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Introducing the Parvome: Bioactive Compounds in the Microbial World

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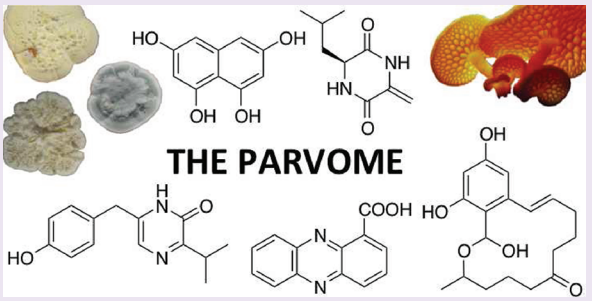
ABSTRACT: We describe and discuss the features and functions of the "parvome", the "-ome" of the chemical world, consisting of the small molecules produced by living organisms. Here, we focus specifically on the world of microbial small molecules. Many years of natural product discovery research, coupled with recent advances and applications of genetic and genomic techniques have revealed the presence of an enormous collection of unique small molecules that are the products of cellular metabolism. As yet, we have a poor understanding of their functions and, in most cases, little knowledge of their routes of biosynthesis, although such information is accruing rapidly. In this review, we attempt to address the raison d'etre of the parvome in the bacterial world, and we propose that a better understanding of the true biological roles of natural products will permit the application of rational approaches to the more effective exploitation of their use in medicine by humankind.



INTRODUCTION TO THE PARVOME AND NATURAL PRODUCT MOLECULES

Modern approaches to small molecule discovery have revealed the existence of an entire world of cell-based molecules; we have proposed to name this the parvome (parv- = small, -ome = group).[1] Just as nearly two decades ago it was farsighted to suggest identifying entire proteomes,[2] we believe it is now prospicient to suggest identifying parvomes. With modern advances in analytical technologies, it will soon be possible to predict all products of cellular metabolism for a given organism. Furthermore, because the biosynthetic machinery is encoded in genomes, it will soon be possible to anticipate structural information for small molecules from genomic annotation. Finally, although understanding and organizing members of a parvome will be challenging, this challenge does not preclude the mission! Our starting point for introducing the parvome is to consider small molecules from microbial species, focusing on the functions of these molecules in the natural world. Accordingly, we must first consider natural products.

Natural products, often called secondary metabolites, are low molecular weight organic molecules made by living organisms such as bacteria, fungi, lichens, marine invertebrates, plants, insects, and (probably) mammals. Important classes of molecules are the polyketides[3] and non-ribosomal peptides,[4,5] and other structural classes are alkaloids, terpenoids, shikimate-derived molecules, and aminoglycosides.[6] These molecules are defined mainly by what they are *not*: they are not broadly distributed among different species, they are not produced at all stages of organismal growth and development, and they are not considered to be essential for the survival of their producing hosts. The interest in these molecules is immense. Natural products have been used by humans since time immemorial for many different purposes: most applications are in medicine, but they are also used as pigments, dyes, fragrances, pain-killers, and poisons. It was not until the mid-19th century until a defined chemical (salicylic acid from plants) was converted into acetylsalicylic acid (aspirin) and used for therapeutic purposes.[7] Subsequently, many more plant compounds became part of the medicine chests of physicians and were appropriately classified as alkaloids, terpenoids, and other structural classes by natural product chemists in the first half of the last century. Their total synthesis continues to challenge generations of synthetic chemists.[8,9] The seminal discovery of the antibiotic activities of microbial products in the mid-20th century led to an explosion of random screening of natural products from fungi and bacteria for therapeutic activity, and hundreds of thousands of microbial metabolites have been isolated and tested as antibiotics.[10,11] It should be noted that the definition of an antibiotic is a substance produced by a microbe that inhibits the growth of other microbes. Many of the isolated antibiotics were characterized chemically by pharmaceutical companies, and it became obvious that the structural diversity of bioactive compounds produced by microbes was beyond man's perception.

