

Microbiota and Host Nutrition across Plant and Animal Kingdoms

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Plants and animals each have evolved specialized organs dedicated to nutrient acquisition, and these harbor specific bacterial communities that extend the host's metabolic repertoire. Similar forces driving microbial community establishment in the gut and plant roots include diet/soil-type, host genotype, and immune system as well as microbe-microbe interactions. Here we show that there is no overlap of abundant bacterial taxa between the microbiotas of the mammalian gut and plant roots, whereas taxa overlap does exist between fish gut and plant root communities. A comparison of root and gut microbiota composition in multiple host species belonging to the same evolutionary lineage reveals host phylogenetic signals in both eukaryotic kingdoms. The reasons underlying striking differences in microbiota composition in independently evolved, yet functionally related, organs in plants and animals remain unclear but might include differences in start inoculum and niche-specific factors such as oxygen levels, temperature, pH, and organic carbon availability.

Physiological Functions of the Vertebrate Gut and Plant Roots

The vertebrate gut and plant roots evolved independently in animal and plant kingdoms but serve a similar primary physiological function in nutrient uptake (Figure 1). One major difference between plant and animal nutritional modes is their distinct energy production strategy. Plants are autotrophs, producing their own energy through photosynthesis (carbohydrate photo-assimilates), while animals rely entirely on the energy originally captured by other living organisms (heterotrophs). Long-distance transport mechanisms ensure the distribution of carbohydrate photo-assimilates from chloroplasts in leaves to all other body parts, including roots. Nutrient acquisition by roots to support plant growth is therefore almost exclusively limited to uptake of mineral ions and water from soil. In contrast, the mammalian gut has evolved to facilitate the uptake of simple sugars, amino acids, lipids, and vitamins in addition to ions. It is typically compartmentalized into sections with low microbial biomass in which the products of host enzymatic activity are absorbed (i.e., the human small intestine, SI) and a section for the uptake of microbe-derived fermentation products (human large intestine or hindgut, LI).

A significant fraction of the soil nutritive complement and of the dietary intake remains unavailable for plants and animals, respectively, and this defines their dietary constraints. Critical

nutrients for plant growth and productivity in soil are nitrogen and phosphorus. However, plant roots can absorb only inorganic nitrogen and orthophosphate (Pi), although phosphorus is abundant in soil both in inorganic and organic pools. Pi can be assimilated via low-Pi-inducible (high-affinity) and constitutive Pi uptake systems (low-affinity) (Lambers et al., 2008; López-Arredondo et al., 2014). Plant species adapted to neutral or higher soil pH, and more aerobic soils have a preference for nitrate and deploy two nitrate uptake and transport systems that act in coordination. By contrast, plants adapted to low pH (reducing soil) as found in forests or the arctic tundra appear to assimilate ammonium or amino acids (Maathuis, 2009). Similarly, a fraction of normal human dietary intake remains undigested and therefore non-bioavailable (fiber). These non-digestible components include plant cell wall constituents such as cellulose, hemicellulose, xylan, and pectin, and certain polysaccharides such as β -glucan, inulin, and oligosaccharides that contain bonds that cannot be cleaved by mammalian hydrolytic enzymes (Tungland and Meyer, 2002).

Plant roots and animal guts are colonized by diverse microbial classes, including bacteria and archaea, fungi, oomycetes, as well as viruses (Table 1). These communities can be regarded as the host's extended genome, providing a huge range of potential functional capacities (Berendsen et al., 2012; Gill et al., 2006; Qin et al., 2010; Turner et al., 2013). Here we focus on

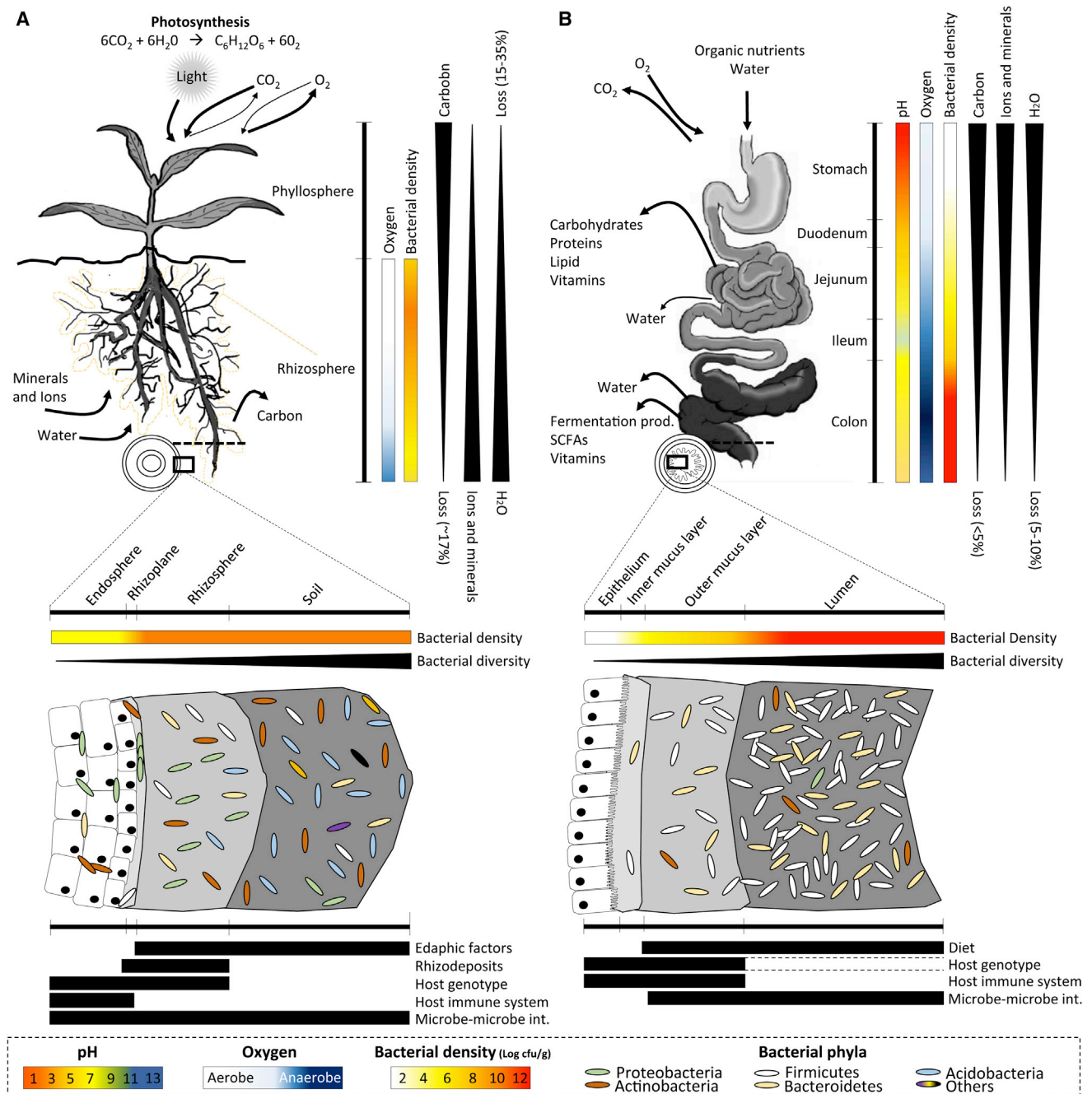


Figure 1. Physiological Functions of the Plant Roots and Human Gut in Nutrient Uptake, Spatial Aspects of Microbiota Composition, and Factors Driving Community Establishment

(A and B) Spatial compartmentalization of the plant root microbiota (A) and the human gut microbiota (B). Upper panels: the major nutrient fluxes are indicated, as well as pH and oxygen gradients in relation with the bacterial density. Lower panels: compartmentalization of the microbiota along the lumen-epithelium continuum in the gut or along the soil-endosphere continuum in the root. For each compartment, the bacterial density, the bacterial diversity, and the major represented phyla are represented for both the gut and the root organs. The main factors driving community establishment in these distinct compartments are depicted with black bars. The gut drawing is adapted from [Tsabouri et al. \(2014\)](#) with permission from the publisher.

bacterial microbiotas because these were shown to form reproducible taxonomic assemblies in animal and plant individuals with well-defined functions.

