# Stress as a Normal Cue in the Symbiotic Environment

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## Abstract

All multicellular hosts form associations with groups of microorganisms. These microbial communities can be taxonomically diverse and dynamic, and their persistence is due to robust, and sometimes co-evolved, host microbe and microbe microbe interactions. Chemical and physical sources of stress are prominently situated in this molecular exchange, as cues for cellular responses in symbiotic microbes. Stress in the symbiotic environment may arise from three sources: host tissues, microbe-induced immune responses, or other microbes in the host environment. The responses of microbes to these stresses can be general or highly specialized, and collectively may contribute to the stability of the symbiotic system. In this review, we highlight recent work that emphasizes the role of stress as a cue in the symbiotic environment of plants and animals.

## Keywords

stress response; symbiosis; host microbe; microbiota

## Stress Structures Beneficial Host-Microbe and Microbe-Microbe Interactions

All plants and animals form beneficial associations with microbes. These host associated communities, or microbiota (see Glossary), induce processes such as tissue development [1, 2], that positively influence the physiology of the whole organism [3, 4]. To sustain mutualism, an ecological structure must be maintained such that host and microbiota derive benefit [5, 6]. Host signaling molecules [7], nutrients [8], and sources of chemical or physical stress [9], contribute to this structure (Figure 1, **Key Figure**). The survival of a microbe in the symbiotic milieu is a function of its resistance to host-associated and microbiota-associated stress (Figure 1). The host-tissue environment imposes chemical and physical stresses that constrain community composition [10]. In this context, the host immune system adds further chemical stresses in response to microbe-associated molecular

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patterns (MAMPs) and metabolic activity (Figure 1). Thus, to understand the function of symbiotic microbial communities, it will be necessary to first recognize the how microbes shape, and are shaped by, the host tissue environment.

Defining the functions of the beneficial microbiota of plants and animals is a frontier field in microbiology [11, 12] and the ecological principles that promote and maintain these communities are still poorly understood. Thus, it is of great interest to identify the mechanisms by which the beneficial microbiota interact both with the host, and with other members of the community. In this review, we focus on recent work that illustrates the role of stress as a cue (Box 1) for bacteria in a diversity of model plant and animal symbioses (Figure 2). Although we do not touch on the response of yeast and archaea to host-associated stress, a comprehensive understanding of the role of stress as a cue for microbial symbionts will require investigation of a diversity of microorganisms. We will consider three sources of stress in the context of symbiosis: (i) host tissues, (ii) microbe-stimulated immune responses, and (iii) antagonism or chemical manipulation by other microbes. The microbial response to these three sources of stress may be integrated, and we discuss the importance of understanding stress in the symbiotic environment as a cue that may originate from multiple sources.

**Box 1**

### Is Stress a Signal or Cue?

In this review, we emphasize the function of stress in the symbiotic environment. To understand the role of stress in this environment, it is first necessary to appreciate that stress is generally a cue, but not a signal. Whereas signals evolve to elicit a response in a target organism, cues are not subject to such selective pressure [96]. It is also worth noting that to perceive a signal, there must be selective pressure for the target organism to evolve a receptor. In contrast, a receptive organism may exploit a chemical or physical cue in its environment to surveil neighboring microbes, or the host environment. In this framework, it is clear that the cue need not have evolved in the producing organism for the purpose of eliciting a response in the responding organism. Cues can be sufficient to coordinate a microbe's response to its environment. Host-derived reactive oxygen species, cationic antimicrobial peptides, and microbially produced antibiotics, siderophores, or bacteriocins may act as cues to coordinate the response of the responding organism to the complex stresses of its environment.

## Host Tissues are a Source of Physical and Chemical Stress for Symbiotic Microbes

The chemical and physical heterogeneity of host tissues defines symbiotic habitats within the host. Secreted products such as urea, bile [13], mucus, and gastric acid [14] in animals, or wax and lignocellulose in plants [15] create chemical and physical barriers that restrict colonization. Abiotic stresses, such as desiccation on skin and leaves [16, 17], ultraviolet radiation, or variations in body temperature among host-tissue sites may also restrict colonization to the subset of microbes that can grow within these parameters. In this section,

we highlight recent studies that reveal both variable and conserved attributes of microbial responses to tissue-derived stress in different plants and animals.

