Biologists have long appreciated the roles that microbes play in the two distinct disciplines of pathogenesis and ecosystem cycling. However, it was not until the late 1970s that Carl Woese and George Fox opened a new research frontier by producing sequence-based measures of phylogenetic relationships, revealing the deep evolutionary history shared by all living organisms (1). This game-changing advance catalyzed a rapid development and application of molecular sequencing technologies, which allowed biologists for the first time to recognize the true diversity, ubiquity, and functional capacity of microorganisms (2). This recognition, in turn, has led to a new understanding of the biology of plants and animals, one that reflects strong interdependencies that exist between these complex multicellular organisms and their associated microbes (3).

Although the biosphere comprises many diverse taxonomic groups, our focus here is principally on the interactions between one group of microorganisms, the domain Bacteria, and one group of complex multicellular organisms, the animals. Although we chose to focus on animal–bacterial interactions, we expect the application of new technology to reveal similar trends among and between Archaea, fungi, plants, and animals. We begin by describing what we know about the evolution of animals and their interactions with bacteria and about the influence that these relationships have had on the present-day genomic makeup of the partners. We review the wealth of new data on the roles of bacteria in animal development and physiology and conclude with a discussion of the nesting of animal–bacterial relationships within their larger ecological frameworks. We argue that interactions between animals and microbes...
are not specialized occurrences but rather are fundamentally important aspects of animal biology from development to systems ecology.

In addition to the references of the main text of this article, we include a list of useful citations to provide the reader a broad opening to the subtopics covered in this contribution (SI Suggested Readings).

**Bacteria and the Origin of Animals**

Understanding how associations among bacteria and animals first evolved may reveal the foundations of ecological rules that govern such interactions today. Animals diverged from their protistan ancestors 700–800 Mya, some 3 billion years after bacterial life originated and as much as 1 billion years after the first appearance of eukaryotic cells (4) (Fig. 1). Thus, the current-day relationships of protists with bacteria, from predation to obligate and beneficial symbiosis (5, 6), were likely already operating when animals first appeared. Attention to this ancient repertoire of eukaryote–bacterial interactions can provide important insights into larger questions in metazoan evolution, from the origins of complex multicellularity to the drivers of morphological complexity itself.

Based on molecular and cellular data, animals and choanoflagellate protists are now considered sister groups, descended from a common choanoflagellate-like ancestor (Fig. 1) (7). The major underpinnings of animal–bacterial interactions—nutrition, recognition, cell adhesion, and signaling—guide two types of choanoflagellate behavior that may have been key to the origin of animals: predation (8) and colony formation (9). Extant choanoflagellates have homologs of animal signaling and adhesion proteins (e.g., cadherins and C-type lectins) that may have arisen as critical facilitators of bactivory (8). Diverse animals respond to bacterial signals as triggers for morphogenesis or behavior (e.g., larval settlement). Thus, the discovery that at least one choanoflagellate, *Salpingoeca rosetta*, responds to signals from specific bacteria to initiate colony formation through cell division hints at an ancient involvement of bacteria in the initiation of multicellularity (9). It will be important to learn whether intercellular cohesion in sponges, which are known to harbor hundreds of bacterial species (10–12), similarly depends on the presence of bacteria. The origin of multicellularity has been a topic of intense debate in biology, and many hypotheses have been developed about how this evolutionary milestone was achieved (13).

A microbial role in animal origins does not obviate other perspectives on the evolution of complex multicellularity but adds a necessary functional and ecological dimension to these considerations.

As early animals diversified, animal–bacterial interactions continued to shape evolution in new ways (Fig. 1C). Bacteria took on a new role in animal nutrition, serving not only as prey but also as producers of digestible molecules in the animal gut. This role may have become more diverse with the evolution of a tubular gut, with one-way passage of food from mouth to anus. Bacterial influence on gut evolution certainly intensified with the subsequent origin of the coelom, a body cavity in which the organs are suspended. The advent of the coelom made gut elongation and regional specialization possible, facilitating both massive ingestion and storage for later digestion. Although the degree to which microbes have driven gut evolution is unknown, the radiation of several animal groups (e.g., ruminants) was undoubtedly enabled by alliances with their gut-associated microbiota. The evolution of form and function in other organ systems (e.g., respiratory, urogenital) may have also been influenced by interactions with bacterial partners (14). Furthermore, it is likely that the evolution of these organ system niches drove radiation of particular clades of animal-associated bacteria (15), such as the genus *Helicobacter* in vertebrate guts (16).