In plant roots, the microbiota mobilizes and provides nutrients by increasing nutrient bioavailability from soil ([Bulgarelli et al.,](#)

2013). Non-nutritional functions include increased host tolerance to biotic stresses, e.g., against soil-borne pathogens ([Mendes et al., 2011](#)), and likely abiotic stresses. In addition, the root microbiota can also affect plant fitness by impacting flowering plasticity ([Panke-Buisse et al., 2015; Wagner et al., 2014](#)).

Table 1. Percentage of Shotgun Metagenome Reads Assigned to Each Kingdom of Life across Metagenome Studies

	Cucumber ^a	Wheat ^a	Soybean ^b	Wheat ^c	Oat ^c	Pea ^c	Barley ^d	Gut ^e
Bacteria	99.36	99.45	96	88.5	77.3	73.7	94.04	99.1
Archaea	0.02	0.02	<1	<0.5	<0.5	<0.5	0.054	
Eukaryotes	0.54	0.48	3	3.3	16.6	20.7	5.90	<0.1

^aOfek-Lalzar et al. (2014) (metagenomics of rhizoplane samples).^bMendes et al. (2014) (metagenomics of rhizosphere samples).^cTurner et al. (2013) (metatranscriptomics of rhizosphere samples).^dBulgarelli et al. (2015) (metagenomics of rhizosphere samples).^eQin et al. (2010) (metagenomics of gut samples).

Similarly, the gut microbiota has a major role in host nutrition. It contributes nutrients and energy to the host via fermentation of indigestible polysaccharides into short-chain fatty acids (SCFAs) in the colon (Martins dos Santos et al., 2010; Tremaroli and Bäckhed, 2012). The human LI has incomplete peristalsis and a longer retention time, allowing fermentative microbiota to break down complex glycan bonds and liberate additional energy from the diet (Stevens and Hume, 1998). Additionally, gut microbiota provide essential vitamins to the host and modulate the absorptive capacity of the intestinal epithelium. An additional common feature of the gut and root microbiota is their protective role by competitive exclusion against invasion by opportunistic pathogens (Kamada et al., 2013).

Homeostatic balance between both microbe-microbe and host-microbe interactions is critical for a healthy host-microbiota relationship. Alteration of this balance via perturbation of the gut or the plant microbiota composition (microbial dysbiosis) may represent an important mechanism of disease (Martins dos Santos et al., 2010; Kemen, 2014; Sekirov et al., 2010). In plants, a healthy status is the norm, and soil-resident microbes contribute to plant health. This is illustrated by a higher disease severity following pathogen inoculation when plants are grown in pasteurized compared to non-pasteurized soils (Weller et al., 2002). In addition, so-called disease-suppressive soils protect plants against particular soil-borne pathogens. For example, specific bacterial genera belonging to gamma-Proteobacteria were associated with a high level of soil disease suppressiveness. The underlying mechanisms comprise competition between soil-borne microbes for plant-derived nutrients and antimicrobial compound production (Berendsen et al., 2012; Mendes et al., 2011). In the gut, commensal microbes can also suppress pathogen invasion through secretion of antimicrobial compounds, alteration of local pH, or stimulation of host immunity (Kamada et al., 2013).

Compartmentalization of the Gut and Root Microbiota

Relevant biotic and abiotic gradients exist in both the gut and root, leading to microbial compartmentalization (Figure 1). Along the soil-root continuum, four compartments can be distinguished: soil, rhizosphere, rhizoplane, and endosphere (Figure 1A). Bacterial diversity in soil is high, with estimates suggesting that >2,000 species populate 0.5 g of soil (Schloss and Handelsman, 2006). The rhizosphere corresponds to the zone of soil directly influenced by root exudation, while the root compartment can be separated in two distinct niches, rhizoplane and endosphere. The rhizoplane harbors a suite of microbes that

tightly adhere to the root surface, while the endosphere is composed of microbes inhabiting the interior of roots. Microbial density is high in the rhizosphere, and species richness gradually decreases along the soil-endosphere continuum (Bulgarelli et al., 2012, 2015; Edwards et al., 2015; Lundberg et al., 2012) (Figure 1A). Therefore, the bacterial community shifts from a dense and diverse soil-borne community to a host-adapted community with reduced diversity.

A spatial heterogeneity of microbial density exists along the digestive track (Stearns et al., 2011). Densities are lowest in the stomach and duodenum (proximal SI) (10^1 – 10^3 bacteria per gram of content) and increase along the length of the SI with a higher density in the distal ileum (10^4 – 10^7 bacteria per gram). Cell densities in the LI can reach 10^{12} – 10^{13} bacteria per gram of content, representing the highest density recorded so far in any environment and exceeding the density detected in the rhizosphere by 2–3 orders of magnitude. Although the density is high, the diversity is relatively low (Stearns et al., 2011; Walter and Ley, 2011). Using low-error 16S rRNA gene sequencing (LEA-seq) of the human fecal gut microbiota (low depth coverage), the number of bacterial species is estimated at 101 ± 27 , which is in alignment with estimates of culture-based techniques (Faith et al., 2013; Mitsuoka, 1992). Compartmentalization exists also from the inside to the outside of the intestinal tube, defined by the intestinal lumen, mucus, and epithelial surface. Similar to the compartmentalization in the root, a decrease in bacterial density is observed from the lumen to the epithelial surface (Swidsinski et al., 2005; Van den Abbeele et al., 2011; Zhang et al., 2014) (Figure 1B). In the LI, the mucus is subdivided into an inner firmly adherent layer largely devoid of bacteria and an outer layer that is looser and non-adherent and allows some microbial colonization (Johansson et al., 2008).

Community Structure of the Vertebrate Gut and Plant Root Microbiota

Where Do They Come from?

