from 12 samples to study in greater detail key transitions in microbial community composition triggered

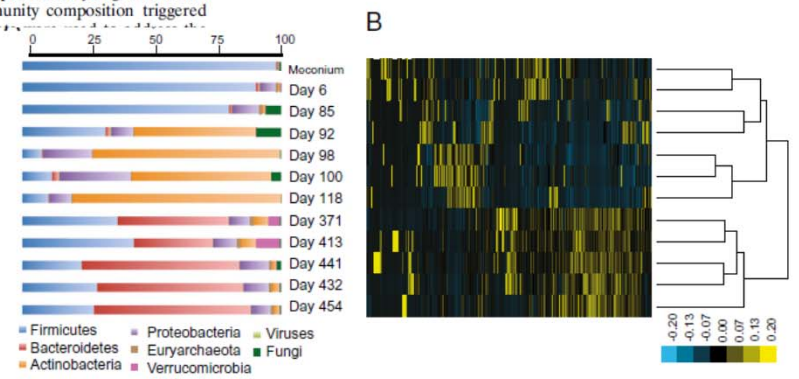

Fig. 6. Metagenomic analysis of DNA sequences extracted from infant fecal DNA. (*A*) Taxonomic assignment of metagenomic sequences. (*B*) Heat map and hierarchical clustering of samples based on MG-RAST subsystem gene content.

The Perinatal Microbiome and Pregnancy: Moving Beyond the Vaginal Microbiome

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The human microbiome, the collective genome of the microbial community that is on and within us, has recently been mapped. The initial characterization of healthy subjects has provided investigators with a reference population for interrogating the microbiome in metabolic, intestinal, and reproductive health and disease states. Although it is known that bacteria can colonize the vagina, recent metagenomic studies have shown that the vaginal microbiome varies among reproductive age women. Similarly, the richness and diversity of intestinal microbiota also naturally fluctuate among gravidae in both human and nonhuman primates, as well as mice. Moreover, recent evidence suggests that microbiome niches in pregnancy are not limited to maternal body sites, as the placenta appears to harbor a low biomass microbiome that is presumptively established in early pregnancy and varies in association with a remote history of maternal antenatal infection as well as preterm birth. In this article, we will provide a brief overview on metagenomics science as a means to investigate the microbiome, observations pertaining to both variation and the presumptive potential role of a varied microbiome during pregnancy, and how future studies of the microbiome in pregnancy may lend to a better understanding of human biology, reproductive health, and parturition.

Table 1. Metagenomic studies pertaining to perinatal health

Reference	Site	Technique(s)	Primers used	Study design	Findings
Nongravid Vaginal Studies					
NIH HMP Consortium 2012	Skin, nares, oral, vagina	Next-Gen sequencing	V1V3 V3V5	Longitudinal	Characterized healthy reference population
Ravel et al. 2010	Mid-vagina (self-collected)	Next-Gen sequencing	V1V2	Cross-sectional	Characterized healthy, nongravid vaginal microbiome
Gajer et al. 2012	Mid-vagina (self-collected)	Next-Gen sequencing	V1V2	Longitudinal	Showed temporal dynamics of the vaginal microbiome
Macklaim et al. 2013	Vagina	Metatranscriptomics		Cross-sectional	Showed potential for metatranscriptomics on vaginal swabs
Gravid Vaginal Studies					
Aagaard et al. 2012b	Vaginal introitus, posterior fornix, and mid-vagina	Next-Gen sequencing	V3V5	Cross-sectional	Characterized healthy, gravid vaginal microbiome
Romero et al. 2014b	Posterior fornix	Next-Gen sequencing	V1V2	Longitudinal	Characterized healthy, gravid vaginal microbiome throughout pregnancy
Walther-António et al. 2014	Posterior fornix, cervix	Next-Gen sequencing	V3V5	Longitudinal	Characterized healthy, gravid vaginal microbiome throughout pregnancy
Beyond the Vagina: Intestinal Microbiome					
Koren et al. 2012	Stool	Sequencing	V1V2	Longitudinal	Characterized first and third trimester stool
Beyond the Vagina: The Placenta					
Aagaard et al. 2014	Placenta	Next-Gen sequencing	V1V3 and WGS	Population-based, cross-sectional	The placenta harbors a unique microbiome profile, most akin to the oral microbiome and varies by virtue of preterm birth and a remote history of antenatal infection
Beyond the Vagina: Neonatal Studies					
Schultz et al. 2004	Stool	Sequencing	Strain-specific	Longitudinal	Vertical transmission from mother to infant
Palmer et al. 2007	Stool	Sequencing, Microarray, PCR	Universal 16S rRNA	Longitudinal	Characterized healthy neonatal microbiome
Dominguez-Bello et al. 2010	Oral, vagina, skin, rectal	Next-Gen sequencing	V2	Cross-sectional	Characterized neonatal microbiome by mode of delivery

Continue

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Table 1. *Continued*

Reference	Site	Technique(s)	Primers used	Study design	Findings
Koenig et al. 2011	Stool	Next-Gen sequencing	V1V2	Longitudinal	Characterized the intestinal microbiome from birth to 2.5 yr
Jost et al. 2012	Stool	Sequencing	Sanger, V5V6	Longitudinal	Characterized healthy neonatal microbiome
Wang et al. 2013	Cord blood, amniotic fluid	Bacterial culture and sequencing	Universal 16s rRNA	Cross-sectional	Neonates with necrotizing colitis had predominantly one bacteria dominating
Milisavljevic et al. 2013	Gastro-esophageal	Sequencing	Universal 16S rRNA	Longitudinal	Characterized the microbiome in VLBW infants
Azad et al. 2013	Stool	Next-Gen sequencing	V5, V6, V7	Longitudinal	Characterized the neonatal microbiome from birth to 4 mo while examining mode of delivery and feeding
Rogier et al. 2014	Stool	Microarray		Murine	Examined the role of maternal IgA on intestinal microbiome
Ma et al. 2014b	Colon, anus, stool	Next-Gen sequencing	V3V5	Nonhuman primate	Examined the role of maternal diet on juvenile microbiome

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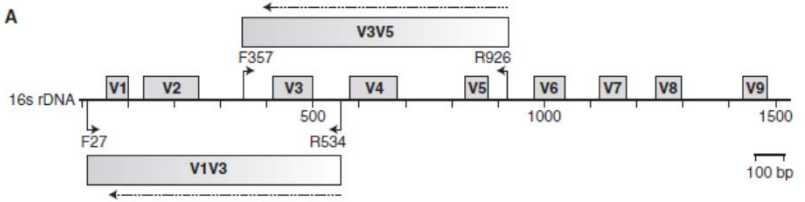

B

	V1V3	V3V5
Lactobacillus	+ +	– –
Prevotella	+	–
Enterobacteriaceae	–	+ +
Bifidobacteriaceae	–	+ +
Staphylococcus	–	+
Clostridium	+	+

Figure 1. The 16S rDNA gene is an ideal target for classifying bacteria. (*A*) The 16S rDNA gene of bacteria contains nine hypervariable regions (V1–V9) that are flanked by conserved regions, which makes this gene an ideal target for PCR amplification and bacterial classification. The V1V3 and V3V5 primers sets used by the HMP consortium are outlined. The dotted line indicates the direction of amplification. (*B*) Advantages and disadvantages to characterizing the vaginal microbiome with V1V3 (includes V2) and V3V5 (includes V4) primer sets. Species identification of *Lactobacillus* is enabled using a V1V3 primer set; however, V3V5 primers sets are better suited to identify Enterobacteriaceae and Bifidobacteriaceae. Thus, experimental design is essential when examining the pregnant microbiome.

16S-Based Metagenomics

Sequencing of the 16S rRNA gene using Next-Gen technology has recently been widely exploited to characterize the human microbiome (Jonasson et al. 2007; Liu et al. 2007). The 16S rRNA gene is an ideal target to classify bacteria because of the nine hypervariable regions in this gene that can be used to distinguish species based on individual nucleotide polymorphisms (Fig. 1A). Ergo, Next-Gen sequencing characterizes both coarse (phylum level) as well as fine (genus and limited species and strain) differences using universal primers to the adjacent conserved regions (Klindworth et al. 2013). However, 16S-amplicon-based approaches are limited to a shorter read length as compared with Sanger sequencing, and as a result, only a few hypervariable regions can be contiguously sequenced at a time. Initial work on approach and validation by the HMP Consortium showed that there is variation in the taxonomy profile identified based on sequencing different variable regions. For example, V1V3 amplicons may underestimate *Acinetobacter* and *Escherichia* genera, but V3V5 provides both breadth and depth of communities dominated by these genera. Furthermore, V6V9 may underestimate *Bacteroides* but provides good coverage for *Pseudomonas* and *Escherichia* (Human Microbiome Project 2012b).

Comparison of the vaginal microbiome data from the HMP reveals that V1V3 will distinguish communities primarily by the relative predominant *Lactobacillus* species present whereas, V3V5 amplicons will reveal either lactobacilli-dominant or lactobacilli-diminished groups. Furthermore, the number of *Lactobacillus* species detected (and thus relative abundance) will vary depending on the 16S region sequenced, with V1V3 revealing more unique *Lactobacillus* operational taxonomic units (OTUs) as compared with V3V5 (Huse et al. 2012). However, unlike V3V5, V1V3 does not

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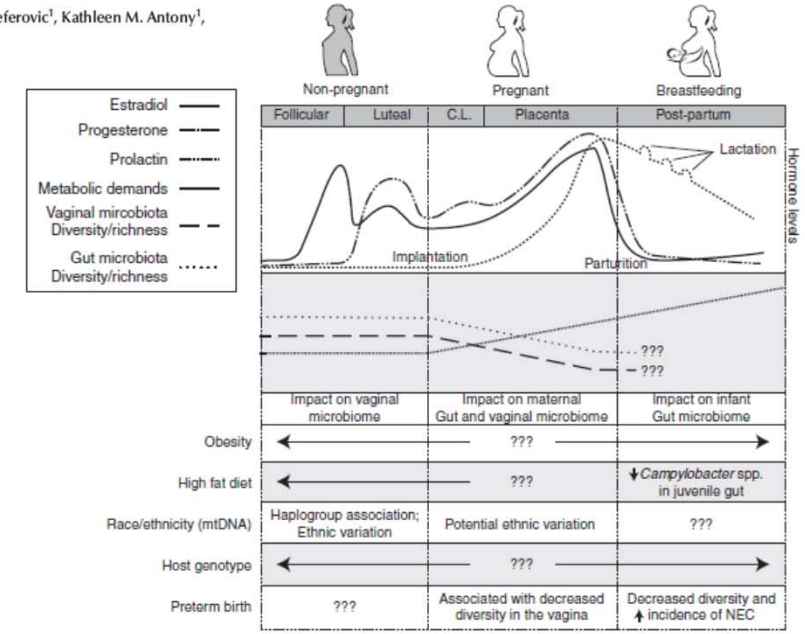

Figure 2. Influences on the pregnant microbiome. A number of hormonal changes, environmental exposures and genetic differences may impact the maternal microbiome before and during pregnancy that may alter the developing neonatal microbiome. During pregnancy, the maternal intestinal and vaginal microbiome have reduced alpha diversity and species richness. Metabolic demands increase throughout pregnancy and after parturition as the mother is lactating. Estradiol, progesterone and prolactin levels gradually increase during pregnancy, although it is unclear how these changes affect the maternal microbiome. Increased estrogen raises glycogen production in the vagina, but how the availability of this substrate structures the vaginal microbiome is unknown. The effect of host genetics on the maternal microbiome throughout pregnancy is relatively unknown. Different ethnicities, which can be inferred by mitochondrial DNA (mtDNA) haplotypes, have been shown to have varied vaginal microbiomes before and after pregnancy. Further studies are needed to understand these differences, and to explore the effect of host genotype on the maternal microbiome. The impact of diet and obesity on the pregnant microbiome is just beginning to be explored. A primate model of maternal high fat diet showed that diet alone can persistently alter the juvenile microbiome at one year of age regardless of juvenile diet. However, how diet alters the maternal environment during pregnancy and how this affects the vertical transmission of bacteria is unknown.

