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Antimicrobial discovery inspired by ecological interactions

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Bacteria represent an unparalleled source of antibiotics used to treat infectious diseases. Yet, genome analyses have revealed that their full biosynthetic potential is much larger than expected. Valuable strategies to unearth hidden antibiotics are genome mining, pathway engineering and triggering, as well as co-cultivation approaches. Nevertheless, there is growing understanding that it is often essential to consider the ecological context and that there is a great potential for antimicrobial discovery from bacteria engaged in well-defined interactions with other organisms. Various ecological scenarios involving antimicrobial agents are outlined in this review: predator–prey and pathogenic interactions, the protection of insect assets such as offspring and cultivars, as well as host protection in symbiotic relationships with plants, invertebrates and animals/humans. The illustrative examples given reinforce the idea that examination of interactions between organisms can yield new antimicrobial compounds, and ultimately further our understanding of the function of these molecules in the environment.

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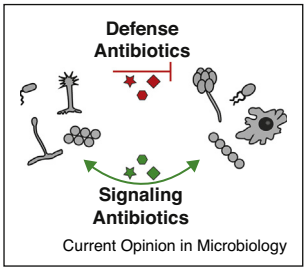
Introduction

With the increasing incidence of infections caused by antibiotic-resistant microorganisms, there is an urgent need for novel antimicrobial compounds [1]. Natural products represent the most important source of anti-infectives in clinical use [2]. Traditionally, scientists have harnessed the abundance of antibiotics found in Nature for natural product discovery, with soil actinomycetes being the dominant source. Bacteria are ubiquitously found in mixed populations, and the antimicrobial compounds they produce are generally considered as weapons for resource and territory defence against biological competitors. However, increasing evidence suggests that natural products initially identified as antibiotics may also serve a more general role as communication cues at sub-inhibitory concentrations [3] (Figure 1). Given the high density of bacteria in the soil, it is not surprising that soil-derived bacteria have provided a wealth of antimicrobials that have evolved and been optimized over millions of years. However, the identification of novel drug leads from such sources has become stymied by the constant rediscovery of known bioactive compounds or compound classes.

With the advent of the genomic era, it has become obvious that under-explored bacteria represent potential sources of antimicrobial diversity [4–6]. Furthermore, even well-studied microbes contain a large untapped biosynthetic potential that remains undetectable in pure cultures under standard laboratory conditions. Obviously, biosynthetic gene clusters are down-regulated or silenced in the absence of appropriate environmental cues or triggers. Thus, known prolific producers have been revisited and attempts made to trigger silent clusters by, for example, varying culture conditions, including simulation of the natural habitat (e.g. addition of soil extract [7]), and performing artificial co-culture with randomly selected microbial interaction partners [8–10]. However, while these approaches proved very fruitful in discovering new natural products, the true ecological context was rarely considered.

Only recently, systematic studies began to focus on drug discovery from well-defined microbial interactions, yielding novel antimicrobial compounds as well as providing insight into their ecological roles. The aim of this review

Figure 1



Antimicrobials play central roles in complex inter-species interactions (e.g. in soil).

is to highlight timely research illustrating the promise that bacterial interspecies interactions hold for antimicrobial discovery efforts. We focus on novel scaffolds with acknowledged or plausible ecological roles, and group the compounds based on their putative ecological function. We first cover bacterial natural products derived from antagonistic interactions (predator–prey, pathogenic), followed by those originating from beneficial interactions (protection of insect assets or host).

Bacterial natural products from predator–prey interactions

Although the soil environment is often viewed as an overmined ecological niche, studying specific microbial interactions and the organisms involved has led to the discovery of new antimicrobials. Perhaps nowhere is this better illustrated than in the characterization of the molecular determinants of predator–prey interactions. Intensive investigation has demonstrated that antimicrobials play a central role in these interactions, being produced by predator and prey alike (Figure 2a). Predatory microbes, including the myxobacteria, actively hunt and kill their prey to consume their macromolecules as nutrients [11]. The Gram-negative, predominantly soil-dwelling myxobacteria are recognized as prolific producers of natural products, including many antibiotics that contribute to lysis of prey bacteria for consumption [12–14].