A relevant difference for experimentation on the plant root and vertebrate gut microbiota is the ease with which the start inoculum of the root microbiota can be defined. This is due to a predominant horizontal acquisition of root endophytes from the surrounding soil biome, although in some plant species there is evidence for additional vertical transmission of seed-borne endophytes (Barret et al., 2014). These endophytes mainly belong to Proteobacteria and can colonize seeds via different colonization routes, including flowers, fruits as well as roots, leaves, and stems (Truyens et al., 2015). Even though vertical

transmission in mammals is not as explicit as in plants (none are transferred with the germline), vertical transmission nevertheless occurs. The transmission from parent to offspring results from the birth process itself, from milk, and from the close contact that comes from parental care (Unger et al., 2015). In humans, vaginal birth inoculates the newborn with a set of strains that can be matched to the mother, whereas caesarean section results in colonization with skin microbes originating from various caregivers (Dominguez-Bello et al., 2010). Breast milk is also an important source of microbiota and antibodies that shape the gut microbiome (Newburg and Morelli, 2015), and introduction of solid foods brings rapid shifts in the bacterial community composition toward an adult-like microbiome (Koenig et al., 2011). Vertical transmission from mother to infant gut microbiota is sometimes behaviorally increased in mammals by feeding mother's fecal matter to their infants. In koalas, for instance, this transmission is believed to participate in the digestion of eucalyptus (Osawa et al., 1993). Additionally, group living is known to aid the transmission of commensal microbes between members of family groups (humans), troupes (primates), and most likely herds as well. Co-habitation in humans leads to sharing of microbiota, which is enhanced when dogs also co-habit in the same house (Song et al., 2013). Ironically, hygiene measures aimed at reducing pathogen transmission may have had broad negative impacts on the transmission of commensals and may underlie the loss of diversity observed in the West (Blaser and Falkow, 2009).

Who Are They?

Despite the vast prokaryotic biodiversity found in the biosphere (currently >80 bacterial phyla are described), the host-associated microbiota is dominated numerically by a few phyla. The rhizosphere and the root endophytic compartment of unrelated plant species is often enriched for bacteria belonging to three main phyla (Proteobacteria, Actinobacteria, and Bacteroidetes). In contrast, abundant soil bacteria belonging to the phylum Acidobacteria are excluded from the endophytic compartment (Bulgarelli et al., 2013). Compared with the surrounding soil, microbiota members belonging to the phylum Proteobacteria are consistently enriched in the rhizosphere/endosphere compartments of monocotyledonous and dicotyledonous plants, including perennial and annual plants (Bulgarelli et al., 2012, 2015; Edwards et al., 2015; Lundberg et al., 2012; Ofek-Lalzar et al., 2014; Peiffer et al., 2013; Schlaeppi et al., 2014; Shakya et al., 2013; Zarraonaindia et al., 2015). This likely reflects niche adaptation (nutrient availability, oxygen levels) and the ability to efficiently invade and persist inside or outside the roots of divergent plant species. Firmicutes and Bacteroidetes are by far the two most-abundant phyla detected in adult human and mouse feces. Other phyla represented include the Actinobacteria, Verrucomicrobia, and a number of less-abundant phyla such as the Proteobacteria, Fusobacteria, and Cyanobacteria (Eckburg et al., 2005). Similar to the rhizosphere compartment, the mucus layer of the gut represents a particular niche favoring the proliferation of specialized inhabitants. It has been estimated that at least 1% of the gut microbiota can degrade mucins as a source for carbon and nitrogen (Hoskins and Boulding, 1981). Select types of bacteria can also attach to mucins, such as *Bifidobacterium bifidum*, which has the ability to stimulate mucin production via butyrate-induced expression of *MUC2*, while

others can degrade the nine-carbon sugar sialic acid found in host glycoconjugates (Almagro-Moreno and Boyd, 2009; Gaudier et al., 2004; Leitch et al., 2007).

Are There Structural Similarities across Diverse Host-Associated Microbial Communities?

Striking physiological (dis-)similarities exist between organs dedicated to nutrient acquisition in hosts belonging to different taxonomic lineages. However, the extent to which microbial communities living in association with phylogenetically divergent hosts overlap with each other is largely unknown. In an attempt to unravel host-specific and conserved signatures in the microbiota, we retrieved and re-analyzed the raw sequencing data contributed by 14 previous large-scale 16S rRNA gene survey studies (Table S1). These comprise >3,200 samples from more than 40 different host species, including human, other mammals, and fish gut, as well from the root and rhizosphere of the flowering plant *Arabidopsis thaliana* and relative species, maize, rice, barley, and grapevine. In addition, we included samples from several species of cnidarian hydra, a freshwater basal animal featuring a gut forming a hollow cavity within the body with one opening, the mouth.

To analyze the data, we followed the QIIME (Caporaso et al., 2010) closed-reference protocol and used SortMeRNA (Kopylova et al., 2012) to cluster the sequences into operational taxonomic units (OTUs) at 97% sequence similarity (see Supplemental Experimental Procedures). Analyses of beta-diversity using principal coordinate analysis (PCoA) revealed a clear clustering of samples according to their respective host species (Figure 2A; Supplemental Experimental Procedures). Although all samples are derived from organs with a dedicated function in nutrient uptake, we found striking qualitative differences between their associated microbial communities. This disparity can be explained by the increased abundance of members of the Bacteroidetes phylum in the mammalian stool samples (particularly those belonging to the orders Bacteroidales and Clostridiales) and the enrichment of members of the families Pseudomonadaceae, Streptomycetaceae, and Comamonadaceae in the rhizosphere and plant root compartments (Figure 3). Intriguingly, the bacterial communities in the fish gut are more closely related to those in the root and rhizosphere samples than to the mammalian gut, partially due to an increased abundance in Proteobacteria (45.08% and 54.44% in root-associated samples and fish gut, respectively, compared with 4.20% in the case of the human gut; Figure 4). In addition, the microbial communities from infant gut (from Koenig et al., 2011) are more closely related to those of plant roots (and therefore soil microbiota) than those associated to adults (Figure S1). Together, this suggests that shared environmental and physiological features, rather than phylogenetic relatedness of the hosts, are decisive for community establishment.

Analysis of alpha-diversity (Figures 2B and 3B) shows that the bacterial richness is low in the gut of aquatic organisms and higher in the root and in the rhizosphere of different plant species, consistent with the bacterial diversity detected in their respective surrounding environments (aquatic versus soil environments; Curtis et al., 2002). For all plant species surveyed, the bacterial diversity is lower in the endosphere compartment (root) compared to the rhizosphere compartment (Figures 2B), in concordance with previous studies (Bulgarelli et al., 2012;