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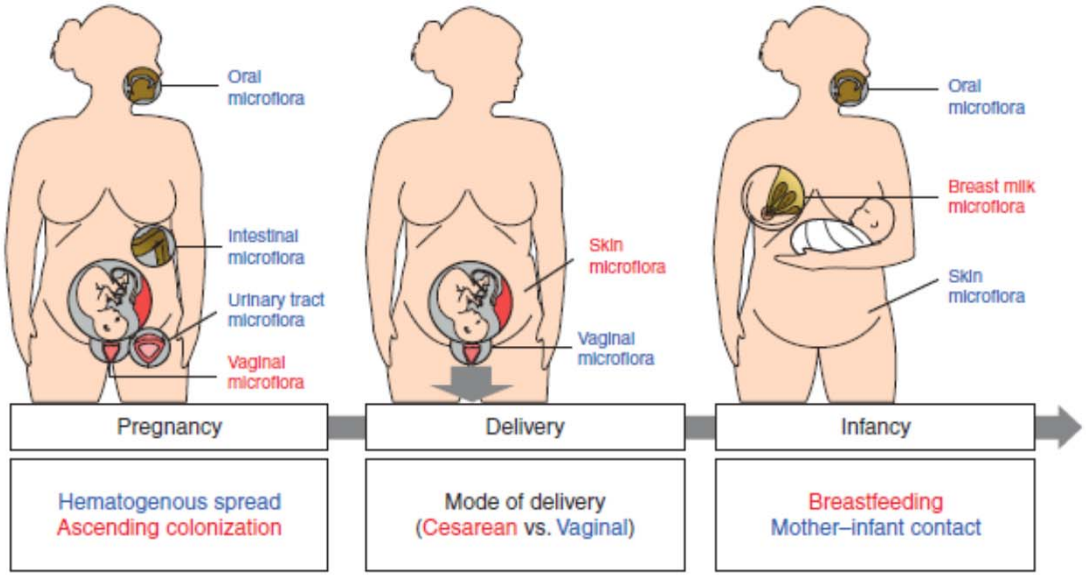

Figure 3. Speculated origins for microbiota colonizing the placenta and seeding the initial neonatal microbiome. Vaginal microflora likely contribute to the initial seeding of the neonatal microbiome during vaginal deliveries, but the discovery that the uterine environment may not be sterile suggests that colonization of the infant may happen before birth. Recent data demonstrating that the placenta has its own unique microbiome most closely resembling the oral microbiome suggests a potential hematogenous route by which bacteria can seed the placenta and the developing fetus. Microbiota from maternal oral, vaginal, urinary tract, and intestine are all potential sources for these colonizing bacteria. Microbiota from breast milk and maternal contact may be an important source of commensal bacteria during early infancy and must be considered when studying the microflora of the neonate.

Ann. Rev. Microbiol. 1988. 42:441–64

MICROBIAL ECOLOGY OF THE SKIN[1,2]

Rudolf R. Roth and William D. James

Dermatology Service, Department of Medicine, Walter Reed Army Medical Center, Washington, DC 20307-5001

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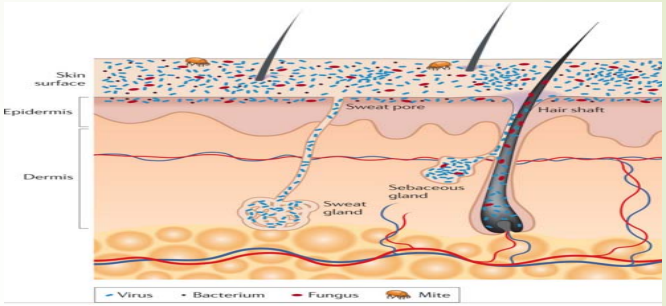

Schema dell'istologia della cute vista in sezione trasversale con microrganismi e annessi cutanei.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3535073/figure/F1/

Microbial Ecology of Human Skin in Health and Disease

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Stanford University School of Medicine, Division of Infectious Diseases, Stanford, California, U.S.A.

Cultivation of human skin reveals numerous bacteria and at least one fungus to be normal inhabitants of this ecosystem; however, most of our knowledge about the microbiology of human skin was acquired decades ago. Modern techniques employing nucleic acid-based microbial identification methods demonstrate the limitations of cultivation for appreciating microbial diversity in many ecosystems. The application of modern molecular methods to the study of skin may offer new perspectives on the resident microfora, and new insights into the causes of antibiotic responsive dermatologic conditions, such as acne and rosacea. ***Key words: acne/microbiology/microflora/rRNA.*** ***Journal of Investigative Dermatology Symposium Proceedings 6:167–169, 2001***

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Skin microbiota: a source of disease or defence?

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Summary

Microbes found on the skin are usually regarded as pathogens, potential pathogens or innocuous symbiotic organisms. Advances in microbiology and immunology are revising our understanding of the molecular mechanisms of microbial virulence and the specific events involved in the host–microbe interaction. Current data contradict some historical classifications of cutaneous microbiota and suggest that these organisms may protect the host, defining them not as simple symbiotic microbes but rather as mutualistic. This review will summarize current information on bacterial skin flora including *Staphylococcus*, *Corynebacterium*, *Propioni-bacterium*, *Streptococcus* and *Pseudomonas*. Specifically, the review will discuss our current understanding of the cutaneous microbiota as well as shifting paradigms in the interpretation of the roles microbes play in skin health and disease.

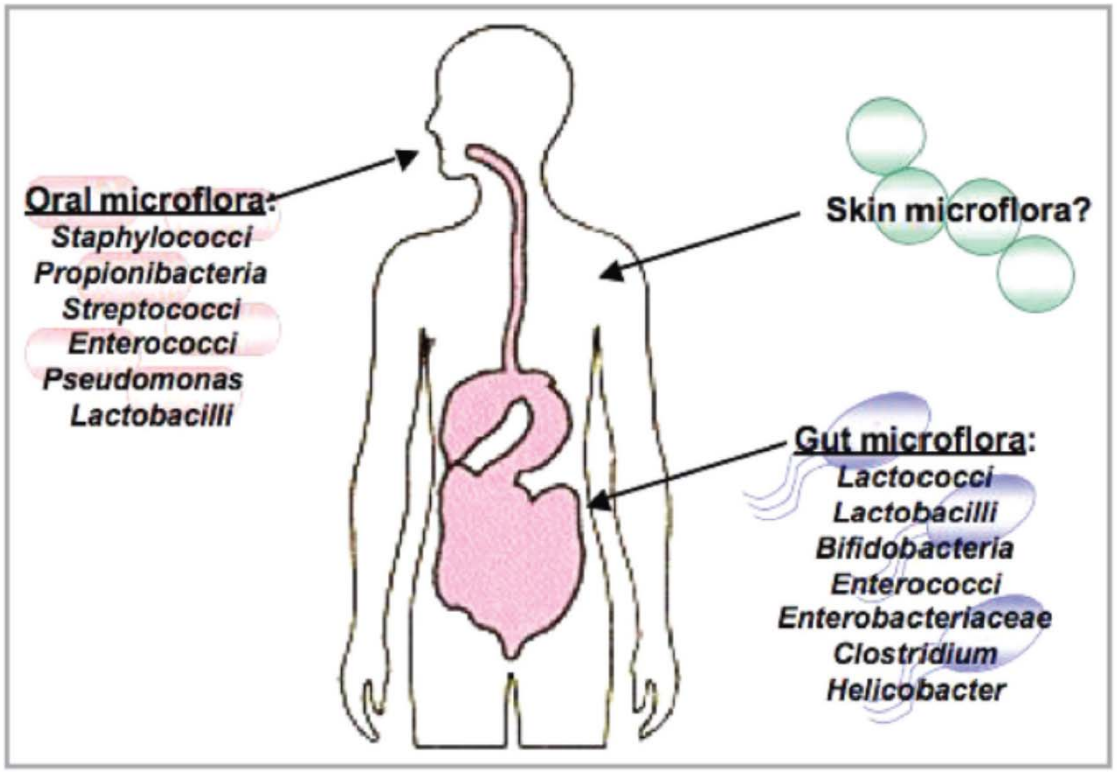


Fig 1.
Resident microflora that are beneficial to the host. The gut and mouth contain many species of microflora. Microbiota in the intestines protect the host by educating the immune system and preventing pathogenic infections. These microflora benefit the systemic immune system of the host and positively affect other organs, such as the lung. In the mouth, over 500 species of bacteria protect the mucosa from infections by preventing colonization of dangerous yeasts and other bacteria. It is yet unclear if the microflora of the skin play a similar role in protecting the host. Image from http://www.giconsults.com with permission.

Table 1

Frequency of microbial colonization through clinical and molecular detection methods[11,12]

Organism	Clinical isolate observations	Molecular detection
Staphylococcus epidermidis	Common, occasionally pathogenic	Frequent
Staphylococcus aureus	Infrequent, usually pathogenic	Frequent
Staphylococcus warneri	Infrequent, occasionally pathogenic	Occasional
Streptococcus pyogenes	Infrequent, usually pathogenic	Occasional
Streptococcus mitis	Frequent, occasionally pathogenic	Frequent
Propionibacterium acnes	Frequent, occasionally pathogenic	Frequent
Corynebacterium spp.	Frequent, occasionally pathogenic	Frequent
Acinetobacter johnsonii	Frequent, occasionally pathogenic	Frequent
Pseudomonas aeruginosa	Infrequent, occasionally pathogenic	Frequent

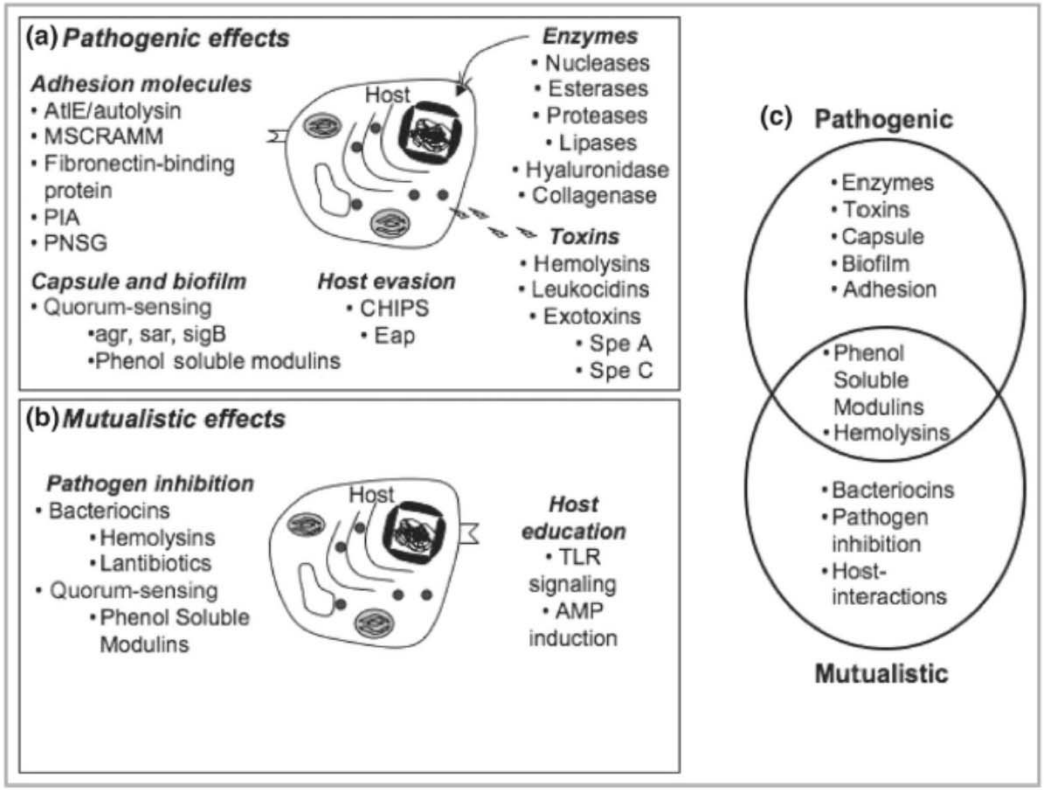


Fig 3.
Staphylococci are pathogenic and mutualistic. (a) Virulence factors and molecules produced by staphylococci that aid in pathogenesis. (b) Staphylococci act mutually by inhibiting pathogens and priming the immune response. (c) Molecules from staphylococci that have dual functions.

