

Competition, Communication, Cooperation: Molecular Crosstalk in Multi-species Biofilms

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Abstract Many microorganisms exist in the environment as multicellular communities, so-called biofilms. Chemical communication is an essential part of the way in which biofilm populations coordinate their behavior and respond to environmental challenges. Recent research has been unravelling a complex web of chemical crosstalk mediating microbial symbiosis, competition and defense against predators and pathogens. Understanding the molecular basis of biofilm interactions in their ecological context bears the potential of refining natural product discovery and the development of biofilm-derived biotechnologies.

Microbial biofilms constitute the major proportion of bacterial biomass and activity in many natural and man-made systems. At the same time, biofilms serve as important environmental reservoirs for pathogenic microbes (Flanders and Yildiz 2004) and are the causative agents for many persistent bacterial infections (Costerton et al. 1999). Rules governing biofilm assembly, function and evolution have been largely unexplored but as with communities of macro-organisms, local interactions between component organisms in spatially structured environments are likely to be of central importance (Hibbing et al. 2010). Structure, composition and function of biofilm communities are predicted to be determined by synergistic and antagonistic interactions among component species (Hassell et al. 1994; Kerr et al. 2002; Battin et al. 2003). Despite the consensus that natural biofilms represent multi-species communities of diverse micro-organisms, studies to date have addressed the physiology and regulation of biofilm functions almost to the exclusion of species–species interactions.

Biofilms in the natural environment are very complex entities that potentially consist of many hundreds of different species. There are real challenges in understanding how different bacteria interact with their own and other species. To study

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organismic interactions in multi-species biofilms, marine biofilms have become a leading model system (Egan et al. 2008). Biofilms in the sea are most evident as slimy surface growth or “Aufwuchs” on docks, boat hulls or intertidal rocks. A glimpse through the microscope reveals, however, that even marine animals and plants or inconspicuous sediments may be covered with biofilms. Marine and freshwater biofilms are complex structures that comprise both bacteria and eukaryotic microbes (Fig. 1). Following the initial attachment of bacteria, surfaces get further colonized by fungi, cyanobacteria, unicellular algae and bacteria-eating protozoa, thus creating a dynamic and diverse community of micro-organisms. In the absence of large shear forces, such biofilm communities can grow extensive mats or slimes. In the process of the successive surface colonization, aquatic macro-organisms such as macroalgae and invertebrates (barnacles, worms, mussels, snails) arrive, by which aquatic surface communities often become visible to the naked eye. These biofilm communities may not quite reach the grandeur of coral reefs, but they may be comparable in their complexity of the interactions between component

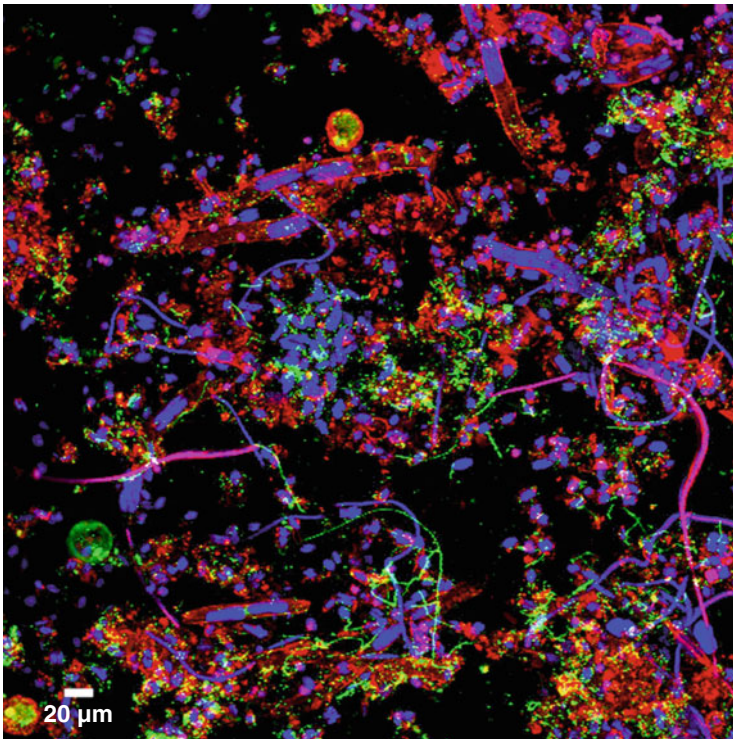


Fig. 1 Laser scanning microscopy image of a marine biofilm community. Bacteria (green) were stained with SYTO9 and extracellular polymeric substances (red) were stained with Alexa568-conjugated lectin AAL (*Aleuria aurantia*). Pink and blue fluorescence is due to the autofluorescence of cyanobacteria and microalgae (diatoms, chlorophytes), respectively. Circular cells (green, red) represent heterotrophic protists. Image courtesy of Dr. B. Zippel