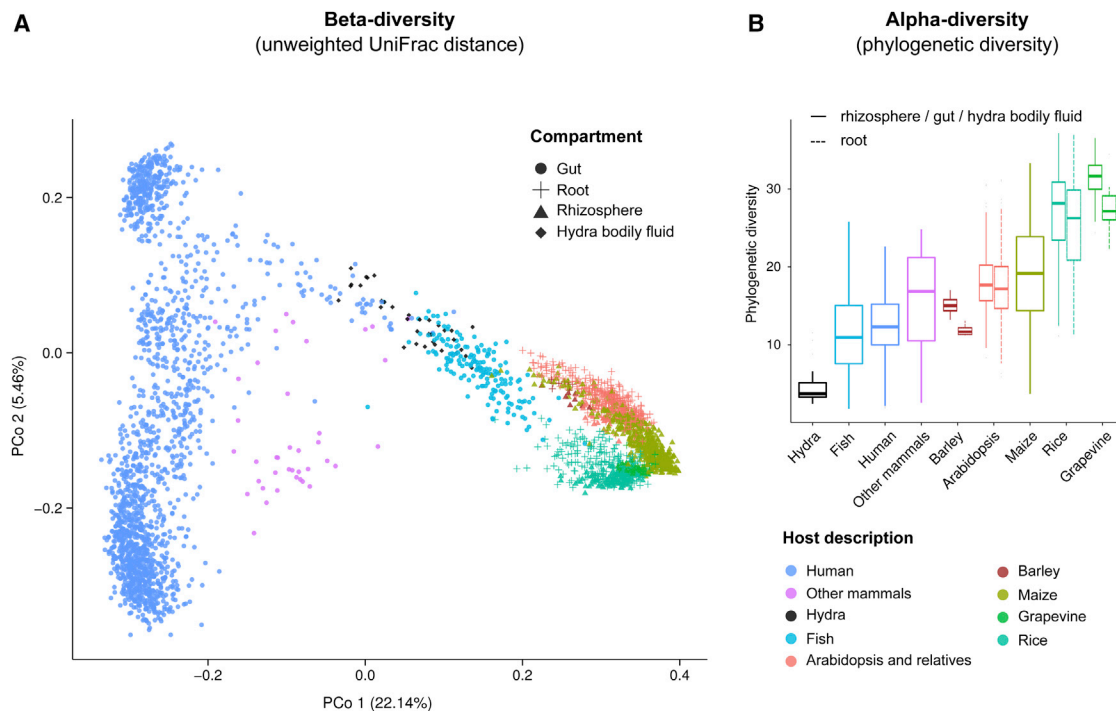


Figure 2. Alpha- and Beta-Diversity Analyses

(A) Principal coordinate analysis (PCoA) of pairwise unweighted UniFrac distances between samples. The color and shape of each point represent the host and compartment, respectively.

(B) Comparison of alpha-diversity between hosts based on the whole tree phylogenetic diversity index (PD), sorted by ascending order of complexity. See Table S1 for more information about the individual host species included in each study.

Edwards et al., 2015; Lundberg et al., 2012). The extent of this gradient in diversity, as well as the differentiation between the two compartments, appears to be dependent on the plant species, indicating a strong host-dependent effect on community establishment.

A phylogenetic comparison of the abundant community members across hosts (OTUs, with a relative abundance higher than 0.1% on average) reveals clear qualitative structural differences between mammalian gut and plant root and rhizosphere samples (Figure 5). These distinct sets of bacterial communities show virtually no overlap even at high taxonomic levels. Samples obtained from human and mammalian guts are dominated by OTUs belonging to the orders Bacteroidales and Clostridiales (34.55% and 51.26% relative abundances, respectively), while these are almost completely absent in the root and rhizosphere samples (0.70% and 0.80%, respectively). This striking difference in community composition in independently evolved, yet functionally related, gut and root organs might be explained by adaptations to specific host and environmental needs, including niche-specific factors such as oxygen levels, pH, and organic carbon availability. Our findings also make a direct transfer and persistence of microbiota members from numerous root-derived dietary plant products in the human gut unlikely.

Do They Fluctuate over Time?

Despite the fact that infancy or the seedling stage for plants are critical windows for microbiota assembly, very little is known about the earliest steps driving host colonization by pioneer bacteria. Assembly of the infant gut microbiome begins at birth (early

reports described it as chaotic), and diversity levels slowly increase until ~2–3 years of age (Koenig et al., 2011; Palmer et al., 2007; Yatsunenko et al., 2012). Sampling from birth to 2.5 years of age revealed the following: (i) community richness increased gradually over time, (ii) the use of antibiotics, changes in diet, and infections led to jumps from one stable consortium of species to another, and (iii) members of the Bacteroidetes phylum were co-dominant with members of the Firmicutes phylum after the introduction of solid foods (Koenig et al., 2011). The adult-like microbiota is characterized by a greater stability (David et al., 2014a; Spor et al., 2011). About 60% of the bacterial strains in the intestine are detected over a 5-year time frame, and Bacteroidetes and Actinobacteria were identified as the most stable phyla (Faith et al., 2013). In contrast to the chaotic microbial succession described for the infant gut, the structure of the root microbiota during the plant life cycle appears rather stable. Despite a higher variability observed during the seedling stage (Chaparro et al., 2014), microbiota acquisition from soil appears to occur relatively rapidly, initiating within 24 hr after sowing and approaching a steady state within 2 weeks (Edwards et al., 2015). Once established, there is little evidence for dramatic changes even late in the life cycle of annual *A. thaliana* plants, when organic carbon and nitrogen are spatially re-allocated during the transition from vegetative to reproductive growth for seed formation (Lundberg et al., 2012). This surprising stability might be explained by the sessile nature of plants, together with a rather stable soil-borne inoculum source, which prevents extreme fluctuations in input communities throughout

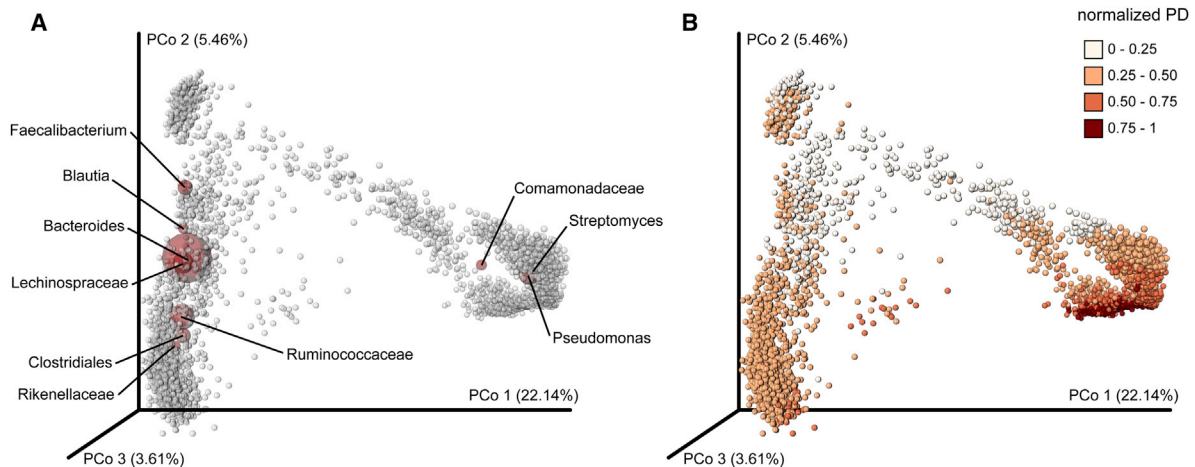


Figure 3. 3D PCoA Plots

(A) Biplots depicting the taxa with the largest contribution to the ordination space (order Clostridiales; families Ruminococcaceae, Rikenellaceae, Lechnospraceae, Comamonadaceae; genera Streptomyces, Pseudomonas, Bacteroides, Blautia, Faecalibacterium).

(B) PCoA plot showing the alpha-diversity variation as measured by the PD index across all samples included in the study.

a rapid annual plant's life cycle. Whether this also applies to longer-lived perennials and to repeated croppings of the same species at the same location remains to be further substantiated (Donn et al., 2015).

Major Factors Driving Community Establishment and Composition

Inter-individual differences in the gut and the plant microbiota are likely to be dictated by many modulating factors, including environmental parameters but also diet/soil-type, microbe-microbe interactions, host genotype, and host immune system (Figure 1).