Induction of microbial responses to tissue-associated stress may be either specific or general, and the mechanisms of resistance in different types of tissues may be equally varied. For instance, specific responses may help to promote the colonization of the gastric mucosa, or of root nodules, where the kind of stress is either relatively stable, or predictable. In the mammalian stomach, the presence of gastric acid creates a chemical barrier that restricts colonization by most microbes. To overcome this specific tissue chemistry, *Helicobacter pylori* both buffers its proximal environment by expressing urease, and migrates by chemotaxis towards the less acidic crypts of the gastric mucosa [18]. In contrast, responses that can be induced in a variety of environments, and that confer protection against multiple stresses, might be of benefit to symbiotic microbes that colonize tissues that experience variable sources and types of stress, such as the integument, the intestinal lumen, or root or leaf surfaces (Figure 2). For instance, symbiotic species of *Burkholderia* expresses polyhydroxyalkanoate (PHA) to persist in the gut of the stinkbug *Riptortus pedestris* (Figure 2) [19]. PHA is a storage polymer that may help *R. pedestris* persist in an environment where starvation, or diverse stresses that limit nutrient uptake, may arise unpredictably. Thus, the formation of PHA granules may be considered a general protective response. Further characterization of the mechanisms by which symbiotic microbes respond to tissue-derived stress may reveal core strategies by which these responses are cued to promote survival in both stochastic and predictable environments.

## The Immune Response of Plants and Animals is a Source of Stress for Microbial Symbionts

The immune system of plants and animals has evolved to sense and respond to environmental perturbations such as wounding or colonization by microbes. Immune signaling coordinates the response to these perturbations. Receptors for damage-associated molecular patterns (DAMPs) and for MAMPs are broadly conserved within the plant and animal kingdoms. A detailed consideration of microbe-immune signaling is outside the scope of this review, and recent reviews have comprehensively addressed this topic in invertebrate [20], and vertebrate [21] animals, and in plants [22]. Instead, we highlight here several recent studies that illustrate how stresses originating from MAMP-induced immune responses act as cues for the symbiotic microbes of plants and animals.

To colonize the rhizosphere of plants, where microbes associate with a host at the root surface or within the root tissue as a nodule, symbiotic microbes induce responses that protect against immune-associated stresses. One well studied example is the legume *Medicago truncatula* (clover), which recruits its nodule-forming symbiont, *S. meliloti,* in a multi-step signaling process that culminates with the terminal differentiation of *S. meliloti* within the symbiosis-induced root nodules (Figure 2) [23]. Host-associated stresses such as reactive-oxygen species and antimicrobial peptides (AMPs; Box 2) promote the association of beneficial microbes in both the rhizosphere and nodule environment. Whereas *S. meliloti*

responds to reactive-oxygen species by inducing a general stress response, more specialized responses may be induced in response to AMPs.

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**Box 2**

**Antimicrobial Peptides: Conserved Stresses in the Symbiotic Environment**

Peptides produced by the immune function of plants and animals represent an emerging class of specific, and selective, innate-immune effectors that function across an evolutionarily vast spectrum of plant- and animal-microbe mutualisms. Immune peptides contribute to the specificity of animal and plant hosts towards microbial symbionts. In animals, immune peptides are generally antimicrobial. Antimicrobial peptides (AMPs), such as the lectin RegIII-gamma, kill microbes by targeting the bacterial membrane [97, 98]]. Modifications made to membrane biomolecules such as lipopolysaccharide (LPS) and peptidoglycan (PGN) change the charge-distribution on the membrane's surface, and lead to electrostatic repulsion of cationic AMPs: a strategy used by pathogenic *Salmonella* to evade innate-immune killing [99]. Both pathogenic and non-pathogenic species of *Enterococcus* [100], *Vibrio* [101, 102] and *Staphylococcus* [103], incorporate host-derived lipids into the bacterial cell membrane. The gut microbe *Bacteriodes thetaiotamicron* [9] modifies its LPS to resist AMPs, while to persist in the gut of the stinkbug, *R. pedestris*, the β-proteobacterium *Burkholderia sp.* modifies its LPS so that the structure is more sensitive to AMPs, but no longer contains the immune-reactive O-antigen [104]. Future characterization of other classes of lectins, and secreted peptides are likely to reveal additional mechanisms by which these immune proteins contribute to stress in the symbiotic environment. In legumes, nodule-specific cysteine-rich peptides (NCR) perform functions that affect nodulation by nitrogen-fixing *Sinorhizobium meliloti.* Multiple NCR peptides are expressed in the root nodule, yet they perform non-redundant functions: the deletion of the NCR169 abolishes root nodule formation in *M. truncatula* [105], while the NCR211 peptide is required to promote the survival of rhizobial bacterioids in a terminally differentiated, nitrogen-fixing state [27]. Elucidating the mechanisms by which the immune peptides of plants and animals act as specific agents of stress, or perhaps cues in the host environment, is an ongoing area of active research.