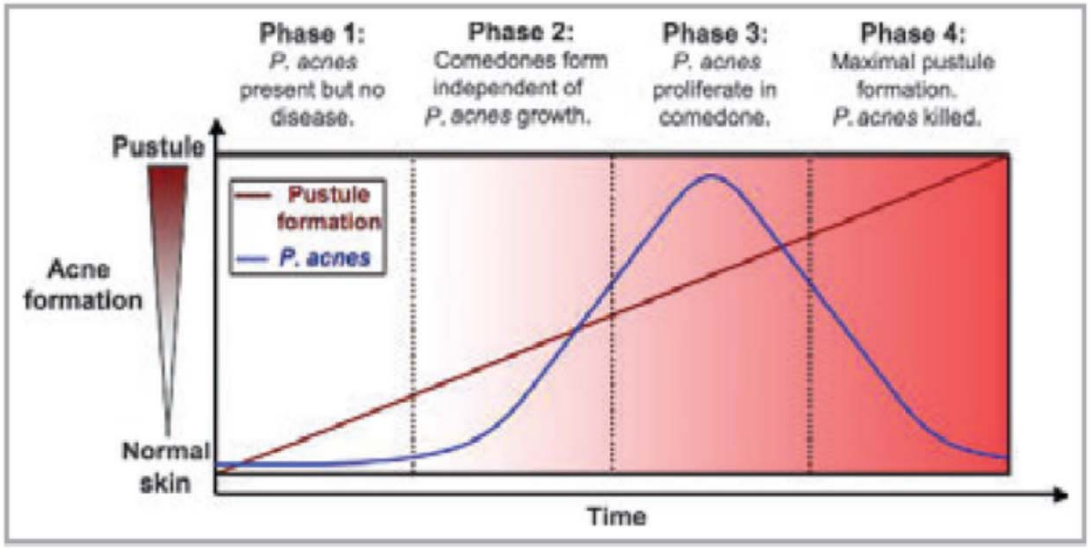


Fig 4.
Hypothetical model for relationship between *Propionibacterium acnes* and pustule formation. The graph depicts pustule formation and *P. acnes* growth over time. In phase 1, *P. acnes* is present, but comedones are not. In phase 2, comedo formation begins, independently of *P. acnes* growth; *P. acnes* begins to proliferate only after comedo forms. In phase 3, *P. acnes* proliferates in trapped comedo. In phase 4, *P. acnes* is killed by an inflammatory response. Disease and pustule formation is maximal despite eradication of *P. acnes*. This model illustrates that acne formation is not triggered by the ubiquitous and resident *P. acnes* and at the maximal disease stage, *P. acnes* has already been eliminated.

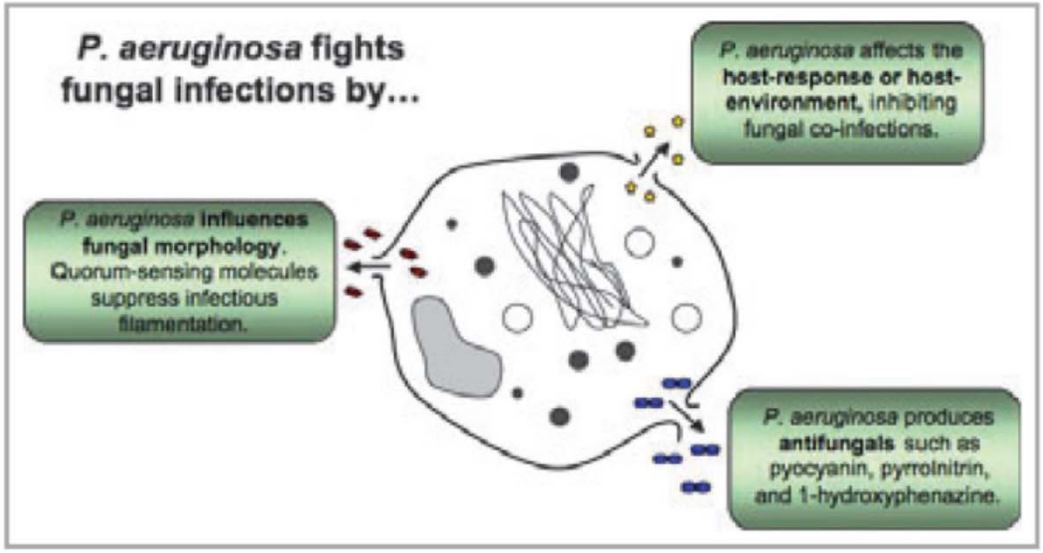
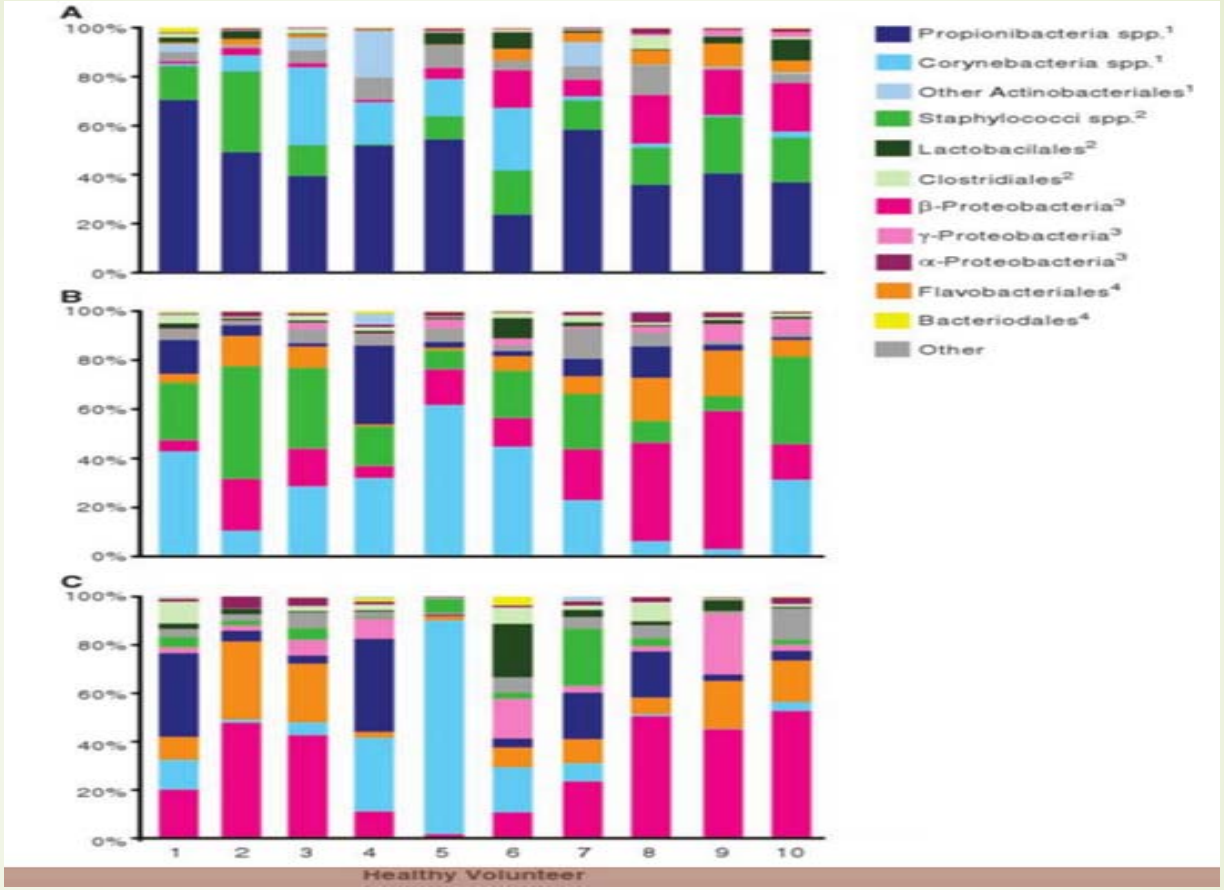
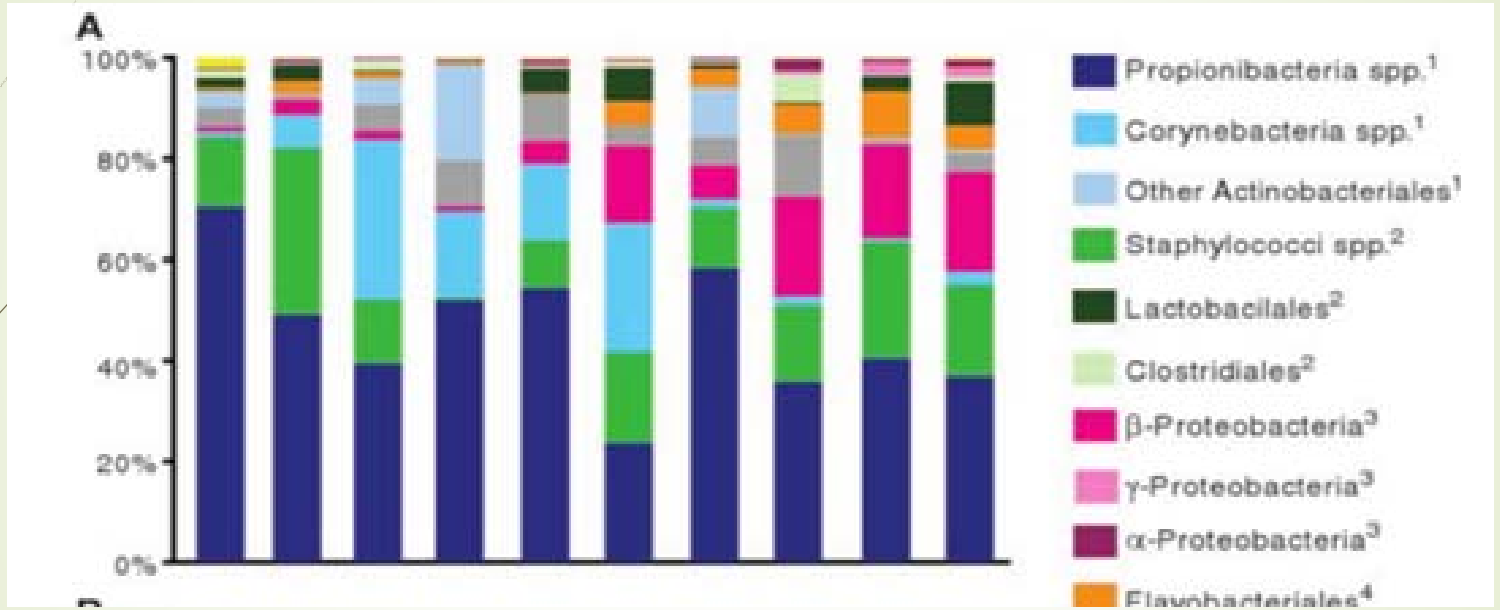


Fig 5.
Pseudomonas aeruginosa fights fungal infections. It produces compounds such as pyocyanin, pyrrolnitrin and 1-hydroxyphenazine which kill and inhibit fungal growth. *Pseudomonas aeruginosa* also prevents the morphological transition of fungi from yeast-form cells to virulent filamentous cells. Filamentation of *Candida albicans* is associated with pathogenesis, adhesion, invasion and virulence-related products. *Pseudomonas aeruginosa* interacts with the host creating an environment inhospitable to fungi.