Environmental Factors

pH. Bacterial community composition is strongly correlated with differences in soil pH, with soils at near-neutral pH showing the highest microbial diversity (Fierer and Jackson, 2006). Roots can acidify the rhizosphere up to two pH units compared to the surrounding soil through release of protons, bicarbonate, organic acids, and CO₂ (Hinsinger et al., 2003). Along the digestive tract, the increase in bacterial titer can be attributed to several factors, such as pH and bile acids. The pH is very low in the stomach (pH 1.5–5), restricting bacterial growth, increases in the SI (duodenum pH 5–7, jejunum 7–9, ileum 7–8) and drops in the colon (pH 5–7) (Walter and Ley, 2011) (Figure 1B). Many types of bacteria, in both the gut and the soil, are sensitive to pH, and this is thought to structure communities to a large degree (Duncan et al., 2009), although it is difficult to disentangle the exact contribution of pH on the overall community structure due to likely interaction with many other factors.

Oxygen. Although both gut and root systems are dedicated for nutrient uptake, O₂ levels are controlled in opposing directions. In the vertebrate gut, luminal microbes generally face anaerobic conditions favoring fermentative metabolism, while in soil and along the root (micro-)aerobic conditions are found (Figure 1). This might be a major factor explaining structural and functional differences between the microbiota of the vertebrate gut and plant roots (Figure 5). The gut microbiota of healthy individuals

is dominated by anaerobic bacteria, which outnumber aerobic and facultative anaerobic bacteria by a factor of 100–1,000:1 (Quigley and Quera, 2006), while the root microbiota is enriched for Proteobacteria, a phylum dominated by aerobic species. Consistent with this, genes encoding high-affinity oxidases that use O₂ as a terminal electron acceptor are overrepresented in gut metagenomes, whereas those encoding low-affinity oxidases are enriched in soil metagenomes (Morris and Schmidt, 2013). It is arguably in the host's interest to limit respiration, because (i) limiting respiration will control bacterial growth and (ii) promoting fermentation will result in SCFA availability. Nonetheless, there is a biologically relevant gradient of oxygen levels in both the soil and the gut that is likely to influence microbial community structure at the micro-levels. Despite the fact that plant roots generally face (micro-)aerobic conditions, soil O₂ levels can also fluctuate as a function of soil wetting/drying (Noll et al., 2005), with anoxic niches in the center of soil aggregates. Similarly, a higher O₂ concentration is found at the surface of the epithelium compared with the lumen. Some facultative aerobes can grow along this oxygen gradient by respiring O₂ close to the epithelium using flavins and thiols as electron shuttles to respire at “long distance” (Khan et al., 2012).

Temperature. While thermal stability exists in the gut of mammals (endotherm), higher temperature fluctuation is observed for plants or ectothermic animals that rely on the external temperature to regulate their internal body temperature. It has been reported that the bacterial community in soil is modulated by temperature (Bárcenas-Moreno et al., 2009), although plant microbiota functions must remain stable under a wide range of temperatures.

Nutritional Drivers

For both plant roots and vertebrate guts, diet (for plants, soil type defines the diet) is a major driver for microbial community structure (Bulgarelli et al., 2012; Cotillard et al., 2013; Carmody et al., 2015; David et al., 2014b; Edwards et al., 2015; Ley et al., 2008a; Lundberg et al., 2012; Muegge et al., 2011; Schlaeppi et al., 2014; Peiffer et al., 2013; Turnbaugh et al., 2009).

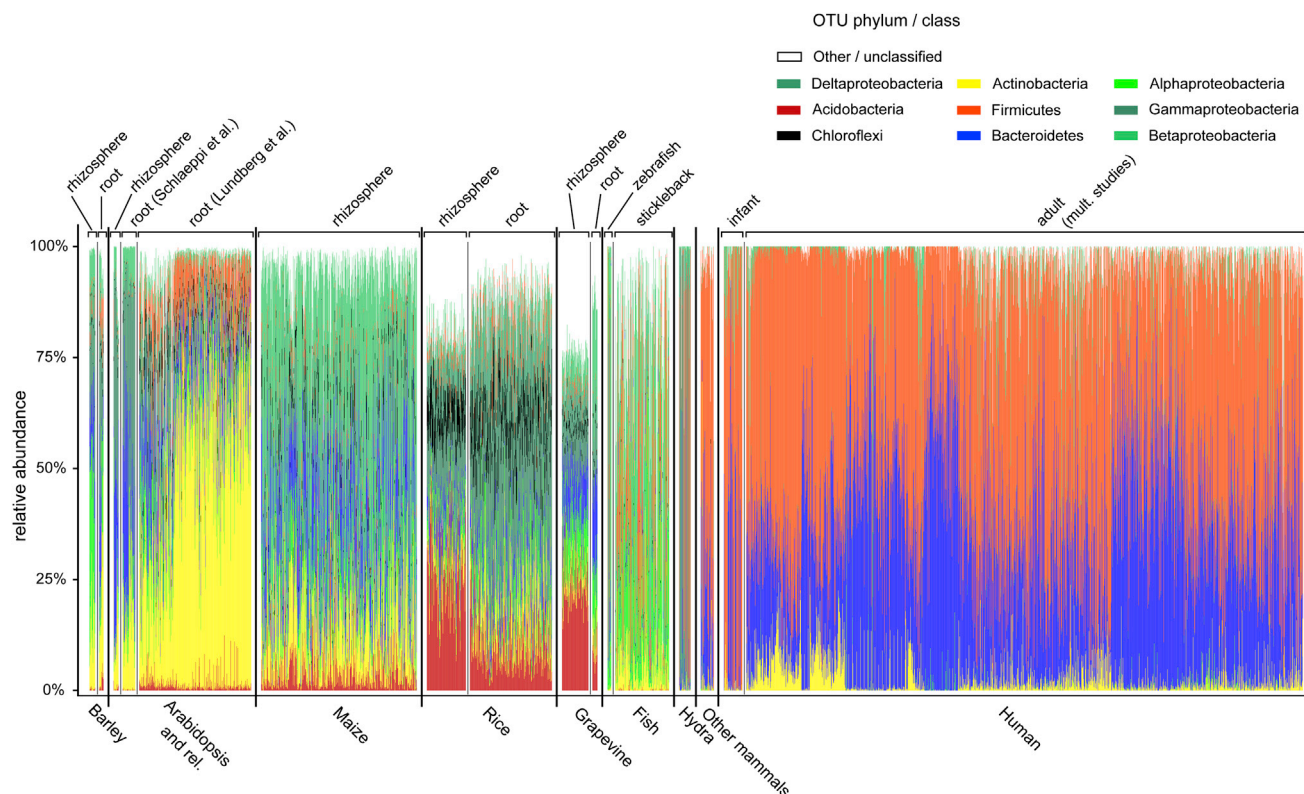


Figure 4. Cumulative Abundance Plots

Relative abundances grouped at the phylum or class taxonomic level for each sample included in the meta-analysis. The bar plots have been arranged along the x axis separating different host groups as well as different species and compartments.