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Upon first contact of *S. meliloti* with the roots of *M. truncatula*, LPS produced by these bacteria signals plant immune receptors, inducing an oxidative burst. In response to this stressful cue, *S. meliloti* produces two extracellular polymeric substances (EPS), succinoglycan and galactoglucan [24] (Table 1). The resulting EPS coating on the bacteria is sufficient to confer resistance to hydrogen peroxide in cultured *S. meliloti* [24], and is required for nodule formation [25], suggesting that EPS may promote symbiont survival in response to prolonged exposure to the plant oxidative burst. In other microbes, EPS confers resistance to diverse stresses in addition to reactive oxygen species, such as antibiotics [26]. Once inside the *M. truncatula* root nodule, the differentiation and senescence of *S. meliloti* are cued by nodule-specific cysteine-rich (NCR) peptides [27] (Box 2). Members of this class of peptide are broadly antimicrobial [28], and can both inhibit *S. meliloti* cell division, and induce transcriptional responses consistent with membrane and cytoplasmic stress [29].

The different responses elicited by NCR peptides suggest that resistance mechanisms may be tailored towards specific classes of peptide. Further characterization of the targets of NCR peptides are needed to reveal the mechanisms by which these peptides act as antimicrobials, and to determine how combinations of these peptides contribute to establishing specific associations with host tissues.

The immune response in the phyllosphere is linked to conditions in the rhizosphere; that is, MAMP signaling that takes place at the roots of plants may systemically propagate signaling molecules to aboveground tissues [30]. Apart from this induced systemic resistance, plant tissues in the phyllosphere may also directly respond to MAMP signaling by leaf surface-associated microbes. Two immune functions that contribute to structuring phyllosphere microbiota, oxidative burst and cuticle formation, have been recently studied. The oxidative burst of plants is induced by ethylene, a plant immunity hormone produced in response to MAMPs and/or DAMPs [31]. Deficiencies in ethylene signaling alter the community structure of the *Arabidopsis thaliana* phyllosphere microbiota [32]. Cuticle thickening is also an immune response to MAMP signaling [31], and, like the oxidative burst, the *A. thaliana* wax cuticle shapes microbial community composition [33]. In rice, colonization of the phyllosphere is associated with the enrichment of microbial proteins related to oxidative-stress resistance [34], suggesting that the oxidative burst may be a common immune-associated stress that structures the phyllosphere microbiota of diverse plants (Table 1). The strategies of stress resistance among phyllosphere-colonizing microbes are still not well characterized, and it remains to be seen whether the induction of general responses that are protective against multiple sources of stress dominates among microbes that colonize this habitat.

Like plant-associated microbes, the microbiota of animals is structured by stress derived from immune function. Much like the initial colonization of *M. truncatula* roots by *S. meliloti* (Table 1), the bioluminescent microbial symbiont of the bobtail squid, *Vibrio fischeri,* produces EPS to survive the chemical barriers created by the immune response of the squid's light organ [35, 36]. The regulation of EPS production is specific to certain strains of *V. fischeri*, and a single regulatory locus is required for squid symbionts to colonize their host [37]. Similarly, the Gram-negative bacteria *Sodalis glossinidius* produces EPS to colonize the tsetse fly gut [38], although it is not known whether EPS production is a determinant of host specificity in this system. As in the rhizosphere of *M. truncatula* root nodules, the mouse immune response secretes AMP into the gut mucosa, where only microbes capable of inducing resistance, such as the gut symbiont *Bacteriodes thetaiotamicron* may survive [9]. The immune proteins of the complement system structure bacterial colonization in the medicinal leech, *Hirudo verbana* [39] (Figure 2). *H. verbana* ingests mammalian blood, and complement-susceptible strains of the gut symbiont *Aeromonas veronii* are unable to colonize the leech [39]. Thus, immune-associated stress contributes to establishing and maintaining specific and selective associations between hosts and their beneficial microbes.

The first contact between an animal and its nascent symbionts can induce immune-associated stresses that cue colonization. In the stinkbug *R. pedestris*, symbiotic *Burkholderia* cells repress the transcription of humoral immune enzymes such as lysozyme

and defensin, while inducing expression of genes encoding secreted cysteine-rich antimicrobial peptides [40]. A similar transcriptional pattern has been noted in the bobtail squid *Euprymna scolopes*, which tailors its expression of antimicrobial factors upon contact with *V. fischeri* [41, 42] to promote colonization (Figure 2). The loss of symbiotic algae and other microbes from coral tissue (*i.e.,* 'bleaching') impairs transcription associated with immune function, even after the symbiotic communities have been restored [43], suggesting that signaling between corals and their symbionts shapes the immune-associated stresses of host tissues. Thus, colonization, and likely other physiological processes of symbiotic microbes, are cued by host immune function, and signaling between host and microbiota determines the specificity of immune-associated stress.