The natural functions and biochemical properties of these molecules were ignored during the intensive half-century of antibiotic discovery; all that mattered was that a compound would inhibit growth or kill one or more microbial pathogens. The importance of antibiotics cannot be underestimated; their discovery revolutionized medicine, especially the treatment of bacterial diseases. As extra benefits they have been employed as

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antiviral and antitumor agents with remarkable success, and the unexpected property of compounds such cyclosporin and fujimycin as immunosuppressive agents has completely transformed the use of organ transplantation techniques. The worldwide production of microbially produced pharmaceutical agents is difficult to estimate (especially since almost every country makes them!), but since the initial discoveries of penicillin and streptomycin, billions of kilograms have been produced and employed for human and agricultural purposes. The situation is such that industrial production of microbial compounds is well in excess of what is produced in nature. Additionally, compounds known as statins, obtained from various fungi and used for the control of cardiovascular disease, generate upward of 15 billion US dollars per year in sales. These financials are mentioned to emphasize the fact that the dominant interest in microbial products is as pharmaceutical agents and not as bioactive molecules that play critical roles in the structure and function of microbial communities. If truth be known, the highly focused search for compounds with pharmaceutical applications almost certainly delayed biological studies of the world of small molecules.

From an industrial production aspect, only a small fraction of the low molecular weight compounds produced naturally by microbes, plants, animals, and humans have been studied; our objective is to focus attention on the world of small molecules from a biological point of view. Schreiber has proposed that they should be considered as part of the central dogma of molecular biology [12] (Figure 1). A better appreciation of the

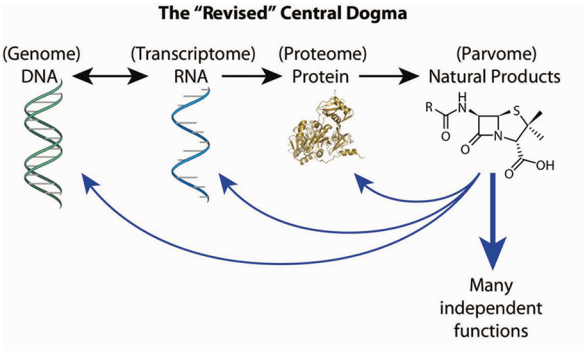

Figure 1. Inclusion of the parvome in the central dogma of biology.

vastness, functions, and diversity of microbial small molecules is needed. What are their roles in their natural hosts in terms of their influence on cell and metabolic effects, such as gene and enzyme regulation and network interactions? Perhaps, more importantly, what are their functions as inter- and intracellular signals or effectors; do they act as controlling agents (antibiotics) as has been suggested from insect/parasite studies in the laboratory,[13] or do they have other functions? What are their host-dependent roles in symbioses and antagonisms, such as pathogenicity? Paracrine, endocrine, and autocrine properties take place at very low concentrations with a wide variety of receptors; how do these activities correlate with small molecule effects on transcription or translation? There are many sources, many functions and most interestingly, numerous medical and other applications that can be exploited, once the manifold roles of the parvome in biology are appreciated.

NATURAL FUNCTIONS OF NATURAL PRODUCTS

Many biological activities have been described for natural products; some may be of natural, environmental significance, but others the applications typical of laboratory or pharmaceutical testing. It is important to realize that laboratory tests of activity do not necessarily represent natural function (however, they may provide valuable clues). Nonetheless they must reflect some aspect of the fundamental biological activities of the compounds. In laboratory testing microbial products demonstrate multiple functions. They may be solids, liquids, or gases and may act in a variety of ways: antibiotics, allosteric regulators, catalysis, catalytic cofactors, regulatory activities at level of DNA, RNA and protein, pigments, mutagens, antimutagens, transcription modulation, riboswitching, codon correction, phage induction, receptor agonists, antagonists, quorum sensing, signal molecules, gene regulation, antitumor, antiviral, antifungal, immune modulation, siderophores, detergents, metal complexing/transporting agents, pheromones, toxins, *etc.* The probability is that small molecules possess a myriad of different natural functions but exhibit antibiotic effects against a given tester strain under the specific conditions employed; the two functions may be related. This may be especially true with microbial cell-signaling agents that bind to specific response receptors; higher (non-physiological) concentrations may "poison" the receptor and result in growth inhibition or cell death.