Organic carbon is widely considered to be the most important factor limiting bacterial growth in different soils (Demoling et al., 2007). Isotope probing experiments using different plant species revealed that an average of 17% of all photosynthetically fixed carbon is transferred to the rhizosphere through root exudates (Nguyen, 2003), highlighting a considerable organic carbon deposition in soil. Low molecular weight carbon substrates such as dicarboxylic acids, exuded by roots in large quantities to acidify the rhizosphere, also enhance the availability of Pi and micronutrients such as manganese, iron, and zinc. These dicarboxylic acids are an important driver mediating soil community shifts, leading to an increase in the relative abundance of beta-Proteobacteria, gamma-Proteobacteria, and Actinobacteria (Eilers et al., 2010).

The evolution of the mammalian gut microbiota has been greatly influenced by host diet. Mammals, their gut microbiota, and their diet types are part of a dynamic tripartite coevolution (Ley et al., 2008b). The majority (80%) of extant mammals are herbivorous, which stands in contrast to the early mammals that were most likely carnivorous based on their tooth morphology. The rise in herbivory could only have been accomplished with the necessary changes in gut microbes, since mammalian genomes lack the necessary genes encoding plant cell wall degrading enzymes. Comparisons of microbiomes between host species highlight the specific adaptations of the microbiota to the host diet, such as an increased abundance of genes encoding the necessary enzymes and their respective

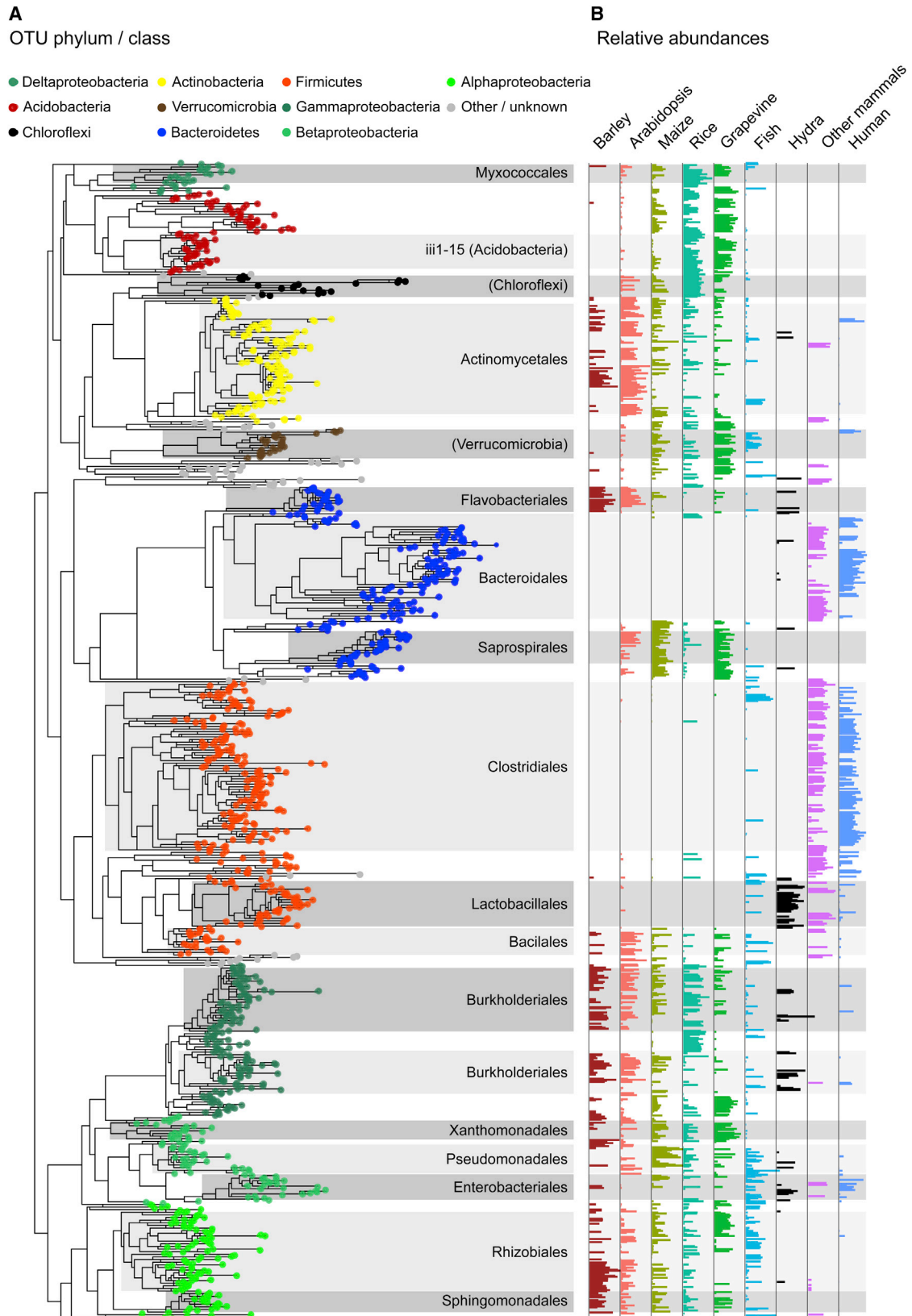
pathways (Eilam et al., 2014), as exemplified in a comparison between the termite hindgut and the bovine rumen metagenome (Brulic et al., 2009). The latter is enriched for genes encoding glycoside hydrolases, cellulose enzymes, and nitrogen-related uptake proteins. In contrast, the termite hindgut microbiome showed an enrichment for genes involved in the degradation of the cellulose backbone and nitrogen fixation. This clearly reflects the differences in diet of the hosts (forages and legumes versus nitrogen-poor wood).

Microbe-Microbe Interactions

The role of microbe-microbe interactions is also critical for shaping microbiota structure in both plant and animal systems (Bulgarelli et al., 2015; Fraune et al., 2014; Hacquard and Schadt, 2015; Trosvik et al., 2010). The combination of synergistic, beneficial, and antagonistic interactions among microbiota members colonizing the gut and plants is likely to have a major impact on overall community structure. Therefore, individual members of a community may contribute to the overall stability of the system, and consequently, each community member must be viewed as a potential internal driver of microbial community assemblage. Microbial co-occurrence and co-exclusion patterns are now emerging as important concepts for understanding the rules guiding microbial community assembly (Cardinale et al., 2015; Faust et al., 2012; Zhang et al., 2014).

Host Genotype

Intra-species plant genetic diversity explains less variation in community structure than soil type and root fraction (soil,



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rhizosphere, and endosphere). Surveys of the bacterial community structure of 27 maize inbred lines, 6 cultivated rice varieties, 3 barley accessions, and several *A. thaliana* accessions each point to a small (~5%–6% of variation) but significant role of the host genotype on community composition (Bulgarelli et al., 2012, 2015; Edwards et al., 2015; Lundberg et al., 2012; Peiffer et al., 2013; Schlaeppi et al., 2014). This suggests a link between host diversification and microbial community establishment (see below).

