

Microbial hub signaling compounds: natural products disproportionately shape microbiome composition and structure

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Abstract

Microbiomes are shaped by abiotic factors like nutrients, oxygen availability, pH, temperature, and so on, but also by biotic factors including low molecular weight organic compounds referred to as natural products (NPs). Based on genome analyses, millions of these compounds are predicted to exist in nature, some of them have found important applications e.g. as antibiotics. Based on recent data I propose a model that some of these compounds function as microbial hub signaling compounds, i.e. they have a higher hierarchical influence on microbiomes. These compounds have direct effects e.g. by inhibiting microorganisms and thereby exclude them from a microbiome (excluded). Some microorganisms do not respond at all (nonresponder), others respond by producing themselves NPs like a second wave of information molecules (message responder) influencing other microorganisms, but conceivably a more limited spectrum. Some microorganisms may respond to the hub compounds with their chemical modification (message modifiers). This way, the modified NPs may have themselves signaling function for a subset of microorganisms. Finally, it is also likely that NPs act as food source (C- and/or N-source) for microorganisms specialized on their degradation. As a consequence, such specialized microorganisms are selectively recruited to the microbiota.

Keywords: microbiome; hub signaling compounds; microbiome composition; shaping microbiomes

Introduction

Nearly every day new data concerning the composition of microbial consortia are published. They impressively demonstrate the diversity of microorganisms in various ecosystems that provide services critical for life. For example, soil offers a habitat for a large diversity of organisms, and is the source of most of our antibiotics. Many of the vital soil functions are due to the activity of microorganisms that regulate nutrient cycling, decompose organic matter, define soil structure, suppress plant diseases, and support plant productivity (Coban et al. 2022, Mason-Jones et al. 2022). However, despite the importance of microbial consortia for a healthy ecosystem, the elucidation of functional interactions between microorganisms that determine the composition of microbial consortia, is still in its infancy. These interactions are decisive for the functioning of microbial communities such as lichens that are composed of microorganisms of different kingdoms like fungi and phototrophic microorganisms, i.e. algae and cyanobacteria, forming complex microbial consortia (Ahmadjian and Jacobs 1981, Grube and Berg 2009). Similarly, microorganisms from different kingdoms drive the assembly of microbiota in preterm infants (Rao et al. 2021).

In most cases, such studies do not answer the questions why distinct microorganisms are members of a defined microbiome and which factors shape its composition. There are abiotic factors like nutrients, oxygen availability, pH, temperature, and so on,

but also biotic factors. The latter include low molecular weight organic compounds that are part of the greater chemical category commonly referred to as natural products (NPs) (Mithofer and Boland 2016, Keller 2019, Traxler and Kolter 2015). However, the ecological role for most of these compounds remains obscure (Macheleidt et al. 2016). An important hint on their role is the finding that their production can be triggered by surrounding microorganisms (Schroeckh et al. 2009). Consequently, many of the gene clusters in microorganisms encoding the biosynthesis of such NPs are silent under conventional laboratory conditions (Bergmann et al. 2007). Their biosynthesis can only be activated when the correct stimulus is provided, which in many cases is another microorganism (e.g. Schroeckh et al. 2009, Hotter et al. 2021). Recently, we discovered a group of special polyketides that we named arginoketides that induce silent gene clusters in diverse fungi (Krespach et al. 2023). Arginoketides have in common a guanidyl group or its reduced form, i.e. an amino group, and are biosynthesized by a specific polyketide synthase containing a loading domain for 4-guanidinobutyryl-CoA (Hong et al. 2013). The guanidyl/amino groups are required for the activity of arginoketides, at least for all the phenotypes tested so far. Arginoketides have a direct impact on microorganisms: they trigger *Chlamydomonas reinhardtii* to hide in fungal mycelia (spatial organization of a microbial consortium) (Krespach et al. 2020) and induce a novel multicellular *C. reinhardtii* structure named gloecapsoids. This way, NPs may