For microbially produced antibiotics, almost nothing is known about their biological roles. The discovery of potent antimicrobial activity produced by soil bacteria in laboratory tests led Waksman and others to conclude that their natural roles were to provide the weaponry for interspecies conflict in the wild (the war-metaphor). Is there evidence supporting the notion of natural chemical warfare? Precious little, in fact! Once it was demonstrated that sub-inhibitory concentrations of "antibiotics" provoke more subtle effects on microbial behavior, their natural roles were queried: to kill or communicate, that is the question! Of course, both might apply depending on the amount of compound made, although there is little direct evidence for inhibitory activity in nature. Studies of the roles of Actinomycete products as protective agents in insect species have been interpreted to support their roles as weapons,[13] but there are some contradictions concerning these conclusions.[14]

It is essential to discuss parvome products in their true context: their many biological activities in nature provoke metabolic changes, influence host-producer interactions, and also play critical roles in signaling in communities and populations. Further, the compounds produced by one community of bacteria may be quite different than another; different populations have different parvomes. For example, the components of the human microbiome are complex and variable; that of the GI tract is different from that of the skin or vaginal tract. Finally, the bioactive molecules comprising the parvome exhibit a wide range of concentration-dependent biological functions, and knowing the natural concentration may be critical to understanding biological function.

NATURAL CONCENTRATIONS OF NATURAL PRODUCTS

A concentration dependence has been observed for antibiotics. At high concentrations, antibiotics are defined by their inhibition of the growth of target organisms. Antibiotics target translation (*e.g.*, erythromycin), transcription (rifamycin),

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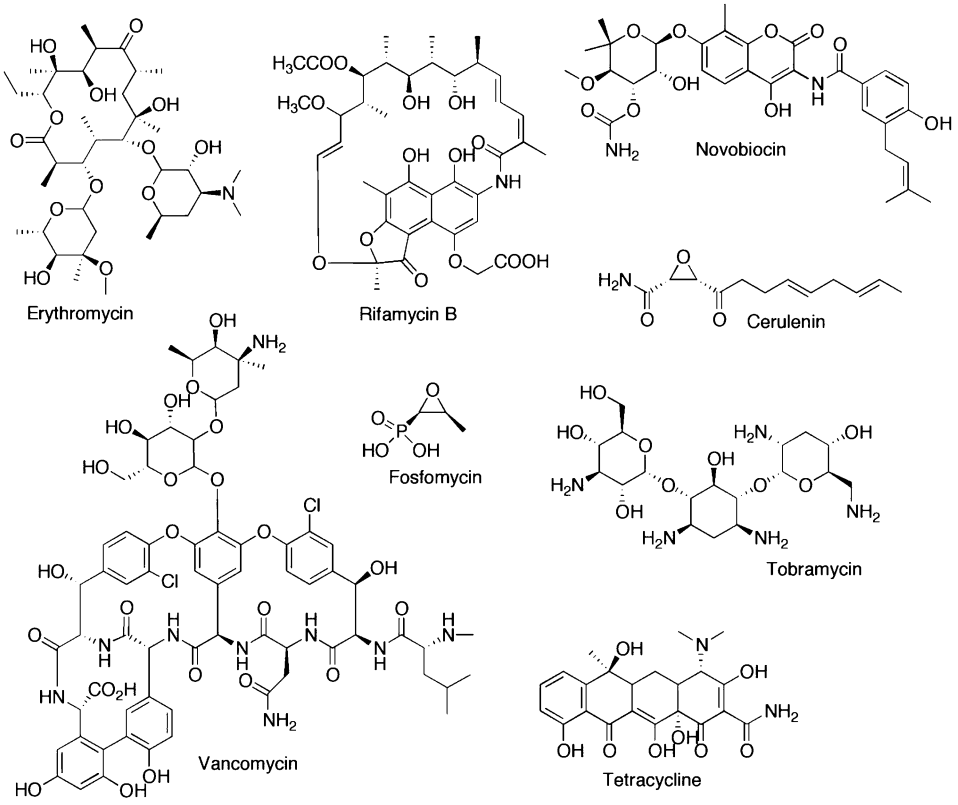

Figure 2. Antibiotics described in the text.