The adaptive immune response of animals may produce targeted stresses. In the vertebrate gut, a subset of the microbiota are targets of the adaptive immune protein immunoglobulin A (IgA) [44]. IgA produced in the murine intestine is raised against specific members of the microbiota, including segmented filamentous bacteria (SFB). The genome of SFB encodes peroxidase, catalase and arginase: genes that mitigate oxidative stress [45, 46], suggesting that recognition of SFB by IgA may be accompanied by an oxidative burst. Immunoglobulins specific to the normal gut microbiota have also been found in murine skin lymph nodes [47], indicating that a population of host antibodies may be raised towards members of the beneficial microbiota of other body sites. The function of this population of antibodies remains largely uncharacterized, although expression of *Proteobacteria*-specific IgA during the development of the mouse gut restricts the abundance of this phylum among the microbiota in the adult gut [48]; in addition, *Alcaligenes spp.* exploit the production of gut-associated IgA to colonize restricted habitats, such as Peyer's patches [49]. Future investigation of the population of immunoglobulins raised against non-pathogenic gut microbes is likely to provide insight into the contribution of adaptive-immune stresses to microbial community structure, and the ecological succession of symbiotic microbial communities.

The host may also modify MAMPs produced by the symbiont to modulate its immune responses, and thereby promote colonization. This effect is achieved through enzymes that modify the chemical structures of MAMPs, such as alkaline phosphatase and peptidoglycan-recognition protein. Specifically, the expression of *E. scolopes* alkaline phosphatase (AP) is required to maintain a stable colonization by *V. fischeri*. The MAMP lipopolysaccharide (LPS) is a substrate of AP, suggesting that dephosphorylation of symbiont LPS may help maintain a stable colonization [50]. Similarly, tsetse fly peptidoglycan-recognition protein protects the obligate endosymbiont *Wiggelsworthia* from damaging antimicrobial peptides during the transmission of the microbe to progeny in adult fly milk, presumably by altering the immune-activating structures of the MAMP peptidoglycan (PGN) [51]. Thus, context-dependent modifications made to conserved MAMP signals may contribute to the establishment of specific symbiotic associations. To the best of our knowledge, it remains to be seen whether similar modifications occur in plants.

## Microbe-Derived Stress Shapes Symbiotic Communities

Nutrient secretions from the epidermis of plants or the epithelium of animals are sufficient to scaffold a beneficial microbial community [52, 53]. Within the scaffolding provided by host-derived nutrients, competition among members of the microbiota may make the community more resilient to external perturbation by pathogens, or chemical agents [54]. Bacteriocins [55], antimicrobials [56], reactive oxygen species [57], and bacteriophage [58, 59] are stresses derived from microbes in the host environment that can structure the competition for nutrients among communties. The production of the bacteriocin coproporphyrin III by a human skin-specific *Propionibacterium sp.* induces EPS production by *Staphylococcus aureus*, leading to co-aggregation of the two species [60] (Figure 2). Similarly, antimicrobial production by the symbionts of leaf-cutter ants constrains the composition of the ant's fungal garden [56] (Figure 2). Hydrogen peroxide produced by *Streptococcus oligofermentans* counteracts lactic acid production by *Streptococcus mutans* in the oral microbiota [57], suggesting that the two species may interact within the diffusive limits of their environment. Bacteriophage-mucin binding interactions have been shown to structure colonization of mucosal layers in the mammalian gut [58, 59], and the accumulation of bacteriophage in sputum or EPS may enhance the protective function of this barrier towards antimicrobials or other chemical stresses [61]. In addition, a functional CRISPR foreign DNA defense system is required for *Xenorhabdus nematophila* to colonize the gut of its nematode host [62] (Figure 2), suggesting that bacteriophage may be a stressful attribute of the nematode gut microbiota. It is likely that these and other microbe-associated stresses, combined with tissue and immune-derived stress, constrain the growth and partitioning of nutrients among microbes in the host environment.