. I 20 siti cutanei e la microflora associata sono rappresentativi di tre microambienti: (A) sebacee , (B) umido , e (C) secco. L'abbondanza relativa dei più abbondanti gruppi batterici associati a ciascun microambiente è illustrato per ciascun volontario sano. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2805064/


A
100%
80%
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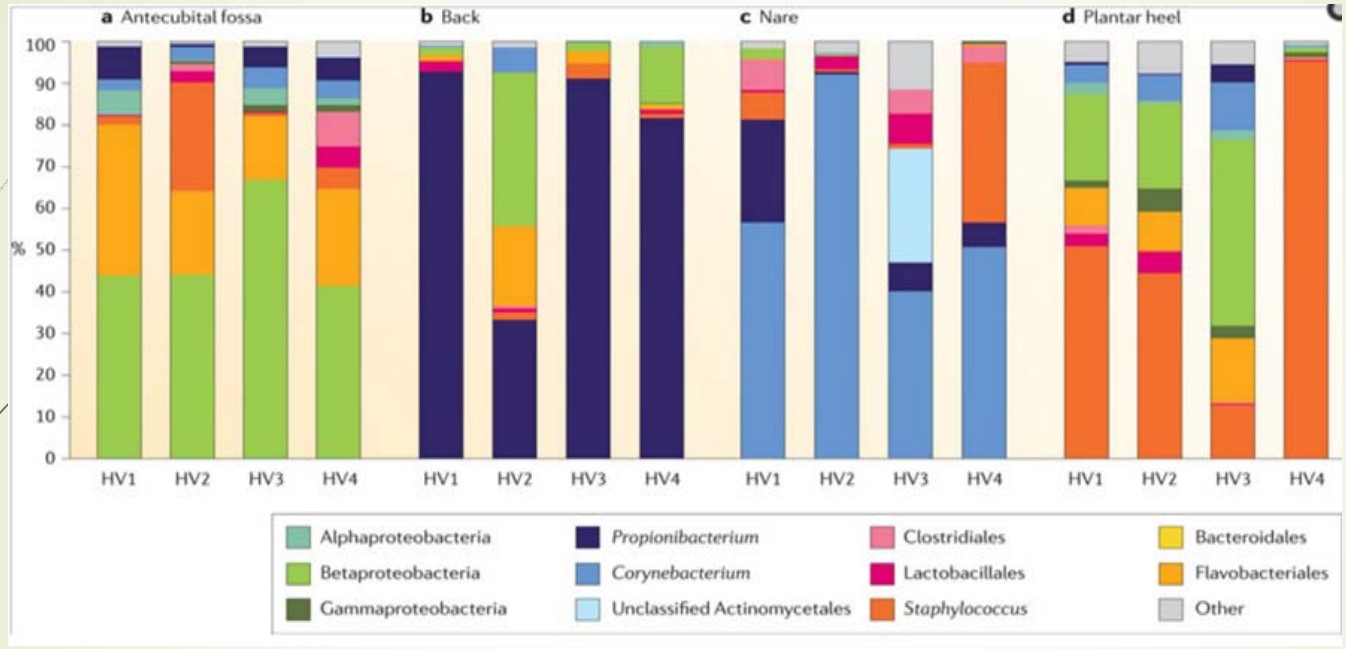
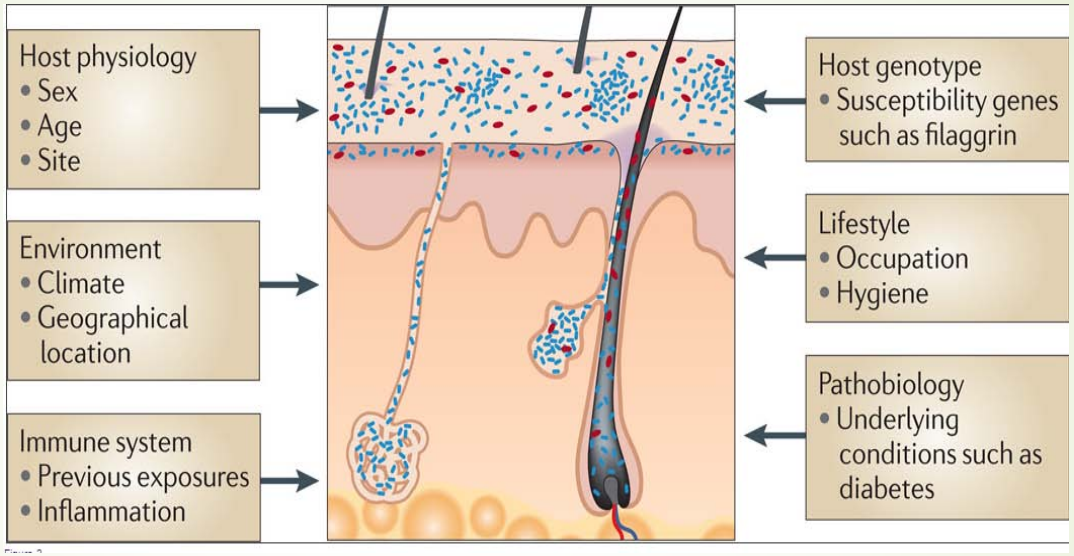
Propionibacteria spp.[1]
Corynebacteria spp.[1]
Other Actinobacteriales[1]
Staphylococci spp.[2]
Lactobacilales[2]
Clostridiales[2]
β-Proteobacteria[3]
γ-Proteobacteria[3]
α-Proteobacteria[3]



. Variazione interpersonale del microbioma della pelle



Fattori che contribuiscono alla variazione del microbioma della pelle.

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Oral Diseases (2017) 23, 276–286 doi:10.1111/odi.12509

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INVITED MEDICAL REVIEW

A practical guide to the oral microbiome and its relation to health and disease

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[1]Department of Microbiology, The Forsyth Institute, Cambridge, MA; [2]New Englan
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Application of metagenomics in understanding oral health and disease

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Keywords: metagenomics, periodontal disease, caries, polymicrobial, biofilm, dental plaque, metabolic pathway, pathogen, oral microbiome, systems biology

Abbreviations: NGS, next generation sequence; OTU, operational taxonomic units; PSD, polymicrobial synergy and dysbiosis hypothesis; PCR, polymerase chain reaction; HGT, horizontal gene transfer; WGS, whole genome shotgun; NCBI, National Center for Biotechnology Information; HMP, Human Microbiome Project; HOMD, Human Oral Microbiome Database; KEGG, Kyoto Encyclopedia of Genes and Genomes; LPS, lipopolysaccharide; COG, Clusters of Orthologous Groups; Mb, mega base

Oral diseases including periodontal disease and caries are some of the most prevalent infectious diseases in humans. Different microbial species cohabitate and form a polymicrobial biofilm called dental plaque in the oral cavity. Metagenomics using next generation sequencing technologies has produced bacterial profiles and genomic profiles to study the relationships between microbial diversity, genetic variation, and oral diseases. Several oral metagenomic studies have examined the oral microbiome of periodontal disease and caries. Gene annotations in these studies support the association of specific genes or metabolic pathways with oral health and with specific diseases. The roles of pathogenic species and functions of specific genes in oral disease development have been recognized by metagenomic analysis. A model is proposed in which three levels of interactions occur in the oral microbiome that determines oral health or disease.

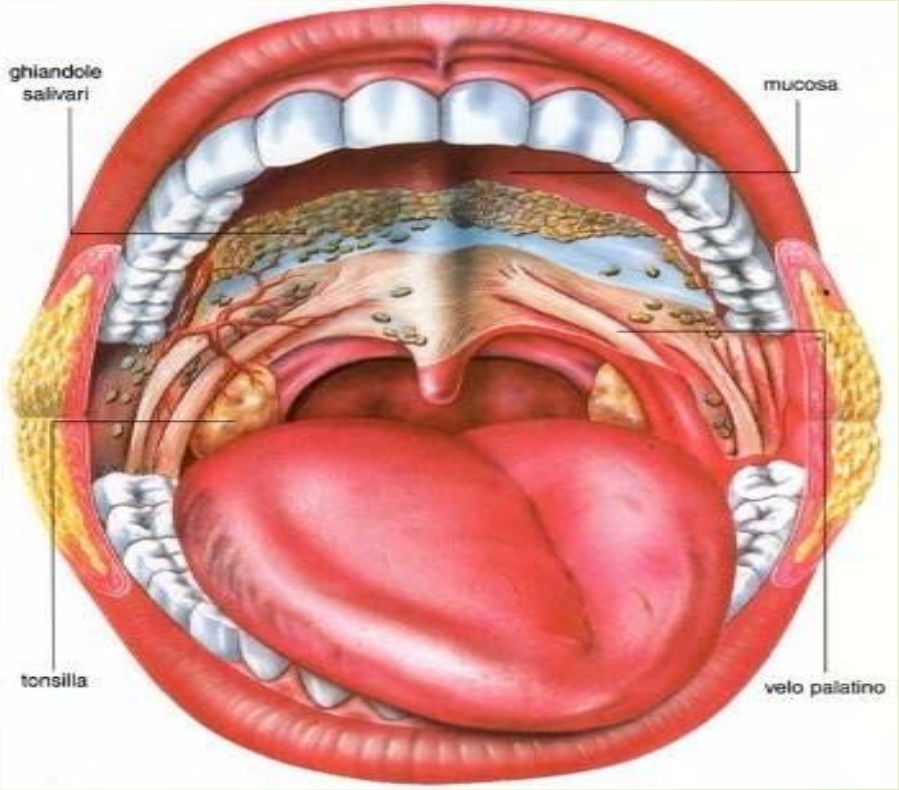
all races of people worldwide.[1,2] It is reported that up to 90% of the population are affected by periodontal disease.[1,3] According to WHO reports, dental caries affects 60–90% of schoolchildren even in developed countries (http://www.who.int/oral_health/publications/report03/en/index.html). Oral diseases are associated with multiple microorganisms of different species in a polymicrobial milieu. The contiguous environment of the oral cavity supports a complex oral community.[4-11] More than 700 species are estimated to occur in the human oral cavity and many of them are uncultivated bacteria.[6,8]

Periodontal disease arises from bacterial infection of periodontal tissues causing gingivitis and periodontitis. Gingivitis involves gum tissue but does not affect the underlying supporting structures of the teeth. In contrast, periodontitis is an inflammatory disease extending deep into the tissues, which causes loss

Il microbiota del cavo orale

- Oltre 750 specie tra cui quelle di:

- Streptococcus;
- Staphylococcus;
- Actinomyces;
- Veillonella;
- Fusobacterium;
- Propionibacterium;
- Lactobacterium.



La cavità orale.