species. Owing to their densely packed nature and limited capacity for diffusion, chemical communication might be an ideal way for species to interact within a biofilm as distances are small enough for the diffusion of signal and effector molecules (Decho et al. 2010). This chapter summarizes first insights into the biomolecular complexity underlying interspecies communication in marine biofilm communities.

1 Competition and Defence by Chemical Weapons

Life in a biofilm is similar to that in a city (Watnick and Kolter 2000): the dense settlement not only allows symbiotic relationships between component species, but also tightens the competition for limited resources (space, nutrients, light) or may attract predators. Relatively high population density and limited diffusibility of the exopolymer matrix support the notion that biofilm residents interact and communicate by small chemical compounds. In the last few years, it has become evident that marine bacteria harbour a broad arsenal of biologically active metabolites, which are predicted to function as chemical weapons and signals (Jensen and Fenical 1994).

The marine gamma-proteobacterium *Pseudoalteromonas tunicata* illustrates the range of target-specific molecules that biofilm bacteria may use to grow and survive in multi-species biofilm communities (Thomas et al. 2008). In the interaction with competing fungi, *P. tunicata* makes use of a secreted inhibitory tambjamine alkaloid (Fig. 2a) (Franks et al. 2005, 2006). The biosynthetic pathway is coded by a cluster of 19 genes (*tamA* to *tamS*) encoding proteins with homology to prodigiosin biosynthetic genes in various other bacteria (Burke et al. 2007).

Microcolonies of *P. tunicata* also produce the antibacterial AlpP lysine oxidase (James et al. 1996; Mai-Prochnow et al. 2008), which has been proposed to keep competing bacterial species in check by the production of H_2O_2 . In photic habitats, unicellular algae such as diatoms are among the strongest competitors of bacteria

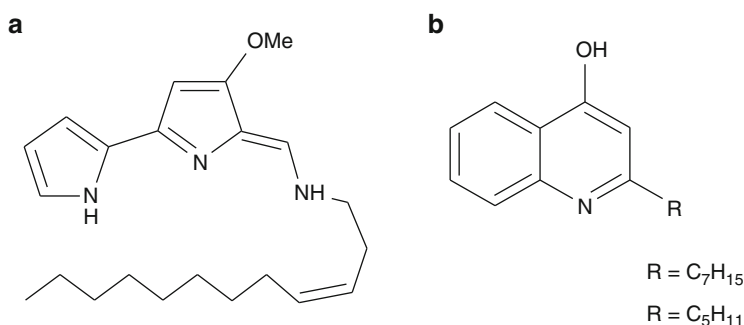


Fig. 2 Metabolites with antifungal and antialgal activities: Tambjamine (a) and alkyl-chinolinols (b) isolated from marine *Pseudoalteromonas* spp.

for micronutrients. In *P. tunicata*, a not-yet-characterized 3–10 kDa peptide is suspected to inhibit the growth of diatoms and the germination of macroalgal spores. Other bacteria of the genus *Pseudoalteromonas* are known for the production of alkyl-chinolins (Fig. 2b) (Long et al. 2003), which were found to inhibit the growth but not to kill various diatom. Generally, the increasing number of reports on allelopathic effects elicited by biofilm-derived bioactives suggests that much of the spatial and temporal dynamics found in natural biofilm communities is controlled by chemical compounds.

A life-threatening ecological factor for attached bacteria is the grazing pressure elicited by bacteria-consuming protists, the protozoa (amoebae, ciliates, flagellates). While bacterial biofilms without grazing defence can be rapidly eliminated by protozoa, biofilm bacteria capable of chemical defence are resistant against grazing and may grow to high cell densities (Fig. 3).