Evolution with animals, whether in symbiosis or via shared habitats, has also influenced the distribution and diversification of bacteria. For example, 90% of the bacterial species in termite guts are not found elsewhere (17). Such specialization, while increasing efficiency, comes with a cost: for every animal species that goes extinct, an unknown number of unique bacterial lineages that have evolved to depend on this animal niche disappear as well (18). On a broader scale, the evolution of animals provided novel physical environments for bacterial colonization, such as aerated deep sediments resulting from animal burrowing. Finally, human activities, which make a range of molecules not previously found in

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**Fig. 1.** Animals through time. (A) Upper atmospheric oxygen concentration, as a percent of current levels, plotted against geological time. (B) Phylogenetic history of life on Earth, scaled to match the oxygen timeline. Note that the origin of the eukaryotes and the subsequent diversification of animals both correspond to periods of increasing atmospheric oxygen. (C) (Left) A phylogeny of choanoflagellates and selected animals, annotated to indicate the evolution of characters particularly relevant to interactions with bacteria. (Right) Interactions between bacteria and eukaryotes, corresponding to the phylogeny. Bacteria are prey, sources of metabolites, inducers of development in symbiosis (morphogenesis) and in larval settlement (environmental cues), and activators of immune systems.
nature, such as halogenated hydrocarbons, have driven selection on bacterial catabolic pathways (19), leaving a signature of our presence in microbial metabolism.

Intertwining Genomes
The long history of shared ancestry and alliances between animals and microbes is reflected in their genomes. Analysis of the large number of full genome sequences presently available reveals that most life forms share approximately one third of their genes, including those encoding central metabolic pathways (20). Not surprisingly, many animal genes are homologs of bacterial genes, mostly derived by descent, but occasionally by gene transfer from bacteria (21). For example, 37% of the ~23,000 human genes have homologs in the Bacteria and Archaea, and another 28% originated in unicellular eukaryotes (20) (Fig. 2). Among these homologous genes are some whose products provide the foundation for signaling between extant animals and bacteria (22).

The intertwining of animal and bacterial genomes is not just historical: by coopting the vastly more diverse genetic repertoire present in its bacterial partners (23), a host can rapidly expand its metabolic potential, thereby extending both its ecological versatility and responsiveness to environmental change. For instance, many invertebrates have intracellular bacterial symbionts whose genes encode metabolic capabilities lacking in animals, such as the synthesis of essential amino acids (24), photosynthesis (25), or chemo-synthesis (26). Certain marine invertebrates that feed on algae maintain algal plastids as photosynthetically active symbionts, a behavior that allows the host to use photosynthese as a food source for extended periods (27). These metabolic add-ons allow the animal to thrive by adapting to otherwise noncompetitive lifestyles (e.g., feeding on nutrient-poor diets such as plant sap) (28) or environments (e.g., oligotrophic habitats) (26). Further, such phenomena fit the definition of epigenetic features. Recent studies have revealed that bacterial pathogens (29) and other environmental factors (30) can alter the activities of epigenetic machinery. It is to be anticipated that such influences will extend to all types of animal–bacterial interactions, including those described above.

Microbial communities in the vertebrate gut respond to the host diet over both daily and evolutionary time scales, endowing animals with the flexibility to digest a wide variety of biomolecules and cope with and even flourish under conditions of diet change (15, 31). For example, the gut microbiome of most people in the United States is adapted to digest a high-fat, high-protein diet, whereas populations in rural Malawi and the Amazonas of Venezuela have distinct microbial consortia and functional gene repertoires optimized for breaking down complex carbohydrates (32). The gut microbiome adapts to changing diets and conditions not only by shifting community membership but also by changing gene content via horizontal gene transfer. For instance, the gut bacterium *Bacteroides plebeus*, found in some Japanese people, bears a gene transferred horizontally from the marine bacterium *Zobellia galactanivorans*, giving the gut symbiont the capacity to degrade seaweed polysaccharides (33). More generally, human-associated bacteria have a 25-fold higher rate of gene transfer than do bacteria in other environments, highlighting the important role of gene transfer in host-associated bacterial communities (34).