Recent work has documented how stable gut communities typically express robustness and resiliency to invasion by pathogens. Specifically, mutualists in the mouse gut prevent colonization by the pathogen *Citrobacter rodentum* by competing for nutrients [63], while the microbial community that inhabits the epithelial surface of the freshwater cnidarian *Hydra vulgaris* is required for resistance to fungal pathogens [64] (Figure 2). In this context, stress is a cue that contributes to the barrier function of the beneficial microbiota. Several other studies highlight the function of microbe-associated stress in colonization resistance. The beneficial mouse-gut microbe *Clostridium scindens* hydrolyzes bile acids, resulting in the inhibition of *C. difficile* [65]. The production of acetate and EPS by *Bifidobacteria spp.* in the gut attenuates the virulence of pathogenic *Escherichia coli* [66] and *C. rodentum* [67], respectively. Antibiotic treatment-induced perturbation of the mouse gut leads to the accumulation of sialic acid, which is liberated from the mucosa by the beneficial microbiota. This sugar promotes the invasion of intestinal pathogens such as *Salmonella enterica* serovar Typhimurium and *Clostridium difficile* [68]. Fermentation by the beneficial microbe *B. thetaiotaomicron* produces succinate, whose accumulation within the antibiotic-perturbed mouse gut creates an additional source of nutrition for enteropathogens like *C. difficile* [69], *E. coli,* and *C. rodentum* [70]. A similar phenomenon has been observed in the antibiotic-treated guts of broiler hens [71, 72], and is a well-known aspect of rumen microbial ecology [14]. In addition, pumpkins have a native microbiota (including members of both the γ-proteobacteria and Gram-positive bacilli) that is antagonistic towards bacterial pathogens of

this plant [73], although the nature of the antagonism is not yet known. Thus, any perturbations of the natural microbial ecology can disturb the flow of substrates in symbiotic communities, thereby either providing nutrition for opportunistic pathogens, or creating a dysbiotic community unable to maintain a stable colonization of the host. Future work that characterizes both the mechanisms underlying these interspecies interactions, and the extent to which microbial community interactions are mediated by the induction of stress responses, will surely provide insight into the role of stress as a cue for the assembly and resilience of symbiotic communities.

## Do Microbial Communities Coordinate Their Response to Stress?

Microbial communities may also structure their response to stress through quorum signaling. The quorum-signaling pheromone AI-2 regulates cellular metabolism and stress responses: *e.g.,* oxidative stress and urease genes are responsive to AI-2 in the gut symbiont *Lactobacillus reuteri* [74], while AI-2 expressed by the mammalian pathogen *Streptococcus pneumoniae* regulates expression of biofilm-formation [75]. AI-2 is encoded by diverse microbial taxa, and can also mediate interspecies communication; in fact, AI-2 produced by *Ruminococcus obeum,* a member of the normal intestinal microbiota, inhibits the transcription of colonization factors encoded by pathogenic *Vibrio cholerae*, thereby mitigating virulence of this intestinal pathogen in the mouse gut [76]. Following antibiotic treatment, AI-2 production by *E. coli* is sufficient to shift the composition of the two main phyla of microbes present in the human gut, *Bacteriodes* and *Firmicutes*, towards a ratio that more closely resembles the composition of a healthy gut [77]. Because AI-2 signaling can mediate communication among species, and targets of AI-2 signaling include elements of the microbial stress response, it will be interesting to discover whether AI-2 signaling coordinates stress responses across species, and perhaps, contributes to the resilience of polymicrobial communities.

## Concluding Remarks and Future Perspectives

The contribution of stress to the physiology and ecology of beneficial microbes is an emerging frontier. Chemical and physical stresses are central to the conserved 'language' of symbiosis, and should be considered a normal attribute of the symbiotic milieu. Similar to MAMP signaling, the ability to produce stresses that cue beneficial host microbe interactions, such as oxidative stress and antimicrobial peptides, is broadly conserved in the plant and animal kingdoms. It is also evident that stress may target specific members of the symbiotic microbiota (*e.g.,* through IgA), or act at the community level (*e.g.,* oxidative burst), and that the microbial response to stress may be general (*e.g.,* secretion of EPS), or tailored towards a specific type of stress (*e.g.,* modifying the structure of LPS to resist host AMP). It remains to be seen whether responses to community-level stress are coordinated by interspecies or inter-kingdom signaling. The diversity of experimentally tractable animal and plant model systems (Figure 2), as well as the ability to study symbiosis in natural populations, will potentiate future work aimed at deciphering conserved and ancient molecular interactions between hosts and their beneficial microbes. Indeed, it may reveal even more central roles for stress in the context of the symbiotic environment.