replication (*e.g.*, novobiocin), cell-wall biosynthesis (*e.g.*, fosfomycin, vancomycin), or metabolism (cerulamin) (Figure 2). These effects are thought to be responsible for the ability of antibiotics to inhibit the growth of other bacteria. At lower concentrations, however, antibiotics also exhibit effects that appear unrelated to their inhibitory properties. Sub-inhibitory concentrations of antibiotics induce significant transcriptional changes in bacteria. As many as 5% of the promoters, which are for genes of known and unknown functions, are activated or repressed for a given antibiotic. These results suggest that antibiotics at low concentrations might modulate transcriptional responses in various pathways in a natural environment and might play roles in mediating microbial interactions and communication[15] (Figure 3). Consistent with these roles, it should be noted that sub-inhibitory concentrations of tobramycin, tetracycline, and other compounds induce biofilm formation in *Pseudomonas aeruginosa*. Tobramycin also increases bacterial motility, and tetracycline activates transcription of the type III secretion system.[16] Other antibiotics, azithromycin and ceftazidime, which are synthetic compounds related to natural products, have been shown to inhibit quorum sensing in *Pseudomonas aeruginosa* at sub-inhibitory concentrations.[17] There are numerous "other" activities of antibiotics. These results suggest that sub-inhibitory concentrations of antibiotics may act as signals in the natural environment and may, in fact, be beneficial for recipient bacteria.

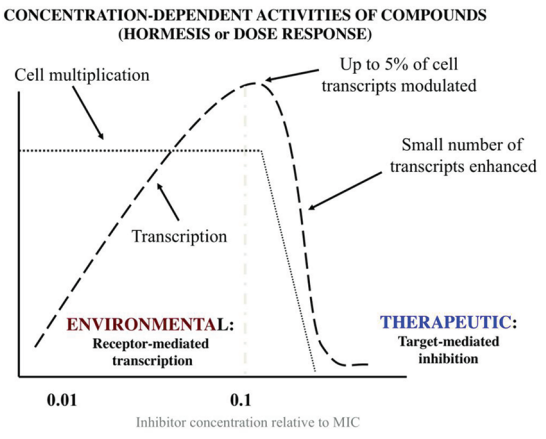

Figure 3. Concentration dependence of activities of antibiotics.

It is clear that antibiotics exhibit different effects depending on their concentrations. However, a caveat of these findings is that the concentrations of antibiotics in the soils, the oceans, and other natural environments are largely unknown. Most investigators suspect that levels are at sub-inhibitory concentrations, but there is no evidence of exact values. Indeed, what is the evidence that such products exist in nature?

■ ARE THEY THERE AT ALL?

Are natural products such as antibiotics produced in natural environments? This question is a prerequisite for addressing the function of these potent bioactive molecules in the natural world.

To some, the question of whether natural products are produced in the environment might seem obviously answered with "of course." After all, the best evidence that natural products are produced comes from natural products research itself. It is relatively easy to harvest plants, fungi, lichens, and marine invertebrates, and samples of such organisms taken directly from the field indeed produce a great diversity of natural products. Compounds found through direct sampling of undisturbed environments include vinblastine from Madagascar

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periwinkle,[18] usnic acid from various lichen species,[19] and bryostatin from the marine invertebrate *Bugula neritina*.[20]

In the case of natural products from bacteria, however, the established route to identification of bioactive molecules is different. Because large samples of bacteria cannot generally be obtained from their environments, different experimental procedures are used to sample bacteria for natural products. In general, bacterial cultures are obtained from a soil or similar complex source, and after successive purifications in the laboratory, pure, individual strains are isolated and grown under controlled conditions in laboratory media to elicit compound production. Solvent extraction of the biomass or culture medium enables the release and purification of molecules. These protocols allow researchers to control, optimize, and reproducibly generate compounds under laboratory conditions. Examples of such approaches in the isolation of bacterial products are numerous and include the isolation of the proteosome inhibitor salinosporamide A,[21] the enediyne uncialamycin,[22] the kinase inhibitor staurosporine,[23] and others.