Again, *P. tunicata* provides a good example for the production of an effective antipredator molecule, the purple indole alkaloid violacein (Fig. 4) (Matz et al. 2008). Violacein is synthesized by a number of marine bacteria and stored in the periplasm between the inner and outer membrane of the bacterial cell (Matz et al. 2008; Hakvåg et al. 2009). Once a bacterium gets phagocytized by a protozoan predator, violacein is thought to be released into the phagolysosome upon the digestion of the outer membrane.

Although the molecular mechanism has not been elucidated in detail, there is evidence that violacein as a redox-active molecule disrupts the membrane potential of mitochondria. This triggers the eukaryotic suicide program (apoptosis) of the protozoan cell, thus leading to the complete lysis of the protozoan predator within a

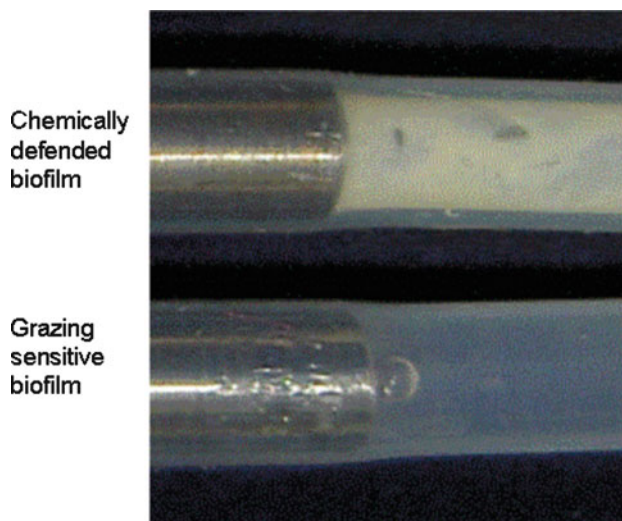
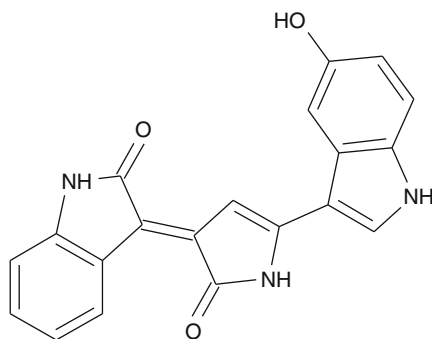


Fig. 3 Biofilms exposed to grazing by *Acanthamoeba polyphaga*. Chemically defended biofilms (top) maintain high biomass, while undefended biofilms are cleared from the tube (bottom). Image courtesy of Dr. M. Weitere

Fig. 4 Predator-active compound: violacein isolated from a range of marine bacteria, including *Pseudoalteromonas* spp. and *Microbulbifer* sp.



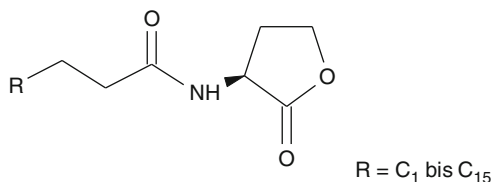
few hours (Matz et al. 2008). The effectiveness of this defence mechanism is illustrated by the fact that a single bacterium, containing about one femtogram of violacein, is sufficient to stop the feeding activity of the protozoan cell within minutes. Other recent studies suggest that such chemically mediated grazing resistance is not uncommon in biofilms (Matz et al. 2004a, 2005, 2008), and could be an explanation for the accumulation and persistence of biofilms, despite the presence and feeding activity of their natural consumers.

2 Cooperation by Chemical Communication

It is striking that the biosynthesis of defence molecules such as violacein is significantly increased in biofilm bacteria in comparison with free-swimming bacterial cells (Matz et al. 2008). One reason for this is that within biofilms bacteria reach relatively high local cell densities even at low nutrient levels. High cell densities in turn facilitate chemical communication between bacterial cells using pheromone-like signalling molecules (Williams et al. 2007). In many Gram-negative bacteria, cell–cell communication occurs via *N*-acyl homoserine lactones (AHLs, Fig. 5), while autoinducing peptides represent common signal molecules in Gram-positive bacteria. Moreover, furanosylesters that are derived from dihydroxypentanedione are described as the AI-2 signalling system for both Gram-negative and Gram-positive bacteria.

