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Editorial

Microbial Biofilms in Healthcare-Associated Infections

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This editorial focuses on biofilms' role in healthcare-related infections resistant to antibiotic treatment, the impact of polymicrobial biofilms on drug resistance and tolerance, and the recent advances in developing innovative anti-biofilm strategies.

The recently acquired knowledge on the pivotal role played by biofilm-forming microbes in healthcare-related infections has given a new dynamic to the detection, prevention, and treatment of these infections [1] in patients admitted in both acute-care hospitals [2] and long-term care facilities [3]. Thus, in nosocomial settings, biofilm-based healthcare-related infections are considered a serious threat to patients, the sessile-growing microbial communities playing a key role in the spreading of these infections often caused by emergent multidrug-resistant microorganisms. Antibiotic therapies to eradicate these infections often fail because of the ability of microbes growing as biofilm encased in a dense exopolysaccharide matrix to be more drug-resistant than planktonic microbes [4].

Therefore, one of the most insidious features of biofilm-associated infections is the higher anti-drug resistance of microbial cells growing as biofilms compared to bacterial and/or fungal cells developing in planktonic mode [5,6]. In fact, as it is well known, biofilms represent an appropriate microenvironment for plasmid exchange, the conjugation frequency being higher in the sessile-growing than in planktonic microbes. So, both naturally occurring and induced antibiotic resistance phenomena are amplified in these microbial communities because some plasmids contain genes coding for multidrug resistance. Among the mechanisms involved in the increased drug resistance of microbes growing as biofilms, the most relevant are the following:

slow and partial diffusion of antibiotics and other antimicrobial agents through the biofilm matrix [7], although the scarce penetration does not account for the observed drug resistance fully. Furthermore, although many different antimicrobial agents are available today, none has been reported to be fully active against the wide range of bacteria and fungi commonly involved in biofilm-associated infections. Anyway, there is relatively little data on their efficacy in inhibiting biofilm formation or disrupting preformed biofilms. A promising approach to the problem of biofilm-associated infections implies the finding of molecules that can disaggregate the exopolysaccharide matrix and keep the single bacterial cells within the biofilm together. A successful example is represented by the hydrolase dispersin B, which has been demonstrated to be able to cause the detachment of biofilms produced by several bacterial species [8–10]. Recently, Li et al. [11] also reported the advantages of applying dispersion-based nanoparticles to reduce biofilm reinfection.

(1) Differential response of microbes to the heterogeneous physico-chemical conditions in biofilm-growing communities. Obviously, nutrients are scarce and possibly toxic at the lower layers of biofilms, while microbial waste products are largely present. On the other hand, in the surface layers of biofilms, oxygen can be almost exhausted, and in the deep layers, anaerobic niches can be presumably present. In fact, by using oxygen microelectrodes, Borriello and coworkers [12] reported that these biofilms contain large anoxic regions, the oxygen penetrating about 50 microns into the biofilms, which averaged 210 microns thick. On the other hand, nutrient depletion can significantly reduce the number of targets for antimicrobial molecules by slowing the microbial growth rate.

(2) Onset of subpopulations of persister cells in a spore-like, nondividing state, which, however, do not seem to be able to be responsible by themselves for the antibiotic resistance exhibited by microbial biofilms [13]. It has been demonstrated that persister cells are phenotypically dormant cells presumably generated under the

pressure of endogenous stresses and exposure to high doses of antibiotics [14]. While persister cells have also been found in planktonic populations of microbes, they are present in relatively higher numbers in biofilms and are considered capable of contributing significantly to biofilm antibiotic tolerance [15,16]. Of interest is that bacteriophages can induce enzymes that degrade the extracellular matrix of biofilms and infect persister cells, remaining dormant within them but re-activating when they become metabolically active [17]. An exhaustive compilation of clinical cases where bacteriophages have shown their efficacy in treating biofilm-based infections where antibiotics have failed has been recently published by Gordon & Ramirez [18].

(3) The polymicrobial nature of biofilms involved in healthcare-associated infections, due to the frequent occurrence of mixed communities of bacteria and fungi, is estimated to be responsible in humans for a large proportion of fungal infections. For example, *Candida albicans* has been reported to form in vivo polymicrobial biofilms with *Staphylococcus aureus* [19,20], and both these microorganisms, often co-infecting critically ill patients, are currently among the leading nosocomial pathogens, causing high morbidity and mortality. It has also been reported that *Staphylococcus aureus* infection is mediated by *Candida albicans* hyphal invasion of mucosal tissue [21]. When multidrug-resistant pathogens are involved in these polymicrobial infections, there are significant implications for patient management due to the difficulties in selecting the most appropriate antimicrobial therapy. Unfortunately, no single antimicrobial agent seems to be effective against the sessile polymicrobial communities. Thus, the currently available evidence suggests a multifactorial approach toward controlling these biofilm-related mixed infections.

(4) In the last decade, several strategies, mainly based on anti-adhesive, antiseptic, and/or antibiotic coatings, have been developed to prevent microbial adhesion and biofilm formation on medical devices as well as on the surfaces of hospital furniture [22–24]. Alternative approaches based on molecules able to interfere with quorum-sensing phenomena have also been set up [25,26].

However, even if a great effort has been made in recent years to develop effective anti-biofilm strategies [27], further scientific and industrial activities are urgent to be planned to reach the singling out of antimicrobial molecules able to overcome the current limits of the far available drugs, claimed to be active against biofilm-growing microbes but not having a clinically proven anti-biofilm effect.

In this regard, the recent publication entitled “Global Challenges and Microbial Biofilms: Identification of Priority Questions in Biofilm Research, innovation and Policy” by Coenye and colleagues [28] is a precious analytical working paper and a stimulating and propositive tool for researchers and policymakers.

In light of the increasingly frequent implication of microbial biofilms in hospital infections and the related worrying spread of multi-drug resistance, it is urgent to make available to clinicians effective antibacterial agents able to counteract biofilm development successfully.

Novel natural or synthetic agents able to counteract microbial biofilm development or promote their dispersal have been illustrated in a comprehensive review by Vuotto and Donelli [29] in which the most promising molecules that have demonstrated their ability to modulate steps involved in biofilm formation or to disperse pre-formed biofilms are reported and discussed. In this regard, several pieces of evidence accumulated in the last two decades demonstrated that many natural products can adequately interfere with biofilm formation and/or development [30]. However, purifying or synthesizing these substances in quantities adequate for their clinical use is difficult also because it requires large financial support from drug companies, which is rarely available, especially in the absence of a registered patent by the discoverer.

Thus, the current target is to realize the manufacture of innovative medical devices refractory to microbial colonization based on antifouling surfaces or treated with anti-biofilm coatings able to prevent microbial adhesion and biofilm formation as main causes of biofilm-based healthcare-associated infections.

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