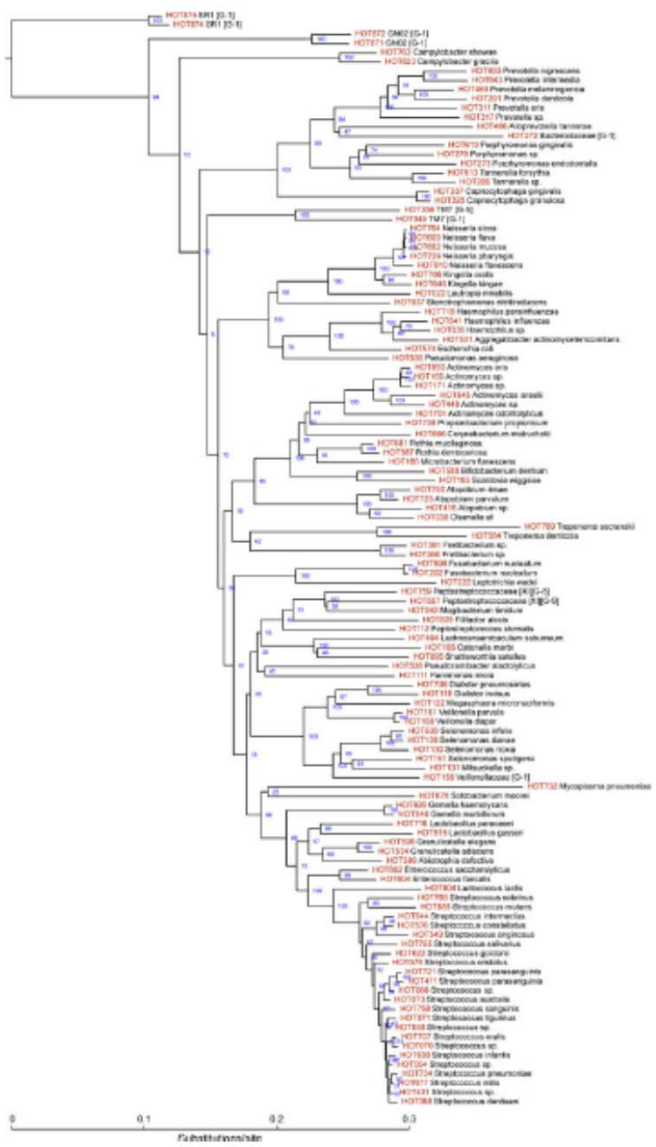


Figure 1 16S rRNA Phylogenetic tree of 118 human oral microbial species. The aligned sequences (HOT designations, printed in red, means Human Oral Taxon) were downloaded from HOMD (www.homd.org), and sequences of selected taxa were subjected to QuickTree software v1.1 (Howe *et al*, 2002) using the Kimura DNA substitution model for pairwise distances. The bootstrap values are printed in blue based on 100 iterations. For those species without a specific epithet (e.g., species name), they are either not-yet-cultured phylotypes or cultured unnamed species

Coaggregazione tra batteri nella placca dentale

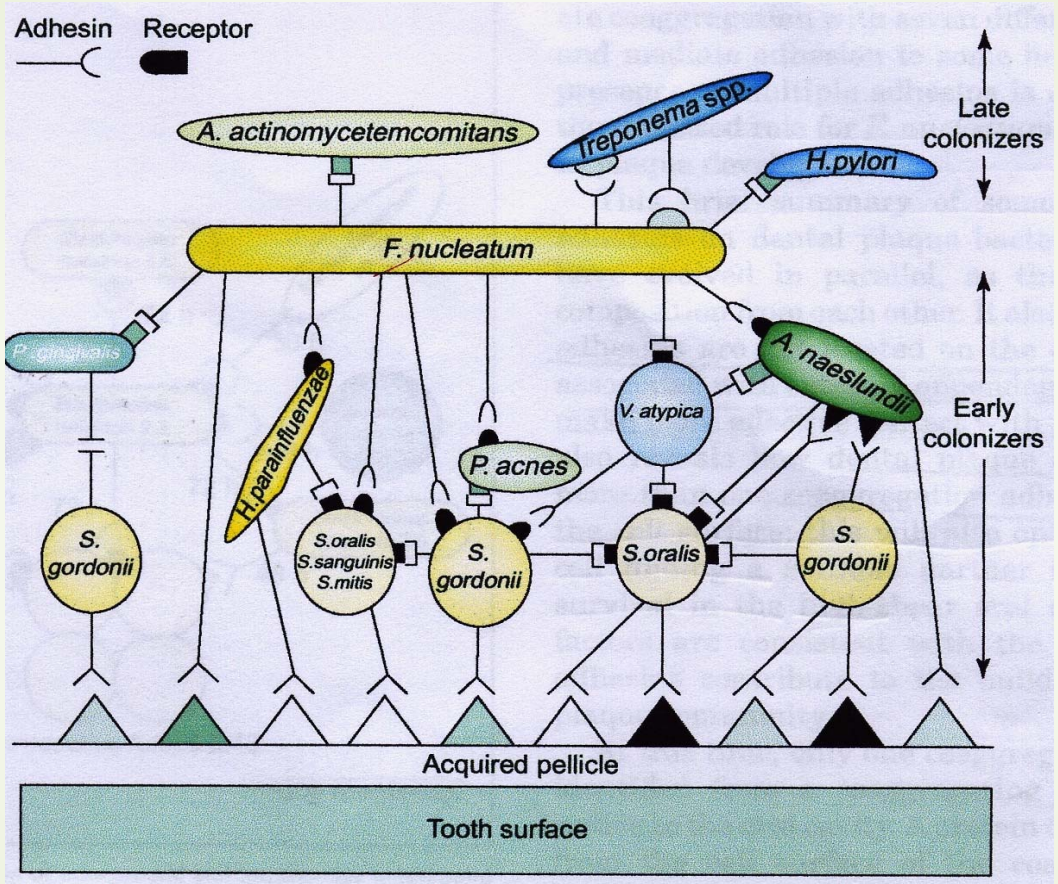


Fig. 3. Diagrammatic representation of the proposed temporal nature of human oral bacterial accretion on the tooth surface. The species represented here are *Streptococcus gordonii, Streptococcus mitis, Streptococcus oralis, Streptococccus sanguinis, Haemophilus parainfluenzae, Propionibacterium acnes, Veillonella atypica, Actinomyces naeslundii, Fusobacterium nucleatum, Actinobacillus actinomycetemcomitans, Helicobacter pylori, Treponema* spp. and *Porphyromonas gingivalis*. The complementary sets of adhesin-receptor symbols (an example is shown at the top) represent different specific coaggregation interactions or adhesion to the acquired pellicle. Coaggregation between *P. gingivalis* and *S. gordonii* is mediated by protein adhesins expressed on the surface of both cell types. Identical symbols are not intended to indicate identical molecules, but they are related functionally. The rectangular symbols represent lactose-sensitive coaggregations, other symbols represent lactose-insensitive coaggregations.

Species	Adhesin	Receptor	Partner species	References
Streptococcus gordonii Streptococcus mitis Streptococcus oralis	Antigen I/II family (SspA SspB)	Bacterial surface proteins, yeast, mannoproteins	*Porphyromonas gingivalis Streptococcus mutans Actinomyces naeslundii Candida albicans*	Rosan and Lamont (2000), Wilson (2005)
S. gordonii	CshA, CshB	Bacterial surface proteins, yeast, mannoproteins	*S. oralis*	Rosan and Lamont (2000), Wilson (2005)
S. gordonii	LraI family (ScaA)		*A. naeslundii*	Rosan and Lamont (2000), Wilson (2005)
S. gordonii	Coaggregation mediating adhesion	Carbohydrate containing lactose or lactose-like moieties	*Streptococcus* spp.	Rosan and Lamont (2000), Wilson (2005)
Streptococcus salivarius	Fibrillar antigen B(VBP)		*Veillonella parvula*	Rosan and Lamont (2000), Wilson (2005)
Actinomyces naeslundii	Type 2 fimbriae-associated protein	Cell wall polysaccharide contraining Galβ1→3GalNAc and GalNAcβ1→3 Gal glycosidic linkage	*Streptococcus sanguis Streptococcus* spp.	Rosan and Lamont (2000), Wilson (2005), Yoshida *et al.* (2006)
P. gingivalis	Fimbrillin	Surface proteins	*S. gordonii S. oralis A. naeslundii*	Wilson (2005)
P. gingivalis	Outer membrane protein	Surface proteins	*S. gordonii*	Wilson (2005)
P. gingivalis	Outer membrane protein		*A. naesdlundii*	Wilson (2005)
P. gingivalis	PlaA	Cell wall polysaccharide containing Galβ1 → 3GalNAc and GalNAβ1 → 3 Gal glycosidic linkage	*Streptococcus* spp.	Wilson (2005)
Prevotella loescheii	Fimbra-associated protein		*Actinomyces israelii*	Wilson (2005)
Fusobacterium nucleatum	Outer membrane protein	Galactose-containing carbohydrate	*P. gingivalis*	Wilson (2005)
F. nucleatum	Corn cob receptor		*Streptococcus cristatus* Immunoglobulin A (L-Arginine)	Wilson (2005), Edwards *et al.* (2006)
Veillonella atypica	Outer membrane protein	Carbohydrate containing lactose or lactose-like moieties	*Streptococcus* spp.	Wilson (2005)
Capnocytopha gingivalis	Outer membrane protein	Cell wall carbohydrate	*A. israelii*	Wilson (2005)
Capnocytophaga ochracea	Outer membrane protein	Cell wall carbohydrate	*S. oralis*	Wilson (2005)
Treponema medium	Outer membrane protein	Fimbriae	*P. gingivalis*	Wilson (2005)
F. nucleatum	RadD		*S. sanguis S. oralis S. gordonii A. naeslundii*	Kaplan *et al.* (2009)

. Coaggregati formati da batteri orali, le loro adesine ed i recettori.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768665/

Principali gruppi di batteri presenti nella placca dentale/BIOFILM ORALE

Placca sopra gengivale ⇒ Carie

Placca sub-gengivale ⇒ Gengivite, malattia paradontale

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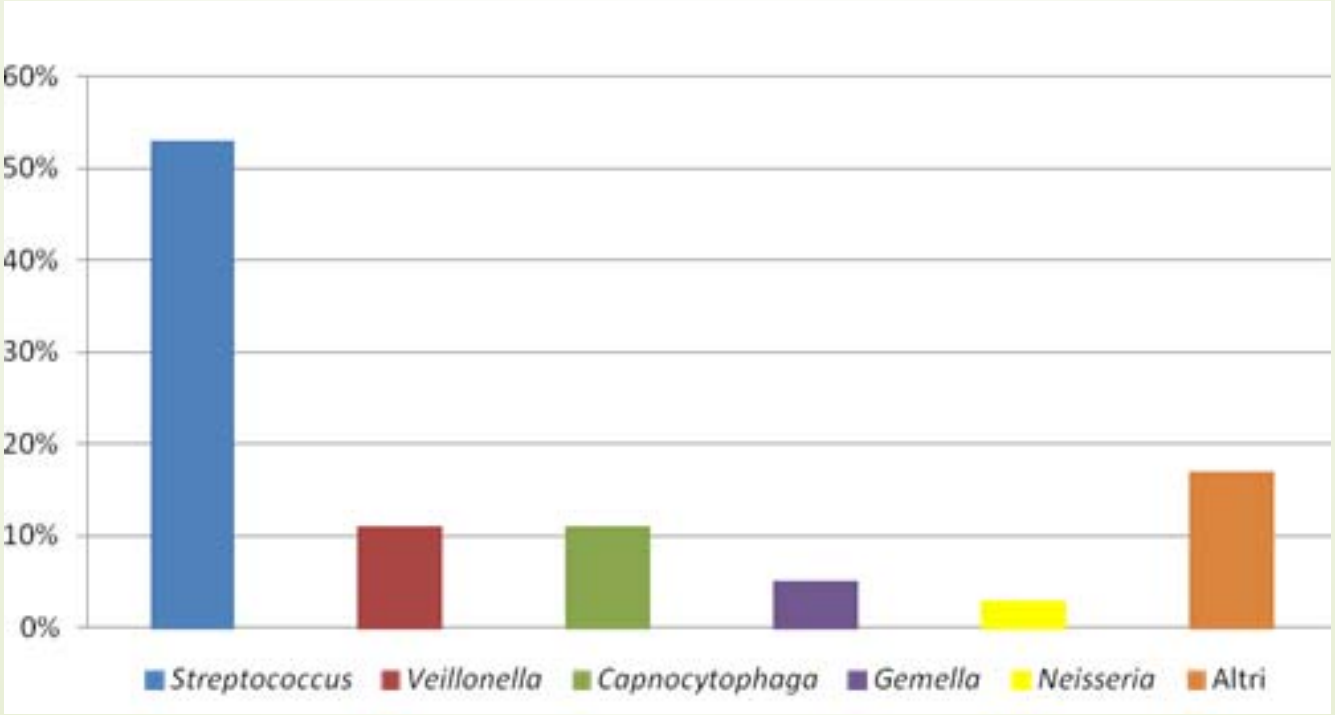