What questions should direct future research (see Outstanding Questions)? Symbiotic environments are structurally heterogeneous [78], and microbial communities are characterized by their own ecological structure [79–81]. Thus, to understand how stress cues microbes in the host environment, molecular processes must be understood in the context of both host biology and microbial ecology. To make this link will require knowledge of physical and chemical rules that govern the activity of stress molecules specific to the host-tissue environment, as well as knowledge of the spatial and temporal constraints of the cue. Beneficial microbes in plants and animals form symbioses in the context of host biological rhythms and, in some cases, actually contribute to entraining these rhythms [82–87]. Techniques are being developed to visualize the spatial structure of microbiota [88–92], and to map the chemical diversity of symbiotic communities [93]. Perhaps, future initiatives to study the diverse microbial communities of plants and animals [94, 95] will catalyze efforts to fully recognize stress as a cue in the symbiotic environment.

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### Outstanding Questions

What are the conserved and variable mechanisms by which stress cues bacteria, yeast and archaea in the symbiotic environment?

How do host- and microbe-associated stressors structure the assembly and maturation of beneficial microbial communities?

What are the conserved chemical and physical stresses in plants and animals, and how does the response of symbiotic microbes to a stress differ among host environments?

Do species-specific, and inter-species signaling coordinate responses of symbiotic microbes to stress?

Are stressors in the host environment subject to intrinsic biological rhythms?

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## Acknowledgments

## Glossary

**Abiotic**　　　　　　　pertaining to a physical or chemical attribute of an environment that is not derived from living entities within that environment

**Antagonism**　　　　　an interaction in which the behavior of one organism damages or inhibits another

**Bacteriocin**　　　　　a peptide toxin produced by one microbe that generally targets other microbes

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| **Complement system** | small proteins of the vertebrate immune system that circulate in the blood. Complement proteins that are activated by immune signaling bind to microbial targets to enhance the function of antibodies or phagocytic cells |
| **Chemical manipulation** | a compound produced by one organism that alters the gene expression or physiology of another target organism, thereby decreasing the fitness of the target |
| **Chemotaxis** | the migration of an organism in response to a gradient of a chemical stimulus. In bacteria, chemical stimuli are sensed by surface receptors, triggering a signaling cascade that regulates the direction of rotation of the flagellar motor |
| **<u>C</u>lustered** | <u>r</u>egularly <u>i</u>nterspaced <u>s</u>hort <u>p</u>alindromic <u>r</u>epeats (CRISPR), a CRISPR element is a chromosomal locus encoded in many microbes that confers immunity towards mobile genetic elements of foreign origin. In conjunction with CRISPR-associated enzymes, short sequences of DNA complementary to foreign DNA are incorporated as spacers into the CRISPR locus. When expressed, the short sequences bind to target foreign DNA, targeting that DNA for cleavage by CRISPR-associated enzymes. These short segments act as a form of adaptive immunity |
| **Cue** | a chemical or physical stimulus sensed by an organism, and that conveys information about the organism's environment, resulting in a coordinate physiological response. In contrast to a signal, cues do not appear or evolve primarily to produce a response in the organism |
| **Damage-associated molecular pattern (DAMP)** | host molecules that, when detected outside of the cell, trigger unfavorable inflammatory responses. For example, extracellular host DNA may trigger inflammation |
| **Extracellular polymeric substances (EPS)** | molecules secreted by microbes that coat the cell surface. EPS can be a variety of biomolecules, including DNA, protein, and carbohydrate. Some forms of EPS contribute to stress resistance |
| **Habitat** | an environment generally inhabited by a particular species |
| **Humoral immunity** | the branch of adaptive immunity mediated by macromolecules (as opposed to cells) found in extracellular fluids such as secreted antibodies, complement proteins, and certain antimicrobial peptides |
| **Induced systemic resistance** | a type of signaling occurring between select beneficial microbes and plants. The microbes induce an immune response that protects both local and systemic plant tissues from damage by either pathogenic microbes or insect predators |