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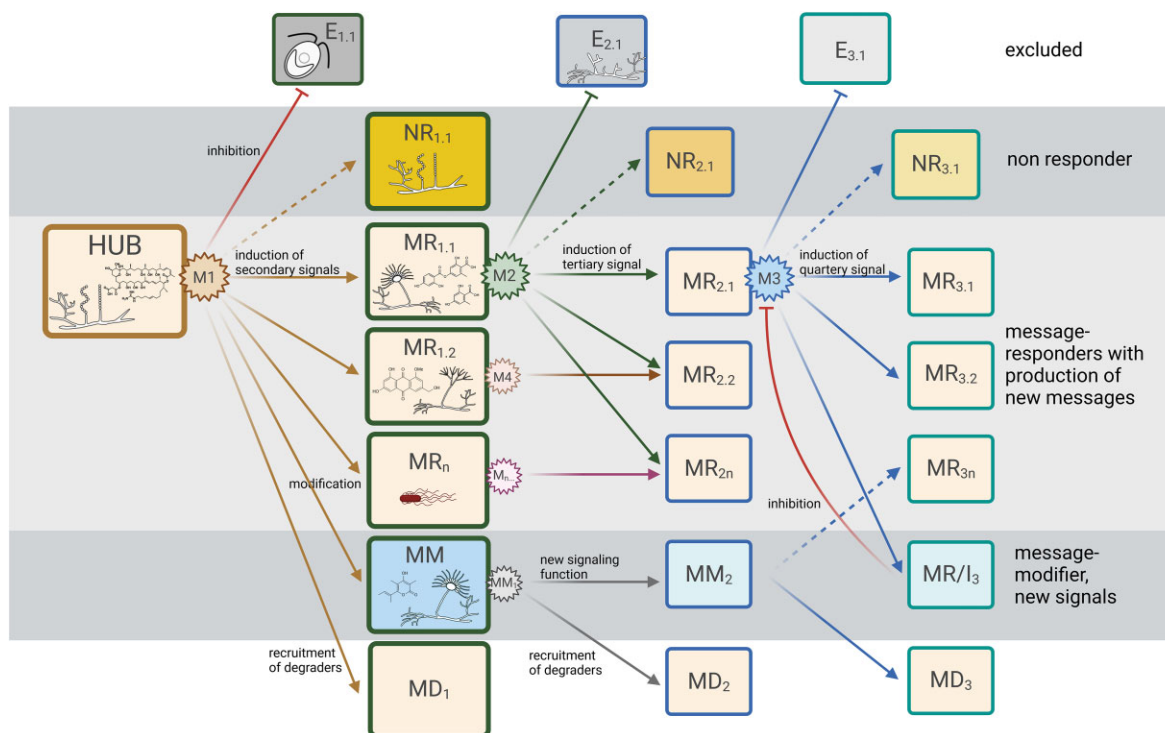


Figure 1. Model of the different effects that Hub signaling compounds can have on the composition and structure of microbiomes. The Figure was created using BioRender.

have contributed to the evolution of multicellularity (Krespach et al. 2021). Arginoketides also have indirect effects, i.e. they trigger in distinct fungi the activation of silent gene clusters (Krespach et al. 2023). The, thus, produced NPs have signaling function themselves, e.g. lecanoric acid of *Aspergillus nidulans* inhibits a plant-pathogenic fungus (Schroeckh et al. 2009, Paguirigan et al. 2022). Arginoketide-producing *Streptomyces* sp. can be found worldwide. Also, from the same soil samples as arginoketide-producing microorganisms fungal responders were isolated. Arginoketides are produced by several phylogenetically diverse *Streptomyces* sp. suggesting that production of this signal molecule is useful for a number of different bacteria in different habitats and that these molecules constitute a cosmopolitan universal signaling system.

Hypothesis

Based on our data and data of others, I hypothesize that arginoketides are ecologically relevant hub signaling compounds that disproportionately impact surrounding microorganisms. This hypothesis is inspired by Agler et al. (2016). The authors postulate hub microorganisms with this function. It is thus conceivable that some of these microorganisms produce hub compounds. Also, producer microorganisms can differ, e.g. the *Streptomyces* species, what is ecologically important is their ability, in this case, to produce arginoketides.

A theoretical frame work could look like the following (Fig. 1). Microorganisms produce distinct hub compounds such as arginoketides. These compounds have direct effects, i.e. they inhibit microorganisms and thereby exclude them from a microbiome (excluded). This is for example the classical antibiotic activity. Some microorganisms do not respond at all (non-responder). Some microorganisms respond to arginoketides by producing themselves NPs like a second wave of information

molecules (message responder). These NPs can have similar functions on other microorganisms like arginoketides, but conceivably on a more limited spectrum of microorganisms and thus extend the spectrum of microorganisms that can be informed by arginoketides. In addition, some microorganisms may respond to the arginoketide signal with its chemical modification (message modifiers) that is known for many NPs (Stallforth et al. 2023). This way, the modified NPs may have themselves signaling function for a subset of microorganisms. Finally, it is also likely that NPs act as food source (C- and/or N-source) for microorganisms specialized on their degradation. As a consequence, such specialized microorganisms are selectively recruited to the microbiota.

It can be expected that there will be several to many hub compounds produced, likely by hub microorganisms, in a microbiome. Thereby signaling foci are generated and influence each other. Also, of course, there will be additional factors including abiotic factors influencing the microbiome composition. Future experiments are needed to falsify this hypothesis.

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