Bioinformatic analyses have revealed that interactions with animals also influence the size and content of the genomes of their bacterial partners. Although not all genome-size reduction occurs in symbiosis, a long history of intimate association with insects has resulted in highly reduced genomes in their intracellular symbionts; for example, the endosymbiont *Candidatus Hodgkinia cicadicola* of the Arizona cicada has a genome size <144 kb, smaller than that of some organelles (35). Recent studies have shown that genome reduction also occurs in segmented filamentous bacteria (*Candidatus Savagella*), members of the mammalian microbiota that are critical for the maturation of the immune system (36). Conversely, in *Bacteroides thetaiotaomicron*, another member of the mammalian intestinal microbiota, adaptation to a gut habitat rich in complex carbohydrates has driven the expansion of at least two gene families: glycogen-utilization genes, which constitute 18% of this species’ genome (37), and diverse sulfatases that allow *B. thetaiotaomicron* to digest host mucin (38). The genomic basis for other microbial adaptations among gut microbes is less clear. One possible selection pressure is host temperature. In aquatic environments such as the deep sea, host fishes and invertebrates conform to the temperature of the environment, so temperature-driven coevolution would be unlikely in these habitats. In contrast, terrestrial environments often have broad, short-term (daily) and long-term (seasonal) fluctuations in temperatures. It is in these habitats that endothermy (maintaining a constant body temperature by metabolic means) evolved as a shared character in birds and mammals. Most enteric bacteria of birds and mammals have growth optima at ~40 °C, suggesting the unexplored possibility that this trait resulted from coevolution of these bacteria with their endothermic hosts. The reciprocal may also be true, i.e., an animal’s microbial partners may have played a role in selecting for the trait of endothermy. Constant high temperature speeds up bacterial fermentation, providing rapid and sustained energy input for the host. These benefits are apparent when comparing conventional to germ-free mammals, which require one-third more food to maintain the same body mass (39). Keeping their microbes working at optimum efficiency likely offered a strongly positive selection pressure for the evolution of genes associated with the trait of endothermy in birds and mammals.

**Fig. 2.** The ancestry of humans reflected in the genomic signature. A phylogenetic analysis of the human genes reveals the relative percentage of the genome that arose at a series of stages in biological evolution (20).

**Partners in Animal Development**
Animal development has traditionally been viewed as an autonomous process directed by the genome. Because it both originated and evolved in a microbe-rich environment, animal development deserves a reexamination, at least in part, as an orchestration of animal-encoded ontogeny and interdomain communication (40, 41). Although relatively few studies have been reported until recently, these early data lead us to anticipate that microbes play a role in providing signals for multiple developmental steps.

From their earliest stages of development, animals use sophisticated mechanisms to manage their microbial environment. Physical barriers, such as capsules, chorions, and mucus, protect eggs by excluding microbes, and chemical barriers, including antimicrobial peptides (AMPs), shape the composition...
of the associated microbiota (42). Conversely, several animals recruit specific bacteria to their embryonic surfaces to provide protection against potential pathogens (43). For example, the shrimp *Palaeomon macrodactylus* is protected from the fungus *Lagenidium callinectes* by 2,3-indolindoline that is produced by an *Alteromonas* sp. on the embryo's surface (44). Although many animals, including a wide variety of insects, have transovarial (i.e., via the egg to the embryo) transmission of bacterial partners (28, 45), we have no persuasive evidence to date that these microbes or their metabolites influence embryogenesis. Whereas developmentally important symbioses have been documented throughout the postembryonic (larval and juvenile) stages of vertebrate and arthropod life cycles, the roles of symbiotic microbes during normal embryonic development are just beginning to be studied. Unlike vertebrates whose embryos develop inside enclosures that physically block bacterial associations, many invertebrates acquire their symbionts through the female germ line. Here, we may expect to find regulatory signals being generated by microbes and interactions between host and symbiont development (46). It is apparent that evolution has selected for anatomical, cellular, and molecular determinants that act during this period to prepare newborn animals for interactions with the microbial world.