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| **Lectin** | a type of protein that can bind to cell membranes. They are sugar binding and become the "glyco" portion of glycoconjugates on the membranes. Lectins perform recognition on the cellular and molecular level, and play numerous roles in biological recognition phenomena involving cells, carbohydrates, and proteins. Lectins also mediate attachment and binding of bacteria and viruses to their intended targets |
| **Microbiota** | the community of microorganisms (beneficial, pathogenic, or commensal) that colonize a particular environment, such as the tissues of a plant or animal |
| **Microbe-associated molecular pattern (MAMP)** | conserved signal molecules produced by both beneficial and pathogenic microbes that elicit host innate-immune signaling |
| **Mutualism** | an association of one or more organisms, wherein each partner provides, and derives a benefit, in relation to the other partners |
| **Oxidative burst** | the rapid release of reactive oxygen species from cells, often as part of an immune response |
| **Phyllosphere** | all parts of a plant that are aboveground (stems, leaves, fruit), and that can be colonized by microbes |
| **Quorum signaling** | a type of signaling in which microbes coordinate group responses by sensing the accumulation of specific secreted molecules (*e.g.*, pheromones) |
| **Rhizosphere** | the plant root surface and zone of the surrounding soil into which roots secrete nutrients and signal molecules |
| **Signal** | a chemical or physical stimulus produced by one organism, with the primary purpose of eliciting a response in a target organism |
| **Specificity** | the characteristic of a symbiotic association that results in the interaction being restricted to the members of particular species |
| **Stress** | a chemical or physical agent that, unless mitigated by the induction of a physiological response, will damage the fitness of an organism |

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**Trends Box**

Stress cues the colonization of specific host niches by beneficial microbes.

Microbes cue, and respond to, immune-associated stress.

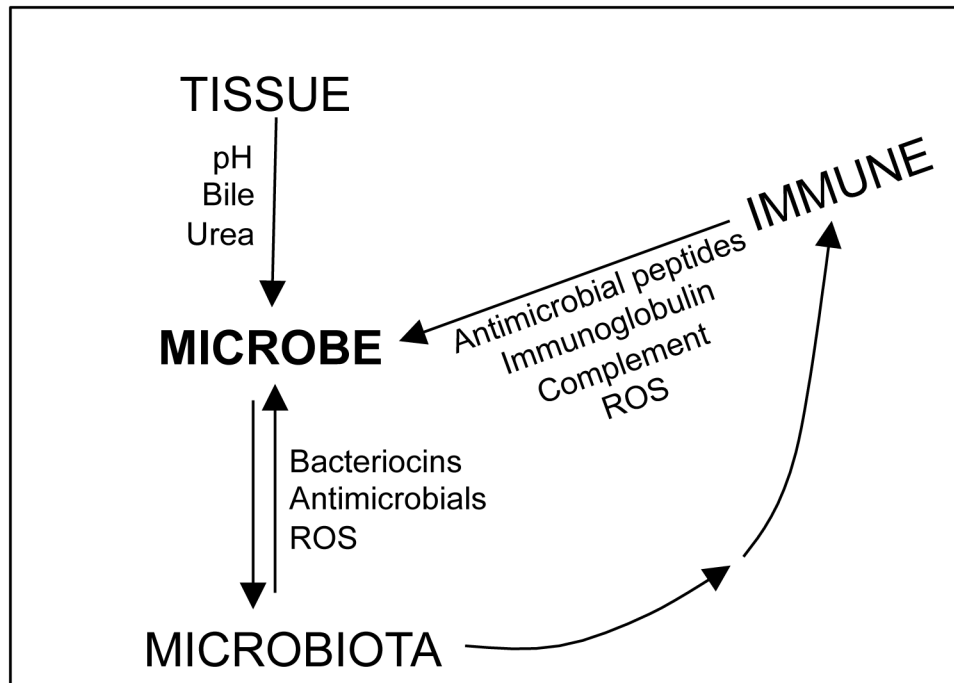Within the beneficial microbiota, stress promotes stability and resilience.

Plant and animal symbiotic communities sense a core set of conserved stresses.