By using quorum sensing molecules, bacteria obtain information on their population size and may coordinate a group behaviour similar to a multi-cellular organism. Temporal patterns of gene expression during bacterial growth indicate that most genes are activated by quorum sensing during the transition from logarithmic phase to stationary phase (Schuster et al. 2003; Wagner et al. 2003); that is, when cell densities markedly increase and nutrients become increasingly depleted. By enabling cooperation and synchronization, quorum sensing is thought to adjust the population response to changing environmental conditions and increase the fitness of dense bacterial assemblages in late logarithmic and early stationary phase (Keller and Surette 2006).

Fig. 5 Quorum sensing molecules: *N*-acyl homoserine lactones produced by Gram-negative bacteria



Predation and the necessity of defence exemplify one facet of the selective advantages in the evolution of bacterial cell-to-cell communication systems: in exponentially growing bacterial populations, predation is not an immediate threat (because bacterial growth rates are usually high enough to compensate for grazing losses) but grazing becomes a serious problem with the onset of nutrient depletion (stationary phase). In fact, evidence has been gathered from studies of four bacterial species, *Pseudomonas aeruginosa*, *Chromobacterium violaceum*, *Vibrio cholerae* and *Serratia marcescens* that quorum sensing mutants have a significantly reduced antipredator fitness compared with their isogenic wild-type strains (Matz et al. 2004a, b, 2005; Queck et al. 2006). In addition to their role in monitoring population density, quorum sensing signals have also been proposed to function as diffusion sensors (Redfield 2002). In the context of grazing resistance, synchronization by a quorum might be required to reach extracellular toxin levels high enough to ward off predators, whereas the secretion of inhibitors by a single cell is likely to be ineffective.

Upon reaching the critical quorum size, quorum-sensing signals induce the expression of grazing defence genes, as in the case of the violacein gene cluster *vioABCDE*. It is well known for plant-associated bacteria that already microcolonies of less than 40 bacteria are enough to turn on the AHL-mediated communication (Dulla and Lindow 2008). Indirectly, the feeding activity of protozoa appears to promote the achievement of the minimum quorum size. In particular, the size selective feeding of protozoa promotes the formation of microcolonies (Matz et al. 2004a), which may lead to the accelerated induction of quorum sensing, and more indirectly to the induction of chemical defence. To what extent the formation of microcolonies, or the synthesis and release of defence molecules also is directly inducible by predator-derived signals (kairomones), remains a question for future investigations.

3 Eukaryotic Response to Biofilm Signals

The colonization of marine surfaces by microbial biofilms entails the settlement of macro-organisms in the form of algal spores or invertebrate larvae. When choosing the appropriate attachment site, the temporarily free-swimming spores and larvae of macroalgae and invertebrates may respond to chemical cues or signals released by biofilms. Deterrents often appear to be nonpolar secondary metabolites (see, e.g.,

P. tunicata), while there seems to be mainly primary metabolites such as carbohydrates and peptides among the water-soluble attractants (Qian et al. 2007). For example, larvae of the tubeworm *Hydroides elegans* searching for suitable attachment habitat rely on the specific composition of the biofilm EPS, and as-yet-unidentified metabolites produced by associated bacteria or diatoms (Harder et al. 2002; Lam et al. 2005).

In addition, macro-organisms are capable of eavesdropping on the chemical communication of biofilm bacteria. Spores of the green alga *Ulva intestinalis* exploit different long-chained AHL signals of communicating biofilm bacteria for their own orientation (Joint et al. 2002). When *Ulva* zoospores reach the surface, they slow down their swimming movement at micromolar hotspots of AHLs and attach directly to the AHL-producing biofilm bacteria (Joint et al. 2007). It has been demonstrated that the detection of AHLs results in calcium influx into the zoospore. Currently, we can only speculate about the ecological and evolutionary benefits of biofilm-mediated habitat choice for spores and larvae: The colonization of abiotic surfaces by “biotic” biofilms could serve as a general indicator/proxy for habitable conditions, or facilitate specific associations with bacterial symbionts.

