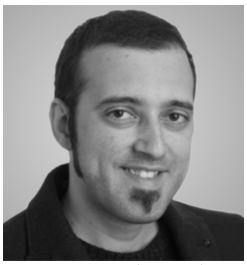
EDITORIAL

Recent Advances in Anti-biofilm Strategies



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Biofilms, for long time overlooked, are now recognized as the preponderant, natural bacterial lifestyle. These sessile, organized and complex communities are highly resilient to harsh environmental conditions, including antibiotic treatment. It is fascinating how bacteria, otherwise considered relatively simple, primitive cells, are able to coordinate collective behaviors that result in the formation of highly structured mono- or –most commonly– multi-species communities. Thus, the 'bacterial citadels' become strongholds when it comes to antimicrobial chemotherapy, being up to 1000 times more resistant than in planktonic culture [1]. It is now evident that biofilms are actually responsible for up to 60-85% of all microbial infections [2]. It is worth mentioning that around half of them are associated to indwelling devices [3]. Only in the US, the annual costs associated to biofilm-related infections exceed $100 billion, and more than half a million deaths are reported for this cause [4]. With such figures, the dimension of this problem worldwide is indeed huge.

The emergence of antibiotic resistance in bacteria is a global healthcare concern. Antibiotic therapy is, however, the method of choice for the treatment of microbial infections. This is because it is generally highly efficient towards most acute infections, but poses two important risks whose consequences we have just begun to experience: on the one hand, the emergence of 'superbugs', *i.e.* multidrug-resistant bacteria. At this point it is quite obvious that we are unable to compete with bacterial evolution. After having imposed a selective pressure on bacterial populations over decades, our 'chemical weaponry' is now becoming obsolete at an alarming rate. On the other hand, antibiotics are virtually useless against biofilms, which are the underlying cause of chronic/recurrent infectious diseases.

In this scenario with stronger enemies and impregnable fortresses, the 'special forces' come into action. In other words, smarter solutions specifically designed to target key physiological processes and biofilm features. In this thematic issue of *Current Topics in Medicinal Chemistry*, we will review the current strategies aiming to thwart biofilm formation at any stage, from engineered materials for the inhibition of bacterial attachment to chemical interference with key signaling pathways.

As highlighted above, biofilms on indwelling medical devices are a major cause of morbidity and mortality in hospitalized patients, leading to recurrent and even life-threatening infections. Often, even with prophylactic treatment, the emergence of an infection sooner or later is just unavoidable. For instance, virtually all patients undergoing long-term urinary catheterization will develop bacteriuria due to microbial colonization of the catheter [5]. Indeed, there is a clear need for novel and more efficient anti-biofilm biomaterials. Tzanko Tzanov's team present a comprehensive review of novel approaches for the generation of advanced anti-biofilm coatings. These new formulations are engineered to maximize the local effects of the active components on the material surface and include a variety of biocidal and non-biocidal strategies, often integrated at the *nano* scale. One of such strategies is the incorporation of compounds that interfere with bacterial cell-to-cell communication or Quorum Sensing (QS).

The formation of a bacterial biofilm is a well-orchestrated process that requires the coordination of complex collective actions. Thus, bacteria need to modulate gene expression in a finely tuned way. In this context, QS plays a fundamental role. By producing, secreting and detecting diffusible molecules, bacteria are able to synchronize gene expression in a population-density-dependent manner. QS-regulated phenotypes are diverse and include not only biofilm formation, but also the biosynthesis of virulence factors and siderophores that allow bacteria to colonize and infect host tissues. García-Contreras and colleagues review the QS systems of two important pathogens, *Pseudomonas aeruginosa* and *Acinetobacter baumannii*, and present 'Quorum Quenching' strategies aiming to control their biofilms both *in vitro* and in clinically-relevant settings.

The transition from a planktonic to a biofilm lifestyle requires a finely-tuned integration of the environmental signals. Hence, bacteria need to adapt their gene expression readily. Nucleotide-based second messengers, especially c-di-GMP, play a key role in signal transduction and regulate a plethora of clinically-relevant physiological processes. Therefore, proteins involved in the biosynthesis and degradation of these second messengers constitute attractive novel targets for antimicrobial chemotherapy. Ute Römling and I present a review on nucleotide-based signaling pathways in Bacteria, with emphasis on small-molecule-based strategies aiming to interfere with them as well as high-throughput approaches for the identification of such compounds. Current trends and future prospects in this field are also discussed. One of such alternative antimicrobial targets are riboswitches, mRNA domains that bind second messengers and other metabolites and regulate gene expression and function. A review of recent advances on the use of riboswitches as antimicrobial targets is presented by Reyes-Darias and Tino Krell.

Biofilm formation by pathogens and other microbes is a universal nuisance. Living creatures with a sessile mode of life such as plants, algae or marine invertebrates are particularly exposed to microbial colonization and have evolved chemical defenses against them. It is also well known the 'chemical warfare' between bacteria and fungi. Hence, an increasing number of natural products with anti-biofilm activities are being identified, with very diverse modes of action. From an innovative standpoint, Rob Huigens leads a review of natural or naturally-inspired compounds that kill biofilm or persister cells. Within a biofilm, cells in very different metabolic states coexist. In particular, those located in the lower layers of the biofilm present

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very low metabolic rates or are in a 'dormant' state. Consequently, antibiotics, which target metabolically active cells, are not efficient against them. Therefore, compounds with this particular mode of action are very promising from a therapeutic standpoint.

An important component of the natural antibacterial arsenal are antimicrobial peptides (AMPs). In higher organisms, AMPs are part of the innate immune system, although they have been identified in all domains of life. A thorough review by Di Luca and colleagues dives into the recent advances in this field with focus on their anti-biofilm activity *in vitro* and *in vivo*. Interestingly, the authors also present administration strategies for AMPs in therapeutic applications, with emphasis on drug carriers and coating materials for biomedical devices.

Biofilms are not only bacterial. Fungal biofilms have indeed an important impact on chronic disease and device-related infections. *Candida* spp. are the most common fungal species associated with clinical biofilms, in particular *C. albicans*. This special issue ends with a review by dos Santos and colleagues that addresses the biology of *Candida* biofilms, their clinical significance, and the recent advances in their study and control.

Altogether, I hope that this special issue of *Current Topics in Medicinal Chemistry* will provide on the one hand, an overview of our current knowledge on biofilm physiology, and on the other hand, an up-to-date perspective on the broad diversity of strategies aiming to thwart microbial biofilm formation in pre-clinical and clinically-relevant contexts, mostly derived from a better understanding of fundamental aspects of biofilm microbiology. I also wish that this special issue constitute a meeting point for microbiologists, organic chemists, pharmacists, physiologists and engineers working in this cross-disciplinary area.

Last but not the least, I would like to acknowledge all the hard work conducted by the anonymous reviewers belonging to academia, clinics and industry that have participated in the revision of the works is presented in this thematic issue.

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