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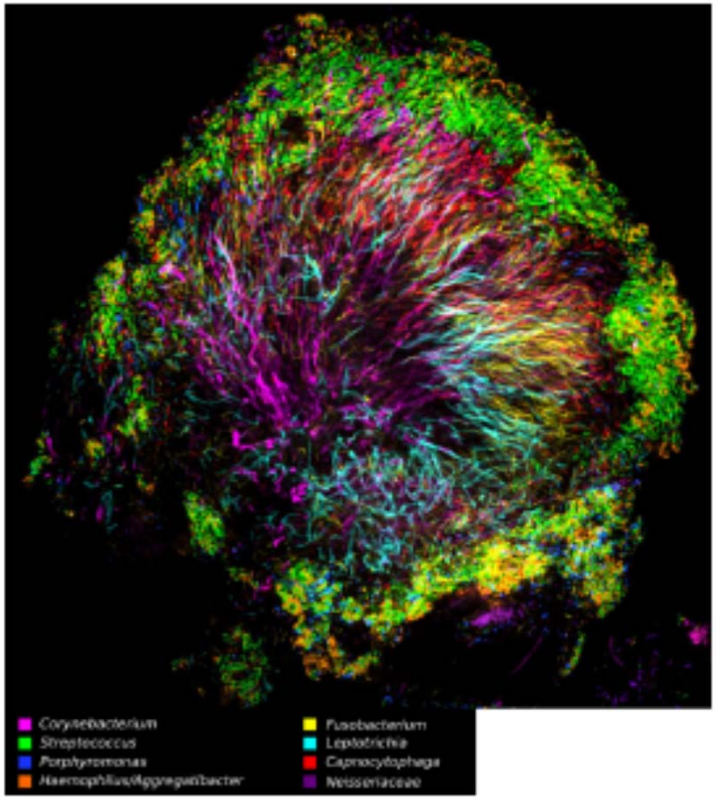


Figure 2 A microbial consortium in human dental plaque. Spatial organization of eight specific bacterial taxa can be clearly seen. Different colors represent different bacterial genera. For example, note that *Corynebacterium* (purple) and *Leptotrichia* (light blue) are centrally localized with *Streptococcus* (green) and *Haemophilus* (orange) on the periphery. Courtesy of Jessica Mark Welch, Marine Biological Laboratory, and Gary Borisy, The Forsyth Institute

Table 1 Newly identified putative periodontal pathogens (from Perez-Chaparro *et al*, 2014)

Bacterial taxa	
Anaeroglobus geminatus HOT 121	Cultivable
Archaea spp.	Cultivable
Bacteroidales [*G-2*] sp. oral taxon 274	Unnamed
Desulfobulbus sp. oral taxon 041	Phylotype
Eubacterium [*XI*] [*G-5*] *saphenum* HOT 759	Cultivable
Filifactor alocis HOT 539	Cultivable
Fretibacterium fastidiosum HOT 363	Cultivable
Fretibacterium sp. oral taxon 360	Phylotype
Fretibacterium sp. oral taxon 362	Phylotype
Mogibacterium timidum HOT 042	Cultivable
Peptostreptococcus stomatis HOT 112	Cultivable
Porphyromonas endodontalis HOT 273	Cultivable
Selenomonas sputigena HOT 151	Cultivable
TM7 [*G-5*] sp. oral taxon 356	Phylotype
Treponema lecithinolyticum HOT 653	Cultivable
Treponema medium HOT 667	Cultivable
Treponema vincentii HOT 029	Cultivable

differed from treatable periodontitis by having a higher frequency of putative periodontal pathogens as listed above and in Table 1. However, they also found additional species that are not commonly detected in treatable periodontal disease, including *Peptoniphilus alactolyticus*, *Brevundimonas diminuta*, *Shuttleworthia satelles*, *Dialister invisus*, *Granulicatella adiacens*, *Veillonella atypica*, and *Mycoplasma salivarium*. A more recent study implicated *Actinetobacter baumannii*, an important nosocomial pathogen that is notoriously antibiotic resistant, as a risk factor for refractory periodontitis (Richards *et al*, 2015).

NRC Research Press

REVIEW

The oral cavity microbiota: between health, oral disease, and cancers of the aerodigestive tract

Pierre Le Bars, Sébastien Matamoros, Emmanuel Montassier, Françoise Le Vacon, Gilles Potel, Assem Soueidan, Fabienne Jordana, and Marie-France de La Cochetière

Abstract: Many studies show that the human microbiome plays a critical role in the chronic pathologies of obesity, inflammatory bowel diseases, and diabetes. More recently, the interaction between cancer and the microbiome has been highlighted. Most studies have focused on the gut microbiota because it represents the most extensive bacterial community, and the body of evidence correlating it with gut syndromes is increasing. However, in the strict sense, the gastrointestinal (GI) tract begins in the oral cavity, and special attention should be paid to the specific flora of this cavity. This study reviewed the current knowledge about the various microbial ecosystems of the upper part of the GI tract and discussed their potential link to carcinogenesis. The overall composition of the microbial communities, as well as the presence or absence of "key species", in relation to carcinogenesis is addressed. Alterations in the oral microbiota can potentially be used to predict the risk of cancer. Molecular advances and the further monitoring of the microbiota will increase our understanding of the role of the microbiota in carcinogenesis and open new perspectives for future therapeutic and prophylactic modalities.

Table 1. Epidemiologic studies of the HUAT microbiome and cancer showing principal results.

Author	Cancer localisation	No. of patients	Technique	Results	Oral hygiene	Biomarkers
Michaud et al. 2013	Pancreatic cancers	405	Plasma antibody detection against 25 oral bacteria	Periodontal pathogens are associated with higher risk for pancreatic cancer	Periodontal disease	Very high correlations were observed for the 2 strains of *P. gingivalis* and *A. actinomycetemcomitans*
Yu et al. 2014	Esophageal squamous dysplasia precursor lesion of carcinoma	333	HOMIM	Lower microbial richness in HUAT	Poor oral health	ND
Chen et al. 2015	ESCC	171	454 pyrosequencing of oral microbiota of saliva	Comparison between salivary bacterial microbiota and ESCC	Poor oral health	Decreased carriage of genera *Lautropia*, *Bulleidia*, *Catonella*, *Corynebacterium*, *Moryella*, *Peptococcus*, and *Cardiobacterium* in ESCC subjects compared with non-ESCC subjects
Mima et al. 2015	Colorectal carcinoma	598	qPCR for *F. nucleatum*	Associations of the amount of *F. nucleatum* with T-cell densities in tumor tissue	ND	Lower density of T cells in tumor tissue
Fan et al. 2016	Pancreatic cancer	361	Bacterial 16S rRNA gene sequencing	Oral microbiota may play a role in the aetiology of pancreatic cancer	Periodontal disease	Higher risk with *P. gingivalis*, *A. actinomycetemcomitans*; decreased cancer risk with phylum *Fusobacteria* and genus *Leptotrichia*
Mitsuhashi et al. 2015	Pancreatic cancers	302	DNA extraction and qPCR for *Fusobacterium* species	Tumor *Fusobacterium* status was not associated with any clinical and molecular features	ND	*Fusobacterium* species are a promising biomarker of pancreatic cancer
Yan et al. 2015	Lung cancer	20	Salivary microbiota qPCR	Association of saliva microbiota with lung cancer	ND	*Capnocytophaga* and *Veillonella* were significantly higher in saliva from lung cancer patients
Guerrero-Preston et al. 2016	HNSCC	787	Saliva microbiota (16S rRNA metagenomic sequencing)	Microbiota associated with oral cancer and human papilloma virus infection	ND	HNSCC saliva samples associated with increase in *Lactobacillus* and *Streptococcus* and a decrease in *Haemophilus*, *Neisseria*, *Gemellaceae*, and *Aggregatibacter*
Momen-Heravi et al. 2014	OSCC	34	qPCR	Endogenous control miRNA are discriminatory in OSCC patients	ND	miRNA profiles in OSCC patients and healthy controls were distinctively different
Nosho et al. 2016	Colorectal carcinomas	551	Metagenomic analyses	Association of *Fusobacterium* with T cells and miRNA expression	ND	*F. nucleatum* possesses immunosuppressive activities by inhibiting human T-cell responses

Note: HUAT, human upper aerodigestive tract; HOMIM, human oral microbe identification microarray; ESCC, esophageal squamous cell carcinoma; qPCR, quantitative polymerase chain reaction; HNSCC, head and neck squamous cell carcinoma; OSCC, oral squamous cell carcinoma; miRNA, microRNA; ND, not determined; *P. gingivalis*, *Porphyromonas gingivalis*; *F. nucleatum*, *Fusobacterium nucleatum*; *A. actinomycetemcomitans*, *Aggregatibacter actinomycetemcomitans*.

Table 3. Associations between oral microbiome and carcinogenesis.

Reference	Study design	Cancer	Study population(s)	Population data: Age	Sex	Ethnic group or country	Main findings
Shiga et al. 2001	Evaluation of the diversity of bacteria in the saliva of subjects with OSCC	Oral squamous carcinoma head and neck cancer	4 subjects 3 subjects	—	—	Japan	Using 454 parallel DNA sequencing, 58 000 PCR amplicons that span the V4–V5 hypervariable region of rRNA from subjects; 15 unique phylotypes were present in all subjects
Narikiyo et al. 2004	Evaluation of bacterial diversity in saliva and in esophageal cancer	Esophageal cancer	20 esophageal cancers tissues	45–69 (mean 57)	—	Japan (Tokyo)	Three periodontitis bacteria (*T. denticola*, *S. mitis* and *S. anginosus*) are present in esophageal cancer causing inflammation and promoting carcinogenic process.
			20 healthy esophageal tissues			Japan	
			20 healthy patients for saliva			Japan	
			58 esophageal cancer tissue			Japan	PCR: 69% are positive for *S. anginosus*, 38% for *T. denticola*
			4 esophageal cancer tissue			China	PCR: 91% are positive for *S. anginosus*, 46% for *T. denticola*
			2 esophageal cancer			France	PCR: 100% are positive for *S. anginosus*, and 100% for *T. denticola*
			5 esophageal cancer			Italy	PCR: 100% are positive for *S. anginosus* and 40% for *T. denticola*
Morita et al. 2004	Molecular analysis of age related changes of *S. anginosus* and *S. mitis* in saliva	Healthy patients (aging)	—	—	—	Japan	Increase in *S. anginosus* with age because of its association with diseases, including cancer
Sasaki et al. 2005	*S. anginosus* in oral cancer	Oral cancer	46 subjects (oral cancer) and 3 precancerous leukoplakia	—	—	Japan	Infection of *S. anginosus* could occur frequently in OSCC and that dental plaque could be a dominant reservoir of *S. anginosus*

Table 3 (*concluded*).

