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The Biofilm Resistance: Many Responses but Still Many Questions

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ABSTRACT

Microbial biofilms (i.e., bacterial and fungal) are often very deleterious due to their exceptional tolerance to treatments, in particular to conventional antimicrobials therapy. The processes involved in this low efficacy of antimicrobials on adherent cells have been widely studied in the last decades. It is now accepted that this tolerance of sessile cells is multiparametric. It involves different mechanisms, physico-chemical and biological. A major characteristic of biofilm microorganisms is that they are subjected to very deleterious environmental conditions which induce in them a large number of stress response mechanisms, some of which are obviously involved in this tolerance. On the other hand, few resistance systems, specifically expressed by sessile cells, have been described so far. Moreover, the fact that most natural and clinical biofilms are polymicrobial raises questions about the relevance of some observations obtained on monocultures.

Keywords: Biofilm; Resistance; Antimicrobials; Antibiotics

Abbreviations: EPS: ExoPolymers; eDNA: Extracellular DNA