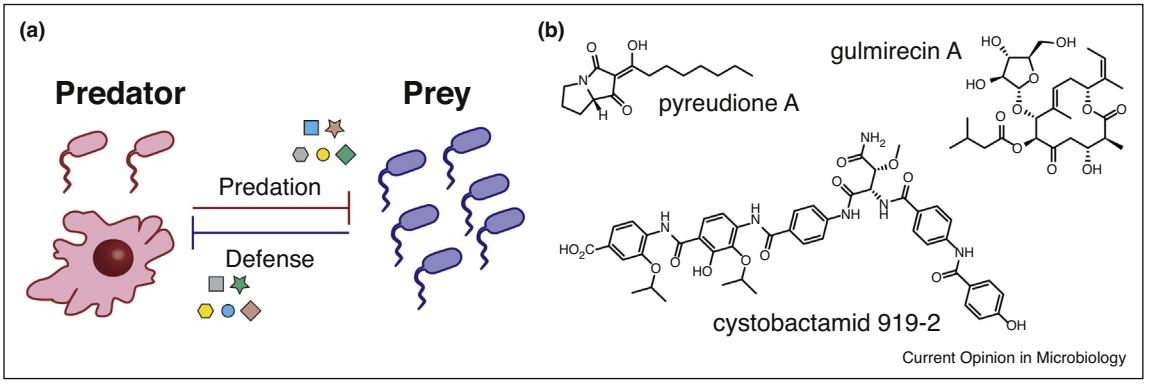
In recent years, diverse antimicrobial scaffolds have been discovered from myxobacterial strains, including anti-Gram-positive polyketides (PKs) [15,16] and antiparasitic [17] and antifungal hybrid polyketide-nonribosomal peptides (PK-NRPs) [18,19]. Although roles in predation have not yet been definitively proven for these antimicrobials, it is worth noting that the antibacterial spectrum of the gulmirecin glycosylated macrolides (Figure 2b) from *Pyxidicoccus fallax* reflects its prey range [15]. Another notable example is the myxobacterial cystobactamids and derivatives [20–23] (Figure 2b), which are unusual nonribosomal peptides (NRPs) that potently inhibit both Gram-positive and Gram-negative bacteria, including ESKAPE pathogens [20–22]. *In vitro* assays demonstrated that the cystobactamids are a new class of gyrase inhibitors with a mechanism of action reminiscent of the well-known quinolone antibiotics [20]. Although it is again tempting to speculate that the cystobactamids are involved in the predatory behaviour of the producer, further research is required to prove this.

Predation exerts intense selective pressure on prey bacteria, which have consequently evolved a variety of protective strategies including the use of antimicrobials [11]. In a recent example, a *Pseudomonas fluorescens* soil isolate was shown to thwart predation by *Dictyostelium discoideum* and other soil-dwelling amoebae by secreting four bicyclic pyrrolizidine alkaloids, pyreudione A–D [24•] (Figure 2b). It is likely that related compounds are widespread since many bacterial genomes harbour genes similar to those involved in the biosynthesis of these amoebicidal agents.

Bacterial natural products from pathogens

Beyond bacteria involved in predator–prey interactions, pathogens that colonize higher organisms potentially represent a rich but understudied source of novel and structurally diverse secondary metabolites with some known to contribute to the virulence potential of the producer [25–27] (Figure 3a). The identification of new antimicrobials from pathogens is not only highly relevant for our understanding of host–pathogen interactions in disease, but also for discovering novel antimicrobial compounds with potential for drug development. For example, bacterial virulence factors that are involved in mushroom or plant diseases may be lead structures for novel antifungals that are active against human pathogens [28,29]. In some cases, the biological activities of virulence factors are fine-tuned and complex, as in *Staphylococcus pseudintermedius*, a commensal of household animals

Figure 2



An arms race exists in predator–prey interactions. A schematic representation of the antagonistic interactions between soil predators and their prey is displayed **(a)** along with representative antimicrobials implicated in such interactions **(b)**.