However, it should be emphasized that these carefully designed processes, typical of laboratory experiments, require conditions that are obviously a far cry from what occurs in nature (Figure 4). From the moment of isolation the selected soil isolates are exposed to extreme conditions; even the

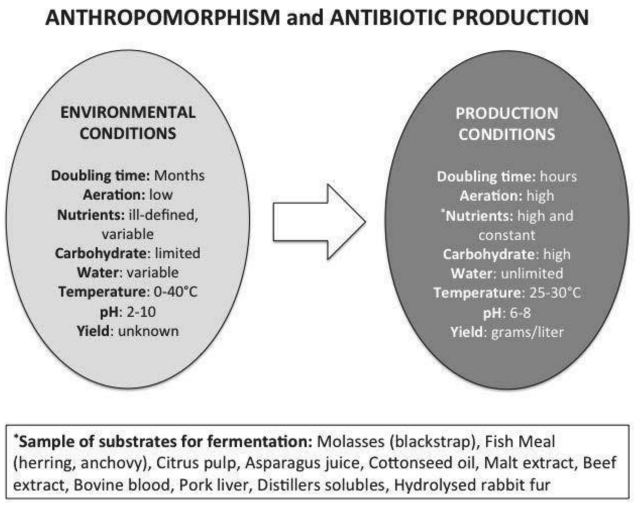

Figure 4. Fermentation *versus* the natural world.

screening processes presuppose desired properties. The production conditions used in industrial and research laboratories include rich and exotic nutrition, constant pH and temperature (often 30 °C), and forced aeration, where growth rates are measured in minutes or hours. Huge industrial fermentation vessels are designed specifically for enhanced, fast growth of producing organisms with high levels of aeration. A great deal of effort is put into the process of yield improvement; the producing strains may be submitted to many rounds of mutagenesis for yield improvement such that the final production strain may be genetically distinct from the original parent. Under these conditions, very high concentrations of antibiotics can be made; commercial fermentations yield up to a hundred grams/liter of product. Such anthropogenic levels of antibiotic production are spectacular.

Compare this to the natural world, where precious little is known about the characteristics of growth of the producing organisms. For example, studies of microbial growth in the wild have shown that it is characterized by slow growth rates (doubling times in months), sparse nutrition, often subaerobic conditions, and usually low cell density.[24−26] In addition, microbial growth in natural environments is dependent on site, season, vegetation, and weather! The populations are frequently complex with only a few dominant bacteria genera/species, depending on the nutritional state of the soils. Are antibiotics produced under these conditions? Do the organisms adopt a static state of metabolism? Unfortunately, most of the microbiological and biochemical studies of these fascinating small molecules carried out since the 1950s have been dictated by practical applications without any consideration of their roles under natural conditions. Nonetheless, the ability to extract natural products from organisms isolated from natural environments, even if the culture conditions are unnatural, is evidence at least that the capacity to synthesize natural products is extensive in the natural world.

In the past decade, the most compelling evidence for the existence of a world of bioactive small molecules comes from the identification of putative biosynthetic pathways by genome sequencing; it is not known under what conditions all these molecules are produced, but heterologous expression of the gene clusters can be employed to reveal the products.[27] In a landmark study the sequence of the *Streptomyces coelicolor* A3(2) genome ("an antibiotic factory") showed a larger metabolic capacity than was predicted from fermentation studies.[28] Some 30 biosynthetic gene clusters could be reliably predicted; pathways for natural products including peptides, terpenoids, and polyketides were identified. At the time, only five of the natural products had been purified in laboratory conditions (actinorhodin, prodiginine, calcium-dependent antibiotic, dodecaketide spore pigment, hopenes). Since then, analysis of *S. coelicolor* culture extracts through "genome mining" has provided evidence for natural product production from 11 additional gene clusters.[29] Subsequent genome projects of soil-dwelling bacteria have added substantially to the number of predicted, but yet unobserved, molecules. *Streptomyces avermitilis* MA-4680,[30] *Streptomyces griseus* IFO 13350,[31] and *Saccharopolyspora erythraea* NRL2338,[32] each sequenced because of their established ability to synthesize therapeutically valuable natural products, were revealed to have the capacity to make many more products than was evident from fermentation studies. *Saccharopolyspora erythraea* was previously known for the production of erythromycin, but the complete genome sequence has indicated the capacity to generate over 20 compounds that had not been observed previously, even with extensive industrial screening.[33] Subsequently, microorganisms previously unknown for natural product production have been shown to encode the catalytic machinery for their synthesis. For example, the genome sequence of *Myxococcus xanthus*, a prokaryote known for collective behaviors of swarming and formation of fruiting bodies, revealed that this microbe has at least 18 gene clusters for secondary metabolites.[34] Subsequent metabolic profiling of 98 strains of *Myxococcus xanthus* identified candidate metabolites for 37 novel natural products.[35] Similarly, three sequenced strains of *Frankia*, nitrogen-fixing actinorhizal symbionts, collectively have over 65 gene clusters for secondary metabolites,[36,37] and *Rhodococcus* sp. RHA1, which is best known for degradation of environmental pollutants, has 18 putative natural product gene clusters.[29,38] It is evident that the capacity to make natural product molecules is present in many bacterial strains,