4 Biofilm Inhibition by Molecular Mimicry

In addition to sediments and rocks, biofilms colonize the “living” surfaces of many marine animals and plants, a phenomenon termed epibiosis. Marine animals and plants are exposed to the constant risk of being literally overgrown by epibionts. One strategy for the host organism to block epibiont settlement is the production of antifoulants. The Australian red alga *Delisea pulchra*, for instance, employs molecular mimicry by releasing halogenated furanones (Fig. 6a), which is remarkably similar in its structure to the AHLs that many biofilm bacteria use for intraspecific

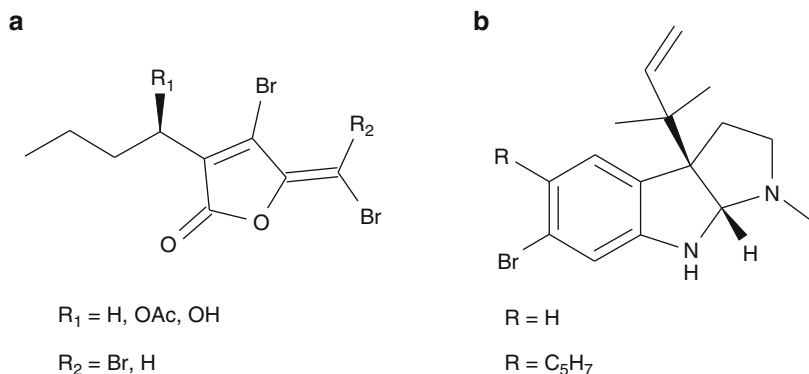


Fig. 6 Host-derived quorum sensing antagonists: brominated furanones and alkaloids isolated from the red alga *Delisea pulchra* (a) and the bryozoan *Flustra foliacea* (b)

communication (Givskov et al. 1996; Manefield et al. 1999). Furanones were found to modulate the activity of the AHL-dependent transcriptional activator LuxR in the bacterial quorum-sensing systems by reducing the half-life of the LuxR receptor proteins (Manefield et al. 2002). Blocking communication between biofilm bacteria leads to the failure of bacterial survival functions. Among other functions, biofilm bacteria may be compromised in their defence against predators in the presence of QS antagonists and thus rapidly grazed by protozoa.

Likewise, marine animals have been reported to produce AHL-antagonists to reduce the formation of epibiotic biofilm. One example may be the brominated alkaloids, which were isolated from the North Sea bryozoan *Flustra foliacea* (Fig. 6b) (Peters et al. 2003). However, the QS-specific antagonism of *Delisea* furanones and *Flustra* alkaloids is limited to a specific concentration range. At higher concentrations, these molecules possess a general biocidal effect, so that – in addition to compromising biofilm homeostasis – the settlement of invertebrate larvae and algal spores is directly inhibited.

5 Host Defence Mediated by Epibiotic Biofilms

Epibiotic biofilms may not only be detrimental to the animal or plant host. In recent years, it has become increasingly clear that many of the natural products isolated from marine plants and animals are produced by epibiotic or symbiotic bacteria (König et al. 2006; Piel 2009). These molecules may assist host organisms, for example, in the defence against parasitic bacteria and fungi. Biofilm bacteria which inhibit the growth of parasitic fungi through the production of isatin (Fig. 7a) and the fungus-specific QS signal tyrosol have been identified on crustacean embryos (Fig. 7b) (Gil-Turnes et al. 1989; Gil-Turnes and Fenical 1992).

Substances produced by epibiotic bacteria include complex polyketides from the class of bryostatins (Fig. 8). Bryostatin was originally isolated from the bryozoan *Bugula neritina* and are in clinical testing phase due to their promising therapeutic properties. It is now known that bryostatin is actually produced by the bacterium *Endobugula sertula* that forms biofilm-like cell clusters on the surface of bryozoan larvae (Sudek et al. 2007; Sharp et al. 2007). One reported ecological benefit of hosting these epibiotic bacteria is that bryozoan larvae deter predatory fish by the bacterial production of bryostatin.

Moreover, selective tolerance, attraction or transmission of primary bacterial epibionts may assist the host to control the composition of the secondary community of epibionts and the intensity of colonization. A good example may be a bacterium such as *P. tunicata* (see above), which has originally been isolated from the surface of the green alga *Ulva lactuca* and the sea squirt *Ciona intestinalis* and which can influence directly and indirectly the colonization of bacteria, fungi, protozoa, algae and invertebrates by a variety of low-molecular-weight inhibitors. Interestingly, violacein which protects *P. tunicata* and other biofilm bacteria from predatory protozoa shows also high activity against herbivorous invertebrates.