Ample evidence shows that microbes act directly as agents of postembryonic development. For example, fucosyltransferases decorate the surface of the embryonic mammalian intestine with fucose residues that provide a nutrient source for gut microbes, including *B. thetaiotaomicron*, as they colonize the newborn (47). In the squid-vibrio system, a complex organ forms during embryogenesis that facilitates subsequent colonization by the symbiotic bacterium *Vibrio fischeri* (48). The products of horizontally acquired microbes can be essential for a range of developmental functions, including influences on larval growth rate and body size in invertebrates (49), postembryonic maturation and renewal of epithelia in invertebrates and vertebrates (50–53), development and specification of the gut-associated lymphoid tissues in vertebrates (54), activation of the immune system in tsetse flies (55), and normal brain development in mammals (56, 57). Intriguingly, the host regulatory pathways that control immune responses to microbes appear also to have central roles in animal development, underscoring the intimate relationships between development and host–microbe interactions (58, 59).

Perhaps the most pervasive example of microbial signaling in animal development is the induction of settlement and metamorphosis of many marine invertebrate larvae (60). This transition is an absolute requirement for completion of the animal’s life cycle and is contingent on induction by exogenous morphogenetic cues, many of which are produced by bacteria associated with a particular environmental surface (60). Marine invertebrate metamorphoses offer valuable models for exploring the basis of bacterial signaling in animal development in a setting where the very persistence of marine ecosystems depends on it.

Coming full circle, the influence of microbes on animal reproduction can be observed with particular clarity in invertebrates (61). Most insect orders carry vertically transmitted parasites that can affect the processes of sexual determination, maturation, and reproductive success. For example, various *Wolbachia* strains feminize crustacean genetic males, kill males, or induce clonal production of females in some insects (62). However, in one case, the association with a *Wolbachia* strain has become essential for reproduction; the wasp *Asobara tabida* requires this microbe for egg maturation (63). Recent studies have shown that, in both invertebrates and vertebrates, the microbiota can even influence reproductive behavior (64). Changes in cuticular-hydrocarbon profiles linked to specific bacterial symbionts in the gut of *Drosophila melanogaster* correlate with mate choice (65), and several lines of evidence suggest that olfactory cues associated with mate choice in vertebrates are produced by their resident microbiota (66).

**Interdomain Communication**

Although animals and bacteria have different forms and lifestyles, they recognize one another and communicate in part because, as described above, their genomic “dictionaries” share a common and deep evolutionary ancestry. One modality of interdomain communication, that occurring during bacterial pathogenesis, has been extensively explored for over a century. However, how might bacterial signaling structure the biology of the healthy host?

Biologists now know that bacteria have social behaviors, communicating with each other through chemical signaling, such as quorum sensing (67, 68); more recently, interdomain quorum signaling between bacteria and their eukaryotic partners has become evident (22, 69–71). In addition to quorum signals, bacteria use cell-surface-derived molecules to communicate with their hosts, affecting host processes both at the cellular level [e.g., apoptosis, Toll-like receptor (TLR) signaling (52, 72)], as well as at the organ-system level (Fig. 3). Conversely, host-derived signal molecules like nitric oxide (NO) can be sensed directly by microbes (73). It is intriguing to consider that these kinds of communication evolved to maintain an association’s balance with its hundreds of beneficial species and that pathogens have “hijacked” these conversations to enhance their fitness through disease. For example, *Salmonella typhimurium* has adapted the quorum-sensing regulator QseC to act as a receptor for the host hormone norepinephrine and thereby tie the regulation of virulence genes to the hormone’s presence in the tissue (74). Some hosts, such as the marine macroalga *Delisea pulchra*, respond to quorum-signaling pathogens by producing halogenated furanones that act as signal mimics, blocking the microbes’ communication (75).