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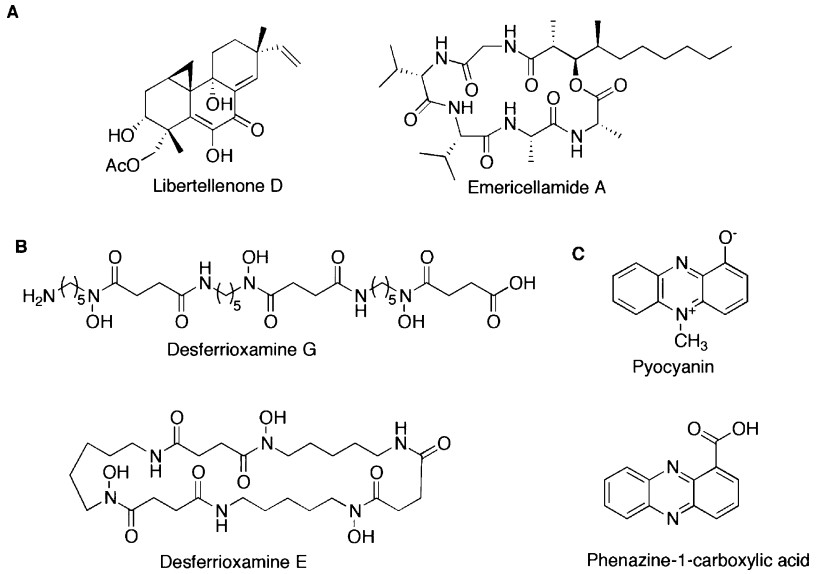

Figure 5. Small molecules described in the text. (A) Molecules produced in coculture. (B) Examples of hydroxamate siderophores found in the Atlantic Ocean. (C) Phenazines discussed in the text.

particularly among the Actinobacteria, which includes the Actinomycete family. While genome sequencing does not reveal whether encoded natural products are indeed made in natural environments, or under what conditions, it provides evidence for a significant inherent capacity of micro-organisms to produce bioactive molecules and suggests that exploration of environmental factors that control natural product production could lead researchers to many novel structures and the discovery of new therapeutically active compounds. The next decade will be excitingly productive as creative methods for the activation of "silent" or "cryptic" pathways are developed!

As an example of the latter it is well-known that natural product production may be enhanced by coculture, the incubation of two microbial species in one production vessel. Such efforts have led to the production and isolation of the diterpenoids libertellenones,[39] the depsipeptides emericellamides[40] (Figure 5a), and the aminoglycosides rhodostreptomycins;[41] the latter being "hybrid" natural products derived from the combined biosynthetic machinery of *Rhodococcus fascians* and *Streptomyces padanus*. Mass spectrometry imaging of cocultures grown on scanning grids similarly shows production of natural product molecules with controlled spatial distributions.[42] While these laboratory-constructed conditions do not necessarily mimic natural environments *per se*, they provide evidence that more complex environments (*i.e.*, different organisms growing adjacent to one another) can elicit different products compared to those found in monocultures. The introduction of new variations in laboratory-generated environments may provide researchers access to more of the so-called cryptic metabolites predicted from genomic data.

