Opinion

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Microbial priming of plant and animal immunity: symbionts as developmental signals

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The functional similarity between root and gut microbiota, both contributing to the nutrition and protection of the host, is often overlooked. A central mechanism for efficient protection against pathogens is defense priming, the preconditioning of immunity induced by microbial colonization after germination or birth. Microbiota have been recruited several times in evolution as developmental signals for immunity maturation. Because there is no evidence that microbial signals are more relevant than endogenous ones, we propose a neutral scenario for the evolution of this dependency: any hypothetic endogenous signal can be lost because microbial colonization, reliably occurring at germination or birth, can substitute for it, and without either positive selection or the acquisition of new functions. Dependency of development on symbiotic signals can thus evolve by contingent irreversibility.

Microbiota as a signal for immunity maturation

In Europe, the arrival of swallows and storks, returning from Africa, announces spring to everyone. They give the tempo of the 'martenitsa' tradition in Bulgaria, a celebration of the spring where people exchange white and red tassels, called martenitsi, in early March. Martenitsi are then pinned on clothes until one sees a stork or a swallow, marking the return of spring. The martenitsa is then suspended on a tree (Figure 1) as a gift to Nature's divinities, which are expected to make you safer and happier in the coming spring.

Biotic components can give information about the environment and often represent more integrative indicators of environmental conditions than punctual physicochemical measurements (e.g., daytime temperature or day-length as proxies for spring). For example, plants are commonly used as bioindicators to monitor the presence of pollutants in water. We show here how multicellular organisms similarly use their microbial symbionts (microbiota, see Glossary) in a martenitsa-like way as a signal to set the maturation of immunity and possibly other developmental

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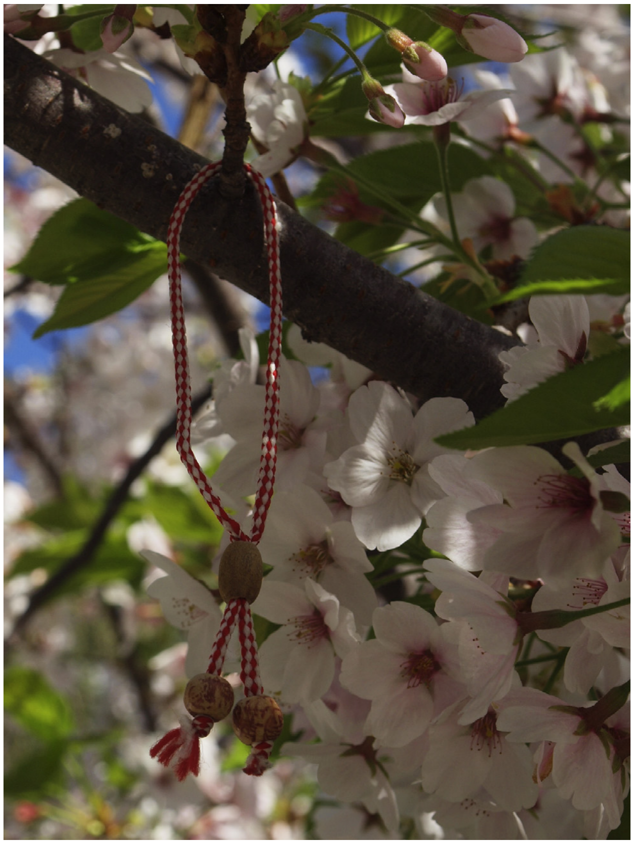
Glossary

Antibiosis: a biological interaction where one organism releases metabolites that are detrimental to one or more other organisms.
Axenic: an environment or an organism that is devoid of microbiota, in other words that is microbiologically sterile.
Contingent irreversibility: an evolutionary mechanism proposed by Maynard Smith and Szathmáry [58] that forces previously independent units to become interdependent without evolution of new functions nor progress, simply by mutational drift (Figure 3). This neutral mechanism, not requiring any positive selection, is often irreversible (ratchet mechanism) because it is unlikely that reversions will restore the previous independence.
Cytokines: small secreted proteins important for cell–cell signaling in animals at low concentrations. They were initially identified in immunity, in which they shape the immune response.
Endophytes: organisms that diffusely grow within living plant tissues, without apparent symptoms of infection.
Immunity: the ability of the organism to resist unwanted, harmful microbes from entering and developing within its tissues. The immune system is the sum of the biological structures and physiological mechanisms taking part in this process.
Induced systemic resistance (ISR): broad-spectrum primed defensive capacity manifested throughout the whole plant, acquired upon local induction by beneficial microorganisms.
Jasmonic acid (JA): plant hormone, structurally similar to animal prostaglandins, with key roles in regulating plant immune responses.
Lymphocyte: white blood cell participating in the vertebrate immune system. The diverse functional types include natural killer cells involved in innate immunity, and cells involved in adaptive immunity such as T cells (that mature in the thymus) and B cells (that produce antibodies). Some T cells (such as regulatory T cells and natural killer T cells) secrete cytokines.
Microbe-associated molecular patterns (MAMPs): conserved microbe-specific molecules such as lipopolysaccharides, peptidoglycans, flagellin, or chitin. Sometimes referred to as pathogen-associated molecular patterns (PAMPs), they are recognized by the innate immune system of animals and plants, but are also developmental signals in plants and animals.
Microbiota (or microbiome): community of microorganisms that live in a specific ecosystem, here mostly referred to the community in close association with a host plant or animal.
Mycorrhiza: symbiotic association between a soil fungus and a plant root, often mutualistic, in which plant photosynthates are exchanged for mineral resources acquired by the fungus from the soil.
Priming: the propensity of a cell, organ, or an organism to react more efficiently to environmental stresses upon appropriate prior stimulation. We focus here mainly on the priming of defenses against biotic stresses, generally of systemic character (see ISR).
Rhizosphere: the portion of soil that surrounds the root and is modified by it. It differs from the bulk soil, especially by its high and differentiated microbial diversity.