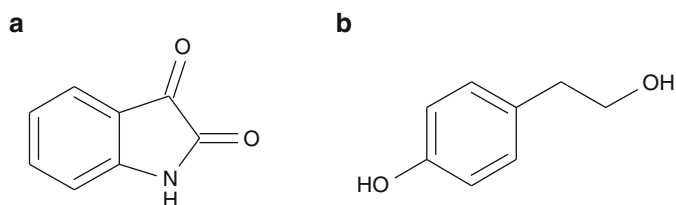
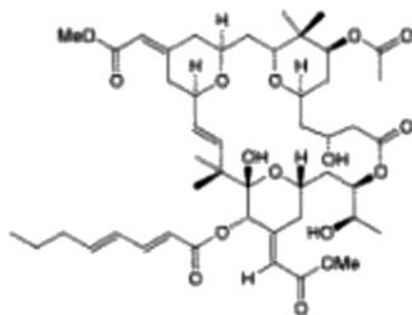


Fig. 7 Fungus-inhibiting compounds derived from epibiotic bacteria: Isatin (a) and tyrosol (b)

Fig. 8 Antifeedant of bryozoan host is produced by epibiotic bacteria: bryostatin



Recent studies suggest that violacein-producing biofilms could protect not only themselves but also deter grazers of the host algae *U. lactuca*.

6 Conclusions

Marine micro-organisms are versatile producers of secondary metabolites. Although the sea has yielded thousands of bioactive metabolites over the past two decades, we are only beginning to explore the natural functions of these molecules. Many micro-organisms exist in the environment as surface-associated biofilm communities. The close spatial proximity of micro-organisms at surfaces drives specific interspecies interactions and generates complex and highly differentiated microbial communities. Chemical communication is recognized to be an essential part of the way in which biofilm organisms coordinate their behaviour and respond to environmental challenges. Recent studies have been unravelling first aspects of the complex chemical crosstalk mediating microbial symbiosis, competition and defence against predators and pathogens (Fig. 9). Future research is anticipated to provide insights into how interspecies communication may shape the structural and functional dynamics of biofilm communities.

Marine biofilms play a central role as hotspots of biological diversity and molecular complexity. From the progressive description of new marine natural products arises the question of their function in the natural context. The study of

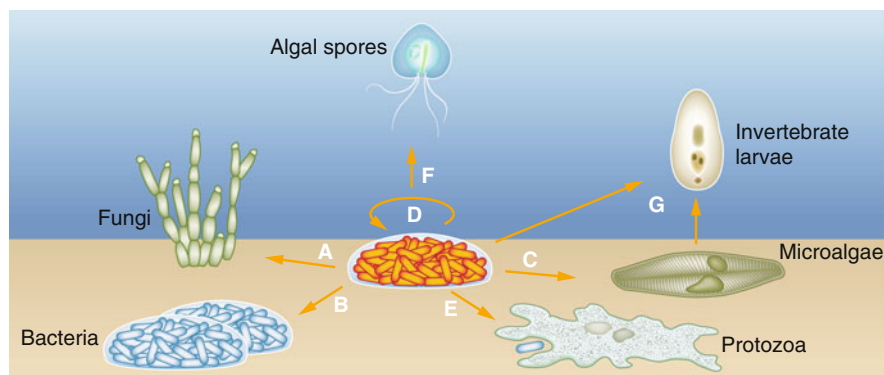


Fig. 9 Chemical warfare and communication in a natural multi-species biofilm. Biofilm communities are shaped by antagonistic and synergistic interactions between microbial species. Bacterial populations may establish in a competitive environment by secreting specific inhibitors that target competing fungi (A), bacteria (B), or microalgae (C). Clonal growth in microcolonies allows bacteria to reach cell densities high enough for quorum sensing (D), which may induce the production of antifeedants against protozoa (E). Secondary colonizers, such as macroalgal spores (F) and invertebrate larvae (G) may be attracted by biofilm-derived cues. Biofilm communities associated with living surfaces may further be modulated by host-derived compounds

chemical interactions in natural biofilms, however, faces the dilemma of dealing with the almost unlimited complexity of communities and the limited culturability of their members. This requires a close integration of analytical chemistry and microbial genetics with innovative cultivation approaches and realistic bioassays. Promising novel approaches also include the development and application of global analytical tools such as metabolomics and metagenomics. Understanding the molecular basis of biofilm interactions in their ecological context bears the potential of refining natural product discovery and the development of biofilm-derived biotechnologies.

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Biofilm Highlights

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