The gut is likely the site of the most dynamic and consequential bacteria signaling that benefits animal hosts, because of the sheer numbers and diversity of its microbes and the inherent permeability and sensitivity of the gut epithelium. For example, acetate, a short-chain fatty acid (SCFA) produced by the gut bacterium *Acetobacter*, stimulates insulin signaling in *D. melanogaster*, thereby promoting host growth rates and reducing sugar and lipid levels (49). In mammals, SCFAs affect fat deposition, appetite-related hormone titers, and food consumption, which in turn can modulate the composition of the microbiota and have major consequences for health and behavior (76, 77). Not surprisingly, the composition of the gut microbiota and its SCFA production are influenced by diet. The resultant interplay among diet, the microbiota, and their metabolites is, in turn, implicated in the development of major metabolic disorders including obesity and diabetes (78). As much as a third of an animal’s metabolome—i.e., the diversity of molecules carried in its blood—has a microbial origin; thus, the circulatory system extends the chemical impact of the microbiota throughout the human body (79), transporting metabolites that influence the physiology and metabolism of distant organs and perhaps other bacterial communities (80, 81). Some dietary constituents can be modified by gut microbiota into deleterious compounds; for example, the conversion of dietary phosphatidylcholine into the proatherosclerotic metabolite, trimethylamine, can jeopardize cardiovascular health (82). Furthermore, recent studies link the gut microbiota to...
Innate immune system can have enormous complexity of components that constitute this system representing the healthy host and its normal microbiota. Some of the signals promoting this balance are mentioned in the text (green), whereas other representatives are not (black; Tables S1 and S2). The microbiota also influences animal behavior, creating a direct interface with other organisms. AMP, antimicrobial peptides; LPS, lipopolysaccharide; PGN, peptidoglycan; PSA, polysaccharide A; SCFA, short-chain fatty acids; TMA, trimethylamine oxide.

Nested Ecosystems

Since the dawn of metazoan evolution, the ecology of animals has depended on bacterial communities. The fossil record provides evidence that some animal forms in the Ediacaran grazed on dense assemblages of bacteria on hard substrates (96) and that burrowing animals originated in association with microbial mats (97). Biologists increasingly recognize that, in extant animals, developmental and physiological signaling are processes whose understanding benefits from an ecological perspective (98).

Viewing animals as host–microbe ecosystems has given us new insights into the maintenance of human health. The application of ecological approaches, including successional assembly and diversity analysis, has proven valuable in understanding how animal–microbial alliances function (99–101). For example, human infants born vaginally have a very different succession during the early phases of gut colonization and possibly long-term composition of their microbiota than those delivered by Caesarean section (102). The effects of this difference in infant delivery on adult health remain to be discovered. We know that imbalances in the mature human microbiome have been correlated with a spectrum of diseases, including obesity and diabetes (77). A recent metacommunity analysis of the gut microbiota of obese and lean twins revealed that obesity is associated with a significantly less stable and more variable microbial community (103). Although most research on consortia is currently focused on humans and vertebrate model systems, such as mice and zebrafish, similarly complex interactions occur in all animal species. Viewing bacterial colonization of animals as an ecological phenomenon adds clarity to an understanding of the mechanisms and routes by which phylogenetically rich and functionally diverse microbial communities become established and evolve on and within animal hosts.

An ecological perspective influences not only our understanding of animal–microbiome interactions but also their greater role in biology. The ecosystem that is an individual animal and its many microbial communities [i.e., the holobiont (104)] does not...
Bacteria are critical determinants of animal population and community structures, even in ecosystems where intimate symbioses are not the driving force. Recent studies demonstrate that the larvae of many benthic marine invertebrates require specific microbial cues for their recruitment from the plankton, and these larval responses to bacteria influence the structuring of many marine benthic communities (60, 107). For example, certain strains of the biofilm-forming bacterium *Pseudoalteromonas luteoviolacea* produce chemical cues that stimulate settlement and metamorphosis by *Hydroides elegans*, a polychaete worm that fouls docks and the hulls of ships worldwide (60, 108), as well as a sea urchin (109) and a coral (107). Surface biofilms on many marine animals serve important functions in determining the very nature of the animals’ ecological interactions with other organisms (110). Similarly, the acquisition of an appropriate microbiome at critical life history stages of many animals affects their subsequent behavioral patterns and thus the stability of their ecological roles in their communities (64). Bacteria feeding on dead animals in the sea, and likely on land, repel animal scavengers by producing noxious metabolites; these products allow the bacteria to effectively outcompete organisms 10,000 times their size (111).

