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Draining the moat: disrupting bacterial biofilms with natural products

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1. Introduction

Bacteria cycle between two distinct lifestyles, planktonic and within a biofilm, and each presents its own unique set of problems for humanity. Bacterial biofilms are tremendously costly to society as they affect industries ranging from petrochemicals to health care.

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In 2001, biofouling and biocorrosion was estimated to cost the oil and gas industries 13.4 billion dollars annually.[1] For example, the biofouling of ship hulls has resulted in an estimated additional $1 billion/year of increased fuel and maintenance costs to the US Navy because of the increased friction from adhered cell matter.[2] Of even greater concern is the effect that biofilms have on the health industry, and more specifically, the growing rate of antibiotic resistance. Bacteria within a biofilm are not only 100–1000 times less susceptible to traditional therapeutics but are also hyper-mutative and prone to horizontal gene transfer events further promoting antibiotic resistance.[3,4] This poses a significant threat to those with chronic infections, as biofilms are the predominant bacterial state in these cases. It has been estimated that 80% of all human infections involve microbial biofilms.[5] Accordingly more work should focus on investigating lead therapeutics against this specific bacterial lifestyle.

Surprisingly, when compared to the number of anticancer and antibacterial compounds only a handful of natural products have been characterized as antibiofilm—that is, compounds effective at inhibiting, killing, and/or dispersing biofilms. We suspect that this stems from the difficulty in both fully and reproducibly evaluating bioactive compounds in the suite of assays that relate to these processes. Below we present an overview that highlights natural products that have been shown to possess these properties in three of the best-studied areas—medical devices, dental caries, and biofouling. Accordingly, this review is by no means exhaustive, instead it is meant to inspire future investigative work and also emphasize that certain privileged scaffolds are repeated in a plethora of natural products.

2. Background

2.1. Biofilm formation

Bacterial life consists of an interplay between planktonic free-swimming organisms and an adhered biofilm state (Fig. 1). Briefly, the stages of development include (I) initial attachment and adherence of planktonic cells to an abiotic or biotic surface; (II) recruitment of adhered cells and production of extracellular polymeric substance (EPS); (III) maturation and the development of the full biofilm architecture; and (IV) dispersion of the biofilm to yield back planktonic cells.[6] The initial attachment and ultimate dispersion events are triggered by a number of factors including environmental stressors and inherent chemical signals.[6,7] Extensive work has demonstrated that bacteria communicate in a population dependent fashion through intercellular signaling, commonly known as quorum sensing. Chemists and biologists alike have targeted these systems to perturb bacterial processes.[8] Several herculean campaigns have been made to modulate biofilm formation and dispersion through these efforts; however, they are outside the scope of this review and will not be discussed.[9]

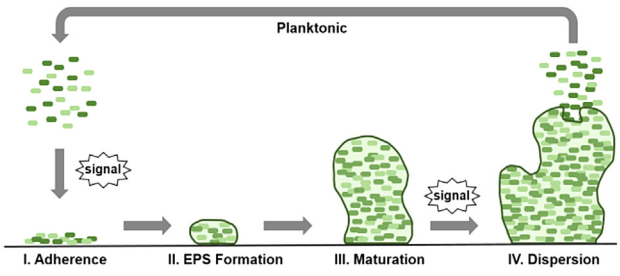

Fig. 1. Bacteria life cycle.

It should be noted that throughout the literature a number of terms are used to refer to identical or similar processes related to biofilm formation making it very difficult for the unacquainted to navigate the field. For example, initial biofilm formation (I. adherence) has been referred to as: initial attachment, cell aggregation, clumping, and formation of microcolonies.[10] Further adding to the confusion, the term 'microcolony' itself has referred to non-adhered aggregations of bacteria, the initial grouping of cells after attachment, and specific groups within an established biofilm.[11] Likewise the extracellular polymeric substance (EPS) has in some instances been used to denote exopolysaccharide, merely a component of the biofilm extracellular matrix.[12] The inconsistent use of terms to describe such biofilm stages has led to ambiguity defining each specific stage and associated processes, thus making literature searches cumbersome.

The term biofilm applies in a general sense to any consortium of microorganisms embedded in an EPS including those films produced by fungal organisms such as *Candida albicans*. The biofilm state provides numerous benefits to both the individual and the group some of which include increased resistance to microbiocides, slower growth rates, a larger population of persistor cells, and increased horizontal gene transfer.[13] The characteristics of these biofilms vary greatly among different strains of bacteria in terms of structure, architecture, and composition. For example, some bacteria, like *Streptococcus mutans*, produce flatter biofilms in order to survive the high shear stress environment of the oral cavity, while others are capable of producing columns, pillars, or canopies.[5,14] Furthermore, the composition of the EPS differs from species to species; Gram-negative bacteria, like *Pseudomonas aeruginosa*, form biofilms that are rich in alginate content resulting in a highly anionic environment.[15] Conversely, the EPS of several *Staphylococcus* biofilms (Gram-positive) contain poly-*N*-acetyl glucosamine, drastically perturbing the chemical makeup.[16] Overall, very little is known about the specific chemical composition of each species' EPS making the area ripe for chemical exploration.

2.2. Medical devices

One of the most significant areas affected by microbial biofilms are indwelling medical devices. These infections occur on implants ranging from bladder catheters, which affect an estimated 3–9 million patients each year, to more invasive devices like mechanical heart valves at an estimated 800–2500 patients per year.[17] The corresponding rise of post-surgery infections are of grave concern and warrant further research in this area.[18] Additional problems arise when the patient is immune-compromised as the infection can lead to higher risks of mortality, specifically with intravascular implants such as mechanical heart valves and cardiac pacemakers.[17,19] The initial adhesion to such devices leads to biofilm formation and persistent illness.

Implant colonization most closely follows the typical model for biofilm growth, with the most deleterious stage being the dispersion of planktonic cells further spreading the infection (Fig. 2). When an infection is identified, the primary treatment consists of removal of the implant followed by antibiotic treatment. However, the infection rate dramatically increases upon reimplantation demonstrating the necessity for more effective treatments.[17] Proper development of drugs to inhibit this formation would allow for further treatment with traditional antibiotics resulting in both a significant medical cost savings and, more importantly, better health outcomes.

2.3. Caries

Dental caries, commonly known as cavaties, is the single most common chronic childhood disease, five times more common than asthma.[20] Caries is directly caused by the formation of biofilm plaques within the mouth, which when dispersed into the blood stream can lead to endocarditis (heart disease).[21] The primary species responsible for caries, *S. mutans*, co-inhabits the oral cavity with natural microflora within a mixed-species biofilm.[22] Within