Metagenomic analyses of soils and the human GI tract have demonstrated the presence of a large number and variety of putative resistant genes (the resistome) for all currently used antibiotics. There are also multiple resistance genes for the same antibiotic. Many of them are present in the Actinobacteria/Actinomycetes, the main producers of the antibiotics that we use; it has been suggested that they are "self-defense" mechanisms in the producing organisms,[43] but there is no experimental proof of this. It is highly likely that these putative resistance genes have other functions in microbial communities (as do the antibiotics themselves). To add to the confusion, a number of studies have demonstrated the presence of resistance genes to commonly used antibiotics in aboriginal populations that have never been exposed to antibiotics and have had little or no contact with our civilization.[44] Also, analyses of tundra and permafrost have shown that they contain known antibiotic resistance genes.[45]

Although all of these results are tantalizing, the most convincing evidence that these natural product molecules are present in non-controlled, natural environments must come from direct environmental sampling. Here we briefly discuss the evidence for bacterial natural products in the natural world, focusing on those with the best understood function (siderophores), to the debated (phenazines), to the unknown (nonribosomal peptide antibiotics).

Siderophores. There is good evidence that siderophores are present in natural environments. These are metal-chelating organic compounds that are believed to allow organisms to extract metal ions from their environment and also play a role in weathering rock surfaces. Hydroxamate siderophores were identified in extracts of 57 soil samples taken from natural environments across the United States.[46] Similarly, hydroxamate siderophores were identified at nanomolar concentrations from soil suspensions taken from coniferous forest soils in Sweden,[47] and picomolar amounts of hydroxamates were found in seawater samples from the Atlantic Ocean[48] (Figure 5b). Siderophores are products for which natural roles are the most obvious and least disputed.[49]

Phenazines. Phenazines are tricyclic heterocycles produced by a number of pseudomonads and other bacterial strains (Figure 5c). The characteristic colors of the redox-active phenazines have made them among the earliest observed natural products; the blue-colored pus from purulent wounds was observed in the 1800s and was later shown to be pyocyanin.[50] As in the case of siderophores, there is strong evidence for production of these molecules in natural environments. Phenazines are found in the rhizosphere, *i.e.* the soil surrounding the roots of plants, where they have been shown to be produced by bacteria such as *Pseudomonas*

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aureofaciens st. 30-84 and *Pseudomonas fluorescens* 2-79. It is known that strains deficient in phenazine production fail to protect plants against fungal plant invasion, suggesting that the phenazines are indeed important in ecological interactions.[51,52] Phenazine-1-carboxylic acid can be recovered from wheat roots at concentrations of 27−43 ng/g of root with adhering soil.[53] A more ominous role for phenazines has been demonstrated in a different natural environment: the human lung. The phenazine derivative pyocyanin can be isolated from the lungs of cystic fibrosis and bronchiectasis patients with *Pseudomonas aeruginosa* superinfections at concentrations of up to 27 μg/mL.[54] Indeed, pyocyanin is thought to play a role in the infectious process.[55] The importance of phenazines in the survival of *Pseudomonas* strains in the rhizosphere and in the lung is believed to be due to their activity as antibiotics or as virulence factors acting through the production of reactive oxygen species. However, mounting evidence suggests alternate roles for these compounds, including as alternate electron acceptors in low-oxygen environments.[56]

Antibiotics. Compounds with antibiotic activity can be readily isolated from soils and water in nature. However, anthropogenic use of these compounds on a large scale in medicine, agriculture, and aquaculture and their random dispersal/disposal largely explains their presence throughout the environment.[57] Therefore, it is challenging to distinguish between anthropomorphically sourced molecules and molecules released by producing organisms. Is there any evidence for natural antibiotics in the environment? Little of consequence, it would seem. Early studies[58] failed to detect the presence of antibiotics in soil; however, Gottlieb was not privy to the highly sensitive spectroscopic equipment available nowadays. As mentioned, siderophores and phenazines have been detected in natural environments. Given advances in mass spectrometry and other related technologies, it would seem there is a world of small molecules waiting to be detected and monitored by new analytical techniques.