TRENDS in Microbiology

Figure 1. Microbial martenitsa. The Bulgarian pagan martenitsa tradition uses the arrival of swallows and storks, migrating back from Africa, as a proxy for the beginning of spring. People exchange white and red tassels, the so-called martenitsi, and wear them pinned on their clothes. When one sees a stork or a swallow, one must hang the martenitsa on a blossoming tree, as seen on this picture. This gift to nature's divinities is supposed to bring luck and success during the next spring. We suggest that an analogous biological mechanism occurs when microbial colonization primes immunity after germination or birth: microbes are proxies for the relevant time of maturation of the immune system, bringing successful defenses against pathogens. This signal allows timely protection of the host, representing a type of microbial martenitsa (photography courtesy of Jilly Bennett).

processes. We first draw a parallel between the priming of plant immunity induced by microbiota surrounding the root and the triggering by gut microbiota of postnatal development of the animal immune system. We then propose an evolutionary framework for the recruitment of symbionts as developmental inducers, and for the use of inter-kingdom rather than endogenous signals for development.

Rhizosphere microbiota warning plants

The soil surrounding roots, termed the rhizosphere, is enriched in dead cells and root secretions, and harbors diverse bacterial and fungal taxa [1]. Rhizosphere microbiota differs from the bulk soil community, and a subset of these microorganisms even enter the root and live as endophytes [2]. This rhizosphere microbiota is extremely dense and diverse, with $>10^{10}$ microbial cells per gram and $>10^6$ taxa [3]. These microbes can be pathogenic or commensal, but most are mutualistic, paying back the host root with nutrients or protection [4,5]. Among other rhizosphere mutualists, mycorrhizal fungi, which form a dual organ associating fungal hyphae and root tissues, are perhaps the best-studied example and have coevolved with land plants since their origin [6]. They provide mineral resources, collected by their soil mycelia, to the root, and receive photosynthates as a reward. Rhizospheric and root endophytic microbes, including mycorrhizal fungi, also protect roots against soil pathogens by competition for space and food, direct antibiosis, and most importantly by inducing plant defense mechanisms that are effective against pathogens [7] (Figure 2).

Mycorrhizal fungi must deal with the plant immune system to colonize the root successfully. A molecular dialog between the symbionts modulates host defenses and triggers a symbiotic program for mycorrhizal development. This modulation acts in two ways. On the one hand, it enhances local tolerance to the mycorrhizal fungus. For example, small secreted fungal peptides injected into root cells [8,9] block specific regulators of plant defense signaling locally, resulting in a partial local desensitization that allows colonization. On the other hand, mycorrhizae also put other tissues or organs of the plant in a warned state, known as 'priming', which allows earlier and enhanced defense responses to pathogen attack compared to non-mycorrhizal (NM) plants [7]. During attack by soil pathogens, primed plants accumulate more pathogenesis-related proteins, callose, and phenolics compared to NM plants [10], and this early and strong reaction is pivotal for successful defense [11]. Priming also spreads systemically in distant parts of the root system and shoots, conferring induced systemic resistance (ISR). Primed plants are thus more efficiently protected than NM plants against foliar pests such as fungal parasites and insect herbivores [10,12].

Other rhizosphere microbes prime local resistance and ISR as well [13]. Plant immunity relies on the recognition of general features of microbial pathogens: the so-called microbe-associated molecular patterns (MAMPs) which include lipopolysaccharides, peptidoglycans, flagellin, and chitin. In addition, damage to host tissues during colonization by pathogens releases damage-associated molecular patterns (DAMPs) that are recognized in plant immunity [14]. MAMPs and DAMPS activate signaling cascades orchestrated by phytohormones such as salicylic acid, ethylene, and jasmonic acid (JA), three major regulators of inducible plant defenses [15]. Beneficial microorganisms also possess MAMPs that trigger immune responses and also may result in the priming of defenses [16]. Several rhizosphere bacteria have been described to induce ISR by way of MAMPs [17], including isolates from diverse bacteria such as *Pseudomonas* and *Bacillus* spp. [17,18]. ISR is also reported for endophytic fungi that colonize root tissues diffusely such as *Trichoderma* spp. [19], sebacinales, and non-pathogenic *Fusarium* strains [20]. Beyond elicitors, the molecular mechanisms involved in priming remain poorly understood, but may include elevated levels of key regulatory proteins such as mitogen-activated protein kinases, transcription factors, and epigenetic modifications [11,21]. Precise molecular crosstalk among the diverse signaling pathways likely explains the apparent paradox between systemic priming of defenses and local desensitization that promotes the establishment of the beneficial microbiota [7,16]. Remarkably, ISR by