In humans, family members are often observed to have more similar microbiotas than unrelated individuals (Tims et al., 2013; Turnbaugh et al., 2009; Yatsunenko et al., 2012). Familial similarities are usually attributed to shared environmental influences, such as dietary preference, a powerful shaper of microbiome composition (Cotillard et al., 2013; David et al., 2014b; Wu et al., 2011). However, host genetics also play a small but statistically significant role in shaping the composition and structure of the gut microbiome. Studies comparing microbiota between human subjects differing at specific genetic loci have shown gene-microbiota interactions (Khachatryan et al., 2008; Rehman et al., 2011). A more general approach to this question has linked genetic loci with abundances of gut bacteria in mice (Benson et al., 2010; McKnite et al., 2012), although diet effects outweigh the host genotype effects (Parks et al., 2013). In humans, earlier twin studies failed to reveal significant genotype effects on microbiome diversity (Turnbaugh et al., 2009; Yatsunenko et al., 2012). However, a recent report by Goodrich et al. (2014) comparing monozygotic (MZ) with dizygotic (DZ) twin pairs identified specific taxa as heritable (i.e., the variability in the relative abundances of these taxa across the population was partially driven by host genotype variation). These taxa include health-associated *Faecalibacterium* and *Bifidobacterium* and lean phenotype-mediating *Christensenella* (Goodrich et al., 2014).

Host Immune Systems and Microbiota Homeostasis

Plants and animals each engage structurally related pattern recognition receptors (PRRs) for recognition of evolutionarily conserved non-self microbial structures (i.e., lipopolysaccharides [LPS], lipopeptides, flagellin, chitin) at the cell surface, and activation of these is typically sufficient to halt microbial proliferation. However, successful plant and animal pathogens have evolved mechanisms to dampen or escape PRR-mediated host responses to foster virulence. In response, members of the NLR (nucleotide-binding domain leucine-rich repeat containing) family of intracellular immune receptors in plants and animals are activated by the action of pathogen virulence factors or by direct binding of the virulence factors themselves (Boller and Felix, 2009; Jones and Dangl, 2006; Maekawa et al., 2011). Active animal PRRs and NLR inflammasomes each can instruct the mammalian adaptive immune system and cause spatially dispersed response in plants, as detailed below.

Detection of microbial patterns via PRRs constitutes the first layer of immunity in plants and animals and triggers a variety of output responses. In animals, these include instruction and

either activation or suppression of the adaptive immune system via cytokine signaling and cell migration to and from infection sites and lymphoid organs. Because there are no circulating cells in plants, PRR- and NLR-dependent signaling can lead to differential local and systemic signals that result in adequate defense outputs at and directly surrounding the site of infection and a poised defense in distal organs. Analogous to cytokines, plants deploy a handful of defense phytohormones that have variable domains of signaling and instruct cells neighboring an infection site, and even systemically to distal organs, to be ready to respond to infection (Pieterse et al., 2012).

The lack of circulating immunocytes also demands that each plant cell in an organ be capable of recognizing all pathogens adapted to that organ. This drives a complicated requirement for coordination of normal cellular functions, mediated by growth-regulating hormones, and immune output mediated by the defense phytohormones. This coordination is manifested as trade-offs between growth and immunity (Belkhadir and Jallais, 2015). Thus, systemic acquired resistance in above-ground organs is triggered by biotrophic pathogens and mediated by salicylic acid (SA), while induced systemic resistance, also active in leaves, is triggered in roots by rhizobacteria and is mediated by jasmonic acid (JA) and ethylene (Spoel and Dong, 2008; van Loon et al., 1998).

Because plant defense phytohormones are key signaling molecules between microbial perception and immune system outputs, their production and perception are common pathways targeted by both potential pathogens and beneficial microbes. Hence, there is evidence that during the early stages of colonization both arbuscular mycorrhizal (AM) and *Rhizobium* species locally suppress SA signaling (García-Garrido and Ocampo, 2002; Stacey et al., 2006), suggesting that defense phytohormones normally act to inhibit microbial survival in the root. Indeed, culture-dependent studies in *A. thaliana* have demonstrated a significantly lower load of culturable bacteria in rhizospheres of plants with either defective JA signaling or, conversely, constitutive SA production (Doornbos et al., 2011). Beyond defense phytohormones, other immune outputs have also been implicated by recent studies. In particular, metagenomic studies in rice uncovered genes present in root endophytic bacteria, notably detoxification of reactive oxygen species (Sessitsch et al., 2012).

The overall structure of the *Arabidopsis* root microbiota remains largely robust to host mutations leading to hypo- or hyper-immunity. However, sets of mutants with altered defense phytohormone biosynthesis and/or perception had specifically altered root microbiome taxonomic compositions compared to wild-type. These alterations were congruent with the known effects of the mutants on immune system outputs in leaves. Experiments using both wild soil and its natural community or synthetic soil microcosms in the presence of a synthetic bacterial community demonstrated that SA and/or SA-dependent processes are major contributors to root microbiome

Figure 5. Phylogenetic Analysis of OTU Abundances

(A) Phylogeny inferred from the representative sequences of all OTUs that had at least 0.1% relative abundance on average for all samples of a host species (1,133 in total). The color of each leaf depicts the taxonomic classification of its corresponding OTU.
(B) Average relative abundances of abundant OTUs across all samples of each host (log-transformed). Note that in the case of plant hosts, abundances are averaged across all root compartments.

composition (S.L., unpublished data). Together, these studies represent some of the insights into mechanisms used by the plant immune system to shape its microbiota.

In the animal gut, a first line of defense consists of the secretion of antimicrobial peptides that are produced deep within the crevices of the epithelial layer, in the crypts between the villi. While some antimicrobial agents are continuously secreted, others are secreted in response to bacterial triggering of specific PRRs (Toll-like receptors, TLRs) on the epithelial cell surfaces. The mucus layer is crucial to prevent systematic activation of these immune responses. When the inner mucus layer is removed chemically (i.e., with dextran sodium sulfate [DSS]) or through gene mutation (*MUC2* mutants), bacteria come into contact with epithelial cells and cause an inflammatory response (Johansson et al., 2010; Van der Sluis et al., 2006). In contrast to plants, the adaptive immune system also plays a role for sequestering symbiotic bacteria in the lumen through the secretion of immunoglobulin A (IgA) that target epitopes of intestinal bacteria. Like the antimicrobial activity of the innate immune system, the adaptive immune system can be regulated in parts by TLR signaling (Iwasaki and Medzhitov, 2010). Together, the adaptive and innate immune systems have mechanisms for detecting surface-associated bacteria and work together to reduce inflammation. Because the adaptive immune system is (largely) unique to vertebrates, and based on the observation that vertebrates, notably mammals, harbor microbial communities with much greater complexity than do invertebrates, McFall-Ngai et al. (2013) have proposed that the adaptive immune system itself is important in the shaping and maintenance of high microbial diversity.

Co-diversification of Host-Microbe Communities

By comparing the bacterial communities associated with maize genotypes or other grasses, a significant correlation between rhizobacterial communities and the host phylogenetic distance has been detected, suggesting that the host's evolutionary history can be a good predictor of root microbiota structure (Bouffaud et al., 2014). A comparison of inter-species host phylogeny and microbiota diversification in four Brassicaceae plant species, including *A. thaliana*, which diverged ~35 Ma revealed only quantitative differences. This diversification cannot be explained solely by the phylogenetic distance of these hosts but likely includes plant species-specific ecological adaptations (Schlaeppli et al., 2014). However, qualitative differences can be observed when comparing more distantly related plant species such as *A. thaliana* and barley (dicotyledonous versus monocotyledonous plants), which diverged ~150 Ma (Bulgarelli et al., 2015). Marked differences in microbiota composition were also reported for *Hydra vulgaris* and *Hydra oligactis*, cnidarian animal groups that diverged approximately 100 Ma and have been cultivated under identical laboratory conditions for decades (Franzenburg et al., 2013).