WHY AN UNDERSTANDING OF FUNCTION MATTERS AND APPLICATIONS OF THE PARVOME

The world of microbial natural products has been viewed traditionally through the vision of these molecules as antibiotics. Cell extracts or compounds were tested directly for their antagonistic properties against strains of pathogens or cell culture lines. Generations of scientists have been excited to observe inhibitory properties and to suffer disappointment when a compound fails to show the desired inhibitory activity, no matter how structurally unique a compound may be. It must be appreciated that the components of the parvome have complex roles in nature that promise a multitude of druggable activities in the world of medicine and that the rich harvest of the parvome can provide continuing opportunities. One example is the story of azithromycin, a semisynthetic derivative of erythromycin,[59] which is derived from *Saccharopolyspora erythraea*.[60] The early discovery of erythromycin, an antibiotic that targets the large subunit of the bacterial ribosome[61] was important because it could be used to treat penicillin-resistant Gram-positive infections. Azithromycin has been found to be effective in treating *Pseudomonas aeruginosa* infections in cystic fibrosis patients, despite failing to act as an antibiotic *per se* against this organism. Indeed, at sub-inhibitory concentrations, azithromycin has proven to be a new tool in the treatment of this drastic infection.[62] This molecule is thought to impair biofilm production,[63] leading to its therapeutic effects, rather than killing the pathogen. Still, this result is treated as anomalous. What if we recognized the multifunctionality in the use of all natural product molecules, taking advantage of their multiple concentration-dependent effects?

The science of hormones (endocrinology) is often considered to be restricted to higher organisms (plants and animals), but a new science of paracrine and autocrine biology in microbes, responsible for many interdomain interactions, is now being explored.[64] Compounds such as auxins (indoleacetic acids) have cross-kingdom activities. Evolutionary approaches will enhance the prediction of chemical interactions between organisms. This is obvious in the explosion of studies on the nature, composition, and function of human, animal, and plant microbiomes. The discovery of the extensive metagenomes of humans (comprising microbiomes of more than 10 sites) will revolutionize research in both health and disease states. Already, numerous human conditions have been linked to microbiome function.[65] Knowledge of the human parvome will surely change existing concepts of disease; there is no doubt that small molecule-based processes will be exploited as therapeutics. Bacterial pathogens such as *Burkholderia* sp., *Pseudomonads*, and others (perhaps all!) have been found to produce bioactive small molecules, identified as antibiotics, of course;[66] are we (once again) drawing incorrect notions of their natural roles from laboratory studies? Will the isolation of bioactive small molecules from human gut, urinary tract, nose, *etc.* provide small molecules capable of subtly modulating the functions of their source microbiomes? Existing examples are the microcins and bacteriocins produced by gut bacteria and well-studied in the laboratory. These compounds are generally considered to be weapons of chemical warfare. However, we suggest that they are made at low concentration in response to specific signals for the benefit of the local microbiome and its associated host cell populations. Might they also be used to treat microbiome-associated diseases? Will this be the medicine of the future? How do all of these molecules act, and where do they act? The scientific study of cell−cell interactions is growing rapidly, and although largely focused on eukaryotic cells, it will likely become miniaturized with new imaging techniques to permit studies of single bacterial cells and their low molecular weight components. During the next decade, these studies should lead to the identification of new cross-domain/kingdom interactions that are essential for living processes.

The enormous pool of available bioactive natural molecules found in the parvome promises many benefits for the future of chemotherapy; up to now we have had access to only a small fraction of natural molecular medicines, and most have been used in complete disregard for their functions in their natural habitats. The way ahead will rely on intelligent applications of new and to-be-developed technologies; there need be no "low hanging fruit" restrictions and availability of a wide range of therapeutic options will be guaranteed. It is time for academic microbiologists, chemists, and biochemists to take the lead in drug discovery!

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KEYWORDS

Microbes: microorganisms, including bacteria, fungi, viruses, and parasites; Natural products: organic molecules from natural sources, such as plants, microbes, and sponges; Antibiotics: compounds with static or cidal activity isolated from microbes; Microbiome: a microbial biome, such as the microbes living on the surfaces and gut of a human; Fermentation: growth of microorganisms in nutrient media in flasks, tanks, or other production vessels; Genome mining: finding gene clusters from sequenced genomes; Coculture: growth of two microbial species in one production vessel; Metagenome: the nucleotide sequences of all organisms in a population, for instance, within a soil sample; Siderophores: iron-chelating organic compounds; Phenazines: naturally produced tricyclic heterocycles; specifically, dibenzo annulated pyrazine and derivatives thereof; Endocrinology: the science of hormones

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