Reference	Study design	Cancer	Study population(s)	Population data: Age	Population data: Sex	Population data: Ethnic group or country	Main findings
Sixou et al. 2006	*Capnocytophaga* in the dental plaque of children with cancer	Lymphoma	31 children with cancer and 30 healthy control children	—	—	France	*Capnocytophaga* decreased in prevalence in the dental plaque of cancer patients during chemotherapy but became predominant in some cases
Souto and Colombo 2008	Detection of *H. pylori* in saliva	—	56 periodontally healthy subjects and 169 with chronic periodontitis	—	—	—	*H. pylori* was frequently detected in the oral microbiota of subjects with periodontitis
Söder et al. 2011	Periodontal disease and breast cancer	Breast	3273 subjects — 1676 were clinically orally examined, 1597 were not clinically examined	30–40	Women	Sweden	Chronic periodontal disease indicated by missing molars seemed to associate statistically with breast cancer
Wang and Li 2015 (a Review paper)	Infections that have been linked to pancreatic cancer	Pancreatic carcinogenesis	Review	—	—	China	*H. pylori* infection may be a risk factor for pancreatic cancer; chronic hepatitis virus and oral microbiota may also play a role in pancreatic carcinogenesis
Galvão-Moreira and da Cruz 2016 (a Review paper)	Relationship between the oral microbiome, periodontitis, and head and neck cancer	Head and neck cancer	Review	—	—	—	Evidence has implicated *P. gingivalis* and periodontitis in head and neck rates
Park et al. 2016	The risk factors and microbiological etiologies	Head and neck cancer (radical neck dissection)	370 patients		Male and female	South Korea	The most common pathogen was methicillin-resistant *S. aureus*

Note: OSCC, oral squamous cell carcinoma; *T. denticola*, *Treponema denticola*; *P. gingivalis*, *Porphyromonas gingivalis*; *H. pylori*, *Helicobacter pylori*; *S. anginosus*, *Streptococcus anginosus*; *S. mitis*, *Streptococcus mitis*; *S. aureus*, *Staphylococcus aureus*.

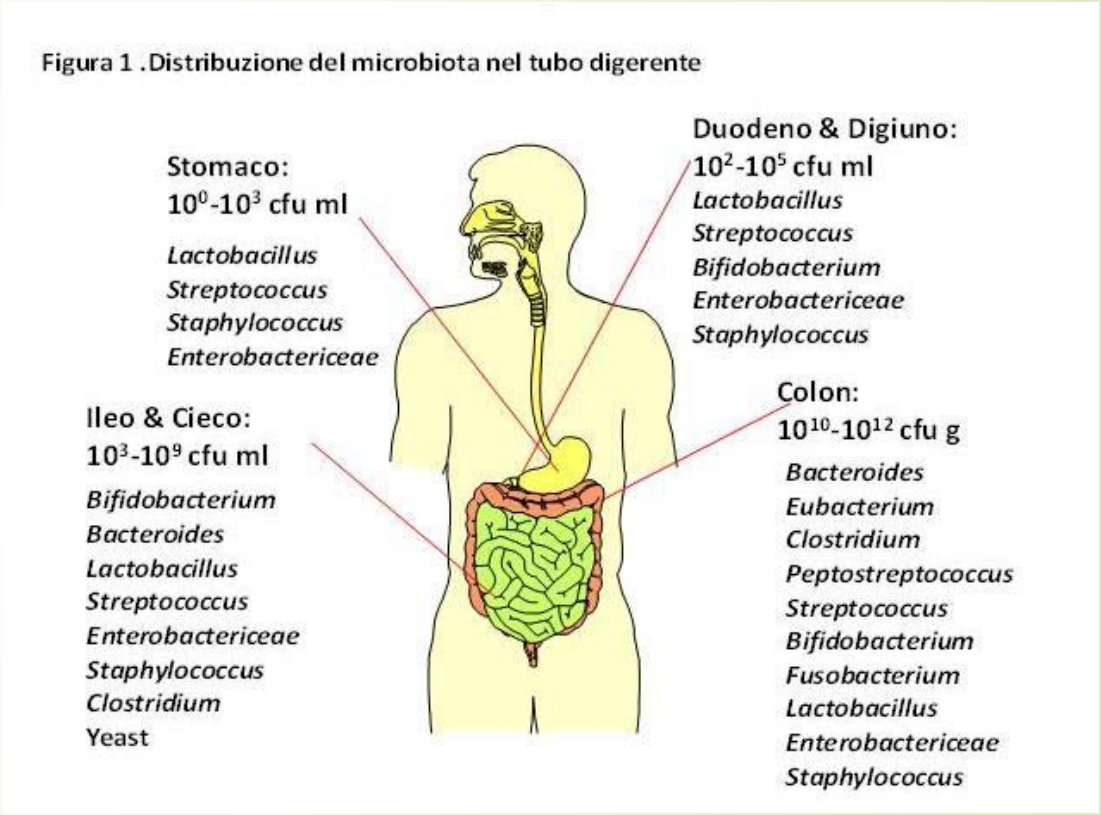
Table 2. Comparative dominant microbiota of different human sites (Ahn et al. 2012; Costello et al. 2009; Kim et al. 2009; Lemon et al. 2010; Nasidze et al. 2009; Takahashi 2015).

Skin	Nostril	Oro-pharynx	Mouth	Gastrointestinal tract, gut	Vagina	Saliva	All
Actinobacteria (44.7%)	*Actinobacteria* (47.9%–70.7%)	*Actinobacteria* (7.3%)	*Actinobacteria* (7.3%)		*Actinobacteria* (14.6%)	*Actinobacteria* (7%)	*Actinobacteria* (36.7%)
Firmicutes (30.3%)	*Firmicutes* (23.7%–37.2%)	*Firmicutes* (52.3%)	*Firmicutes* (52.3%)	*Firmicutes* (35.1%)	*Firmicutes* (60.0%)	*Firmicutes* (37.8%)	*Firmicutes* (34.0%)
Proteobacteria (11.6%)	*Proteobacteria* (2.9%–9.6%)	*Proteobacteria* (19.7%)	*Proteobacteria* (19.7%)	*Proteobacteria* (4.9%)	*Proteobacteria* (20.6%)	*Proteobacteria* (28.0%)	*Proteobacteria* (11.7%)
Bacteroidetes (3.0%)	*Bacteroidetes* (1.1%–1.6%)	*Bacteroidetes* (15.6%)	*Bacteroidetes* (15.6%)	*Bacteroidetes* (59.9%)	*Bacteroidetes* (12%)	*Bacteroidetes* (20.0%)	*Bacteroidetes* (8.5%)
Cyanobacteria (10.5%)	*Cyanobacteria* (5)	—	*Cyanobacteria* (0.01%)	—	—	—	*Cyanobacteria* (7.3%)
—	*Fusobacteria* (0.1%)	*Fusobacteria* (5.0%)	*Fusobacteria* (5.0%)	—	*Fusobacteria* (3.6%)	—	*Fusobacteria* (1.0%)
Other	Other	Other	Other (0.08%)	Other	Other	Other (7.2%)	Other

Il Microbiota intestinale

- Lungo tutto l'intestino, la composizione della flora mostra variazioni. I phyla più rappresentativi sono:

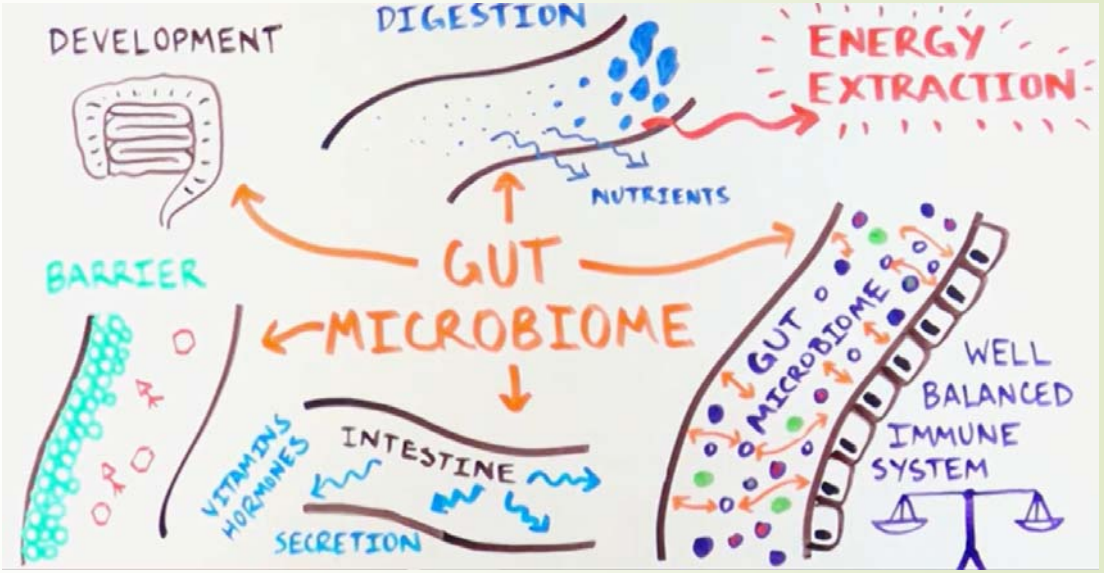
- Bacteroides
- Firmicutes
- Proteobacteria
- Actinobacteria
- Faecalibacteria
- clostridium



Distribuzione del microbiota nel tratto digerente.

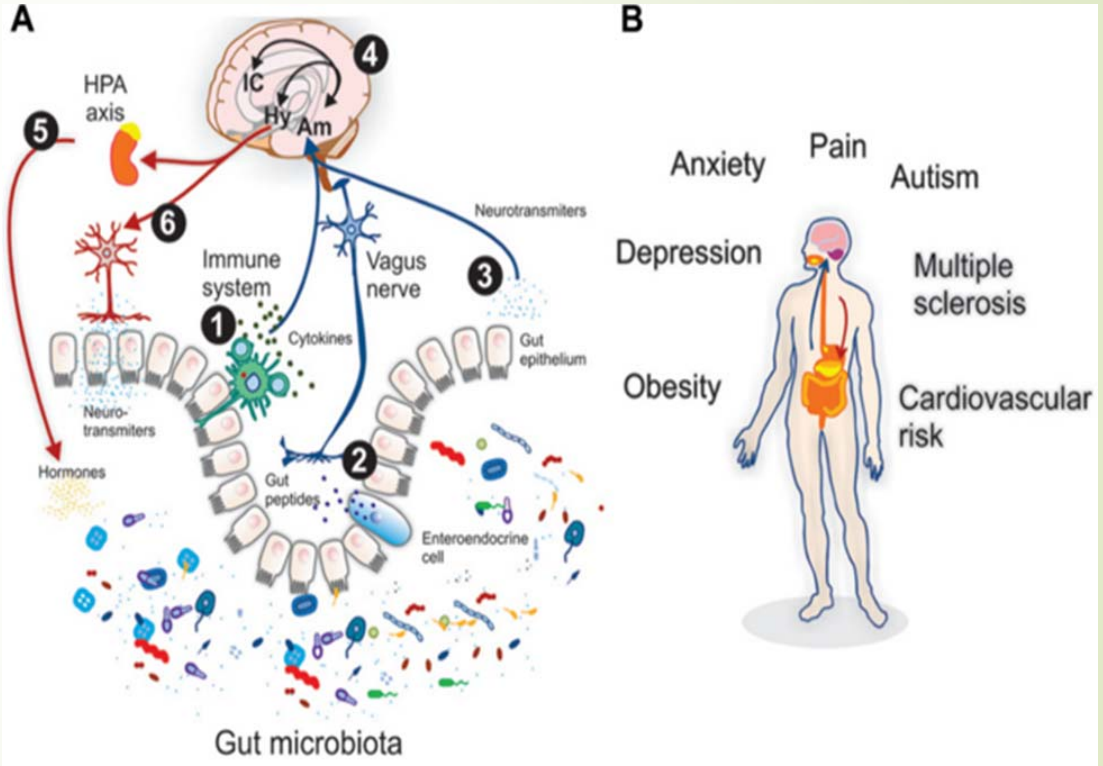
I RUOLI DEL MICROBIOTA INTESTINALE

- Prevenzione della colonizzazione di potenziali patogeni attraverso meccanismi di antagonismo (produzione di sostanze come acidi grassi, perossidi o batteriocine);
- Funzioni nutritive- metaboliche:
  - 1) partecipa alle funzioni digestive e permette l'assorbimento di carboidrati altrimenti non utilizzabili dall'uomo come fonte di energia;
  - 2) Sintetizza vitamine (K, B12) e altre sostanze assorbite dall'ospite.
- Fornisce continui e dinamici stimoli che influenzano lo sviluppo e l'omeostasi del sistema immunitario dell'ospite.