**Figure 1. Three Sources of Stress Define the Host Environment**
Host tissues may be a source of chemical and/or physical stress. The presence of tissue-associated stress is not dependent on microbes. Microbes that can grow within the constraints of the host tissues may, themselves, produce stress through competitive or antagonistic interactions. Microbial activity in host tissues, or interactions with specific microbial taxa within the community, may induce immune-associated stress. Abbreviation: ROS; reactive oxygen species.
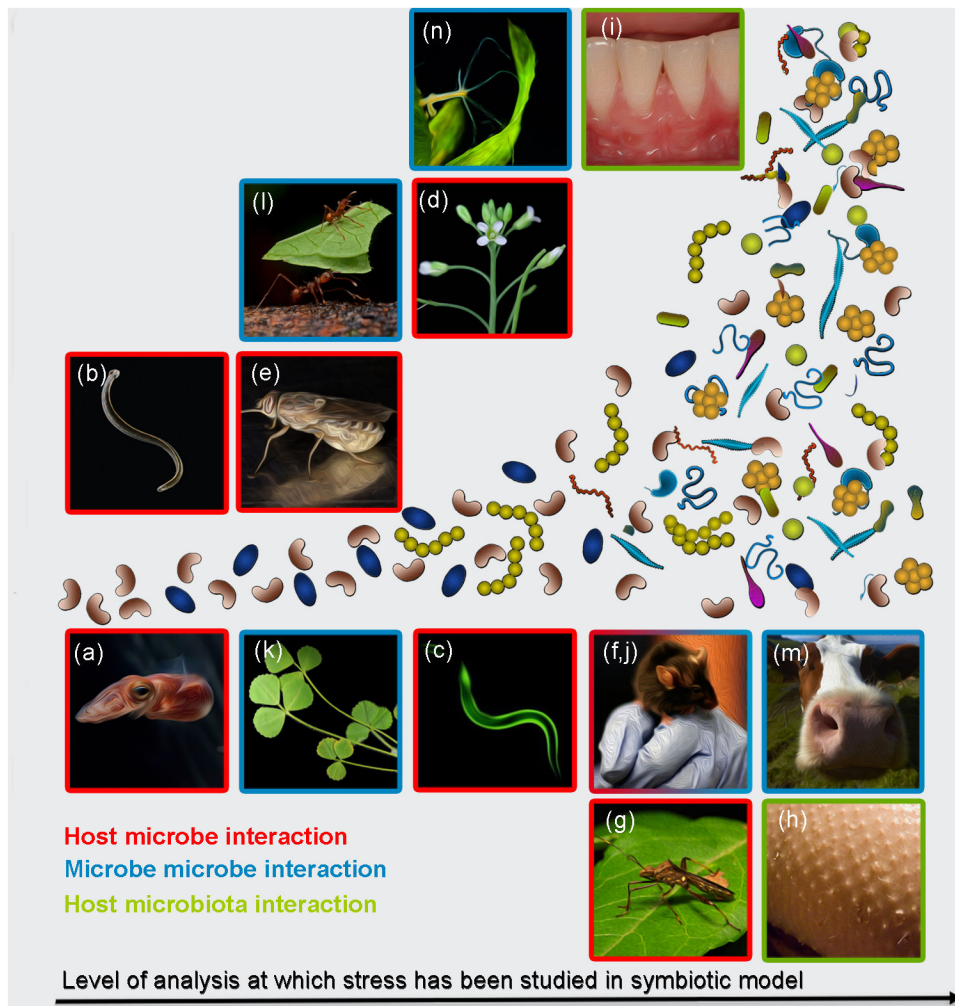
**Figure 2. Host-Microbe Interactions May be Studied at the Level of an Individual Microbial Taxon, or at the Community Level**

Examples of model systems for investigating how a single species of microbe colonizes a host: **(a)** squid-*Vibrio fischeri,* **(b)** leach-*Aeromonas veronii,* **(c)** nematode-*Xenorhabdus spp.*, **(d)** legume-*Sinorhizobium meliloti,* **(e)** tsetse fly-*Sodalis glossinalus,* **(f)** gnotobiotic mouse stomach-*Helicobacter pylori,* and mouse gut-diverse microbes, **(g)** stink bug-*Burkholderia spp.* Tissue sites that have been used to study microbe microbe interactions: **(h)** skin and **(i)** teeth. Examples of host that have been used to study microbial communities: **(j)** the mouse gut, **(k)** *Arabidopsis thaliana,* **(l)** leaf-cutter ants, **(m)** the bovine rumen, and **(n)** *Hydra vulgaris.*

**Table 1**

Conserved Stress Responses Among Microbes in Diverse Host Environments

| Symbiont response | Host Environment | Symbiont | Ref. |
|---|---|---|---|
| EPS[a] production | Squid light organ | *Vibrio fischeri* | [35, 36] |
| | Tsetse fly gut | *Sodalis glossinidius* | [38] |
| | Clover root | *Sinorhizobium meliloti* | [24] |
| Oxidative stress resistance | Leaf surface | Various microbiota | [34] |
| | Roots | *Sinorhizobium meliloti* | [104, 105] |
| | Mouse gut | SFB[b] | [45, 46] |
| Antimicrobial peptide resistance | Hydra mucosa | Various microbiota | [106] |
| | Squid mucus | *Vibrio fischeri* | [107] |
| | Mouse gut | *Salmonella enterica* serovar Typhimurium | [99] |
| | | *Bacteroides thetaiotamicron* | [9] |
| Incorporation of host lipids | Squid light organ | *Vibrio fischeri* | [101] |
| | Mouse gut | *Enterococcus sp.* | [100] |
| | | *Staphylococcus sp.* | [103] |

[a] EPS, extracellular polymeric substance.

[b] SFB, segmented filamentous bacteria. The response is predicted from transcriptional profiling.