In mammals, similarities in microbial community composition between members of the same species raise the question of whether the bacterial communities track mammalian phylogeny. This would be expected if the bacteria are passed vertically from parent to offspring, which some mammal species encourage behaviorally. Patterns of relatedness of the bacterial communities were compared to the mammalian phylogeny (Ley et al.,

2008a). For subsets of the mammalian phylogeny, the trees matched at a rate that is greater than expected by chance. For instance, this pattern was observed in the case of bears, which are an animal group candidate for mother-offspring transmission due to prolonged contact between the cub and the mother, implying that an ancestral microbial population diversified at the same time that bears speciated. A comparison of the microbial communities associated to great ape species, including *Homo sapiens*, also revealed that the host species phylogeny was congruent to the pattern of relatedness of their gut microbial communities, which diverged in a manner consistent with vertical inheritance (Ochman et al., 2010). However, a comparative analysis of the gut microbiota of humans with the ape species indicates an accelerated change in the microbiota composition of humans that cannot be explained by evolutionary distance (Moeller et al., 2014). A recent study of one isolated Amazonian tribe revealed the highly diverse gut microbiota, in both composition and functions, including a broad range of antibiotic resistance genes, suggesting that the Western lifestyle has dramatically reduced bacterial diversity (Clemente et al., 2015).

Taken together, these data indicate generally that a correlation between microbiota and host phylogeny can be explained by co-diversification from common ancestors. Nonetheless, the hugely different generation times of bacteria compared to their associated eukaryotic hosts together with the high density of microbes in the gut or surrounding the root system suggest that the evolution of host-microbe communities is mainly determined by other selective forces, including microbe-microbe and host-microbe-environment interactions.

Metagenome Analysis-Inferred Functions of the Gut and the Plant Microbiota

The gut microbiota is dominated by a few bacterial phyla, but more variation is observed when focusing on lower taxonomic levels. The relative abundance of individual species can vary over a 10-fold range among individual humans (Spor et al., 2011). In contrast, at the level of gene functions, less variability is observed among individuals, pointing to functional redundancy within the bacterial microbiota and the existence of a conserved functional core (Huttenhower et al., 2012; Turnbaugh et al., 2009).

Given the critical function in nutrient acquisition, it is not surprising that gene functions found in the gut microbial community are influenced by both long- and short-term changes in diet (David et al., 2014b; Muegge et al., 2011; Suez et al., 2014; Wu et al., 2011). Pathways found over all human body parts ("core" pathways) include translational machinery, nucleotide charging, ATP synthesis, and glycolysis (Huttenhower et al., 2012). The functional categories found specifically enriched in the gut microbiota are related to metabolism categories (genes involved in starch, sucrose, and monosaccharide metabolism, including many glycoside hydrolase families). More specifically, functions related to fermentation of complex sugars and glycans to SCFAs, methanogenesis, synthesis of essential amino acids and vitamins, and hydrolysis of phenolic glycosidic conjugates are enriched (Gill et al., 2006; Huttenhower et al., 2012; Qin et al., 2010; Turnbaugh et al., 2009). Some of these functions, such as fermentation and carbohydrate metabolism and vitamin biosynthesis, are also highly expressed in the gut microbiome,

as assessed by metatranscriptome analysis (Turnbaugh et al., 2010).

For plant studies, experimental design is more standardized across individuals, which often allows for direct or indirect tests of functional enrichment (Bulgarelli et al., 2015; Mendes et al., 2014; Ofek-Lalzar et al., 2014), in contrast to the human gut microbiome. Shared functional categories found across at least two plant rhizosphere studies relate to iron transport and metabolism, nitrogen metabolism, transport and secretion systems, as well as chemotaxis and motility (Mendes et al., 2014; Ofek-Lalzar et al., 2014; Sessitsch et al., 2012). Similar functions were also found in a metaproteogenomics study of the rice rhizosphere, although in addition, a major role for one-carbon compound recycling could be identified (Knief et al., 2012). However, considerable differences were found in these studies, and additionally no specific function can be assigned for a large proportion of annotated genes in metagenomic studies (42%–86% in the gut; 59% in the plant rhizosphere) (Gill et al., 2006; Huttenhower et al., 2012; Ofek-Lalzar et al., 2014; Qin et al., 2010). A striking commonality between the gut and root metagenome studies is the significant enrichment/high abundance of phage-related functions (Bulgarelli et al., 2015; Qin et al., 2010), but the exact role of these functions is not known.

To gain further insight into the evolutionary forces acting on genes in relation to their functional roles, natural selection was assessed using dN/dS ratios for gene families in the barley rhizosphere and human gut microbiomes (Bulgarelli et al., 2015; Schloissnig et al., 2013). Positive selection is a hallmark of protein families implicated in molecular arms races between two competing organisms. In the rhizosphere, proteins involved in host-pathogen interactions showed significant signs of positive selection, such as the type III secretion system and its associated effectors, phage elements, and microbial CRISPR proteins (Bulgarelli et al., 2015). Similarly, CRISPR-related families, as well as transposases and families related to antibiotic resistance, showed signatures of positive selection in the human gut microbiome (Schloissnig et al., 2013).

Concluding Remarks and Perspectives

To complement large-scale community profile and metagenome studies, reference collections of several hundred isolates from different human body sites and their corresponding genome sequences have been generated (Goodman et al., 2011). For plant-associated microbial communities, similar projects aiming to maximize phylogenetic diversity of cultured bacteria through cross-referencing with culture-independent community profiling experiments are about to be concluded (P.S.-L. and J.L.D., unpublished data). In the future, these genome collections may allow determination of multi-locus reference gene collections for the identification of individual strains within a community, as an alternative to lower-resolution 16S rRNA-based taxon identification, as well as comparative analyses of thousands of genomes for association-based analyses, to link genes and genetic variants to particular phenotypes. The construction of defined (synthetic) communities and their assessment under controlled environments with germ-free eukaryotic hosts allows studies of community resilience and responses to perturbation at the level of individual members and simplifies testing of specific hypotheses relating to individual attributes of other community

members and the host (Faith et al., 2014; Guttman et al., 2014). Controlled experimental systems will reduce the noise inherent to any natural environmental sample and will drive the next phase of plant and gut microbiota research in which scientific conclusions are based on causation rather than correlations.

For a detailed description of the meta-analysis, see [Supplemental Experimental Procedures](#). The OTU count matrices and taxonomic information as well as the scripts used to analyze the data and generate the figures of this study are available at http://www.mpipz.mpg.de/R_scripts.

SUPPLEMENTAL INFORMATION

Supplemental Information includes Supplemental Experimental Procedures, one figure, and one table and can be found with this article online at <http://dx.doi.org/10.1016/j.chom.2015.04.009>.

AUTHOR CONTRIBUTIONS

S.H., R.G.-O., S.S., and P.S.-L. designed research. R.G.-O., A.G., and R.K. designed and R.G.-O., A.G., and G.A. performed the computational analysis. S.H., R.G.-O., S.S., S.L., A.C.M., J.L.D., R.K., R.L., and P.S.-L. wrote the paper.

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