Brian-gut-axis-microbiota

- La segnalazione bidirezionale tra il tratto gastrointestinale ed il cervello è regolata al livello neurale (entrambi i sistemi nervoso centrale ed enterico), ormonale e immunologico;
- I meccanismi esatti che disciplinano tale comunicazione non sono chiari;
- disturbi nell'interazione asse cervello-intestino e microbiota sono stati collegati a disturbi psichiatrici legati allo stress, come l'ansia, e disturbi gastrointestinali, tra cui disturbi del colon irritabile (IBS) e disordini infiammatori intestinali (IBD), nonché a disturbi neurologici, tra cui sclerosi multipla (SM), autistismo e morbo di Parkinson.



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Brian-gut-axis-microbiota

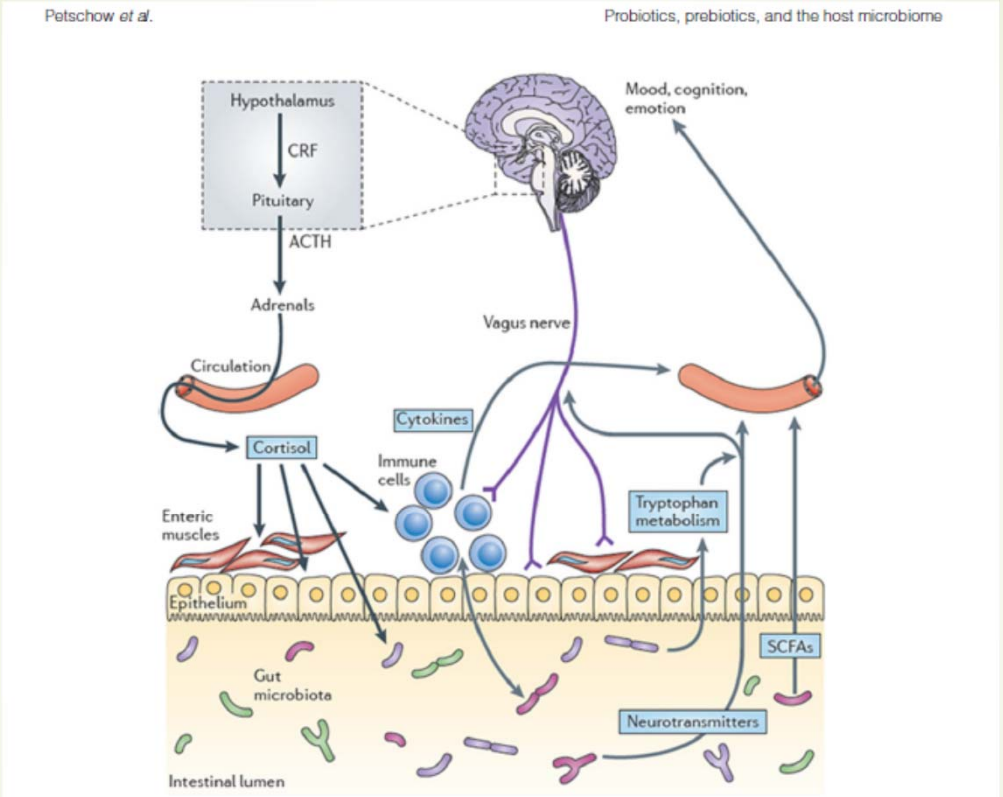

Figure 4. Pathways involved in bidirectional communication between the gut microbiota and the brain. Multiple pathways exist through which the gut microbiota can modulate the gut–brain axis. They include endocrine (cortisol), immune (cytokines), and neural (vagus and enteric nervous system) pathways. The brain recruits these same mechanisms to influence the composition of the gut microbiota, for example, under conditions of stress. The hypothalamus–pituitary– adrenal axis regulates cortisol secretion, and cortisol can affect immune cells, alter gut permeability and barrier function, and change gut microbiota composition. Conversely, the gut microbiota and probiotic agents can alter the levels of circulating cytokines, and this can have a marked effect on brain function. Both the vagus nerve and modulation of systemic tryptophan levels are strongly implicated in relaying the influence of the gut microbiota to the brain. In addition, short-chain fatty acids (SCFAs) are neuroactive bacterial metabolites of dietary fibers that can also modulate brain and behavior. ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor. From Cryan and Dinan.[57]

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Targeting the Human Microbiome With Antibiotics, Probiotics, and Prebiotics: Gastroenterology Enters the Metagenomics Era

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Abstract

Studies of metagenomics and the human microbiome will tremendously expand our knowledge of the composition of microbial communities in the human body. As our understanding of microbial variation and corresponding genetic parameters is refined, this information can be applied to rational remodeling or "tailoring" of human-associated microbial communities and their associated functions. Physiologic features such as the development of innate and adaptive immunity, relative susceptibilities to infections, immune tolerance, bioavailability of nutrients, and intestinal barrier function may be modified by changing the composition and functions of the microbial communities. The specialty of gastroenterology will be affected profoundly by the ability to modify the gastrointestinal microbiota through the rational deployment of antibiotics, probiotics, and prebiotics. Antibiotics might be used to remove or suppress undesirable components of the human microbiome. Probiotics can introduce missing microbial components with known beneficial functions for the human host. Prebiotics can enhance the proliferation of beneficial microbes or probiotics, to maximize sustainable changes in the human microbiome. Combinations of these approaches might provide synergistic and effective therapies for specific disorders. The human microbiome could be manipulated by such "smart" strategies to prevent and treat acute gastroenteritis, antibiotic-associated diarrhea and colitis, inflammatory bowel disease, irritable bowel syndrome, necrotizing enterocolitis, and a variety of other disorders.

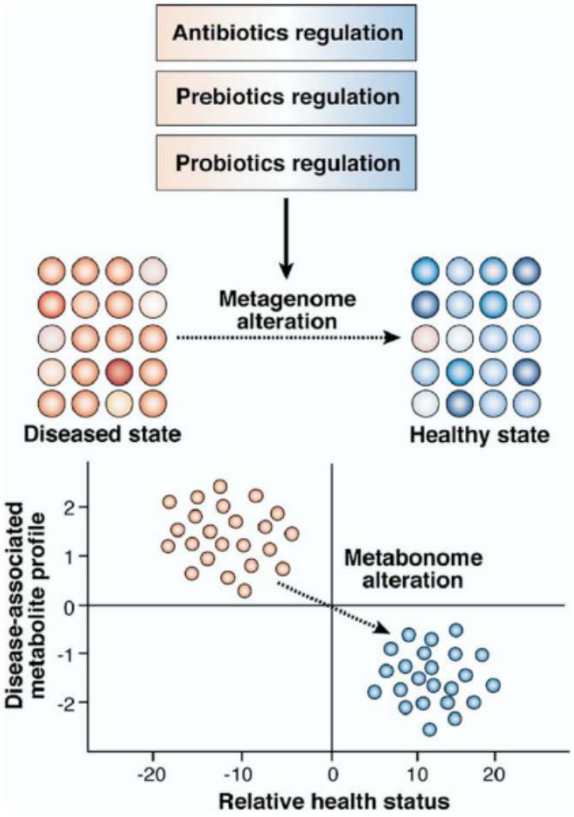

Figure 1.
The gut microbiome as a therapeutic target: the "drug the extended" genome strategy. Perturbed metagenomic or metabonomic profiles associated with complex disease states can be restored to homeostasis with rationally selected antibiotic, probiotic, prebiotic, or combination treatment strategies. Adapted with permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery,[23] copyright 2008. http://www.nature.com/nrd/.

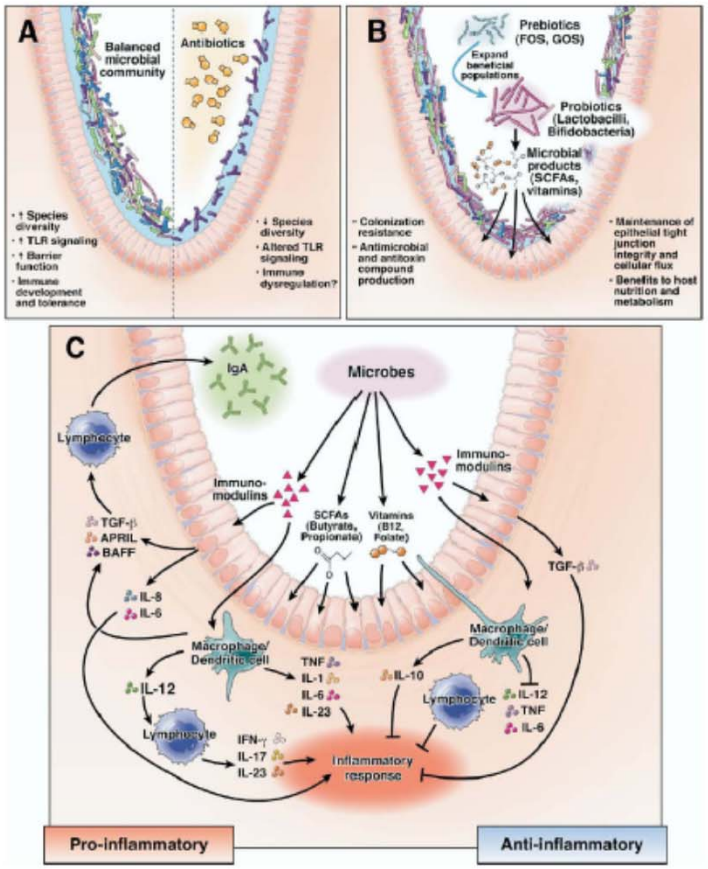

Figure 3.

Microbial manipulation strategies and effects on intestinal biology. (*A*) The composition and aggregate functions of mixed microbial communities are dramatically altered by antibiotics. Various functions affected include gastrointestinal physiology and innate and adaptive immunity, resulting in increased host susceptibility to human disease. (*B*) Manipulation of the microbiota with rationally selected prebiotics or probiotics can inhibit pathogens, strengthen epithelial barrier function, and supply the host with key nutrients, including short-chain fatty acids (SCFAs) and vitamins. (*C*) Specific microbes modulate mucosal immunity by secreted factors and by direct interactions with immune cells and the intestinal epithelium. Anti-inflammatory responses are mediated by TGF-β production by epithelial cells and IL-10 from mononuclear cells. Immunostimulatory responses occur as a result of a wide variety of proinflammatory cytokines from stimulated epithelial cells, mononuclear cells, and lymphocytes, in addition to IgA production from B lymphocytes. FOS, fructo-oligosaccharides or oligo-fructose.

CONCLUSIONI

- L'organismo umano ospita un numero di microrganismi che è superiore al numero delle cellule che lo costituiscono
- Studi sempre più numerosi sottolineano l'importanza fisiologica del microbiota umano
- Dall'attività di questi microscopici colonizzatori non solo dipende il nostro stato di salute, ma il nostro benessere in generale grazie alla produzione di metaboliti in grado di influenzare persino il nostro comportamento e il nostro umore.