Conversely, invasive animals can alter the activities of indigenous bacteria, with significant effects on their shared habitat. For example, rats introduced onto small Pacific islands decimated seabird populations, resulting in decreased sea-to-land transport of nutrients (guano) and altered decomposition and nutrient cycling by soil microbes (112). In another study, European earthworm species introduced to North American hardwood forests led to significant changes in soil microbial biomass and the metabolic quotient of the soil ecosystem (113). In each of these situations, an introduction led to a substantial reduction in ecosystem productivity. Applying metacommunity and network analyses (114) to such animal–bacterial interactions will be essential for the design of effective strategies for managing ecosystems in the face of the environmental perturbations, such as pollution, invasive species, and global climate change, that challenge the biosphere.

**Challenges**

For much of her professional career, Lynn Margulis (1938–2011), a controversial visionary in biology, predicted that we would come to recognize the impact of the microbial world on the form and function of the entire biosphere, from its molecular structure to its ecosystems. The weight of evidence supporting this view has finally reached a tipping point. The examples come from animal–bacterial interactions, as described here, and also from relationships between and among viruses, Archaea, protists, plants, and fungi. These new data are demanding a reexamination of the very concepts of what constitutes a genome, a population, an environment, and an organism. Similarly, features once considered exceptional, such as symbiosis, are now recognized as likely the rule, and novel models for research are emerging across biology. As a consequence, the New Synthesis of the 1930s and beyond must be reconsidered in terms of three areas in which it has proven weakest: symbiosis, development, and microbiology (115). One of these areas, microbiology, presents particular challenges both to the species concept, as formulated by Ernst Mayr in 1942, and to the concept that vertical transmission of genetic information is the only motor of selectable evolutionary change.

It is imperative that human societies recognize the centrality of the relationships between microbes and other organisms for the health of both individuals and the environments in which they live. The current focus on studies of humans and their microbiota has provided compelling evidence that the composition and activity of resident microbes play crucial roles in shaping the metabolic and regulatory networks that define good health, as well as a spectrum of disease states. Nonetheless, the underlying ecological mechanisms are still poorly defined, and the development of tools to translate this understanding into novel therapies presents an ongoing challenge.

In broader-scale ecosystems, evidence is mounting that seemingly minor environmental perturbations have major long-term impacts. A full understanding of the consequences will require us to expand our investigations of the associated changes in microbial communities in soil, freshwater, and marine habitats. How are such microbial assemblages affected by the introduction of nonnative species of plants and animals, the increases in temperature due to global climate change, and the acidification of the oceans? Although a few studies (116, 117) have revealed its importance, the impact of acidification has thus far focused largely on eukaryotic calcification processes (118). This emphasis leaves us still ignorant of how marine ecosystems may be changed if small shifts in seawater pH or temperature alter the compositions of bacterial...
communities that are crucial for recruitment of plants and animals into their native habitats. The maintenance and restoration of ecosystems that support sustainable agriculture and carbon-neutral energy production depend on recognition of the interactions between microorganisms and animals, plants, and fungi, and the robustness of these relationships in response to anthropogenic and other perturbations. Whether an ecosystem is defined as a single animal or the planet's biosphere, the goal must be to apply an understanding of the relationships between microbes and other organisms to predict and manipulate microbial community structure and activity so as to promote ecosystem health.

These challenges present a vast and exciting frontier for the field of biology and call on life scientists to alter significantly their view of the fundamental nature of the biosphere. Ambitious large-scale interdisciplinary research efforts, such as the Human Microbiome Project and the Earth Microbiome Project, aim to provide a basic understanding of microbial variation across a wide range of body and environmental habitats in both the normal and perturbed states. Effective project design and the resulting large data sets are driving advances in quantitative methods, such as the creation and refinement of techniques to improve approximation algorithms, dimensionality reduction, and visualization of the results (119). These efforts have highlighted the need for genomic standards, open-source integrated pipelines, and increased low-cost computational power. A compelling goal for the future is to apply these technologies, the resultant data, and the emerging intellectual framework to a wide array of biological questions. Such a synthesis promises to generate a more accurate vision of life on earth.

Successful development of research on our microbial world will result only with the breakdown of intellectual barriers, not only between the subdisciplines of biology, but also across the natural sciences, mathematics, computer science, and engineering. Such integration will be fostered by the active promotion of cross-disciplinary units at universities, collaboration among professional societies, and novel approaches by the funding agencies to support the development of this new frontier (120). The progress of change across the field will also need reformulation of educational goals, including development of ways of teaching biology that are as revolutionary as those that occurred in the 1950s in the wake of both the New Synthesis and the launch of Sputnik. Because of advances described here, we foresee a day when microbiology will be a centerpiece not only of biological research, but also of high school, undergraduate, and graduate biology education.

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regulated by the Wnt pathway and microbial signaling via MyD88. Proc Natl Acad Sci USA 105(10):4570-4575.


Supporting Information

McFall-Ngai et al. 10.1073/pnas.1218525110

Suggested Readings


### Table S1. Examples of signals and receptors used in bacteria to animal communication

<table>
<thead>
<tr>
<th>Bacterial signal</th>
<th>Animal receptor/enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-3 (quorum signal) (1)</td>
<td>Epidermal growth-factor receptor (EGFr)</td>
</tr>
<tr>
<td>Homoserine lactone (quorum signal) (2–4)</td>
<td>?</td>
</tr>
<tr>
<td>Acetate (5)</td>
<td>?</td>
</tr>
<tr>
<td>Butyrate (6, 7)</td>
<td>G protein–coupled receptors (GPR41 and GPR43)</td>
</tr>
<tr>
<td>Bile-acid derivatives (8)</td>
<td>G protein–coupled bile acid receptor 1 (gpbar1)</td>
</tr>
<tr>
<td>Polysaccharide A (PSA) (9)</td>
<td>?</td>
</tr>
<tr>
<td>Trimethylamine (TMA) (10)</td>
<td>Macrophage scavenger receptor</td>
</tr>
<tr>
<td>Tripeptides (12)</td>
<td>Angiotensin converting enzyme (ACE)</td>
</tr>
<tr>
<td>Invasion (13)</td>
<td>Integrin</td>
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<tr>
<td>Peptidoglycan (PGN) (14–16)</td>
<td>Toll-like receptor 4 (TLR4)</td>
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<tr>
<td>Lipopolysaccharide (LPS) (17)</td>
<td>Toll-like receptor 3/9 (TLR3/9)</td>
</tr>
<tr>
<td>N-formyl peptides (19)</td>
<td>Formyl peptide receptors</td>
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<tr>
<td>Several other ligands (20)</td>
<td>Other TLRs, NLRs, RLRs, lectins, etc.</td>
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**Table S2. Examples of signals and receptors used in animal to bacteria communication**

<table>
<thead>
<tr>
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<th>Bacterial receptor/enzyme</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine/norepinephrine (1, 2)</td>
<td>QseC</td>
</tr>
<tr>
<td>Antimicrobial peptides (AMP) (3)</td>
<td>?</td>
</tr>
<tr>
<td>Furanones (4)</td>
<td>LuxR homologs</td>
</tr>
<tr>
<td>Dynorphin (5)</td>
<td>?</td>
</tr>
<tr>
<td>Nitric oxide (NO) (6)</td>
<td>HnoX</td>
</tr>
<tr>
<td>SIgA (7)</td>
<td>?</td>
</tr>
<tr>
<td>E-cadherin (8)</td>
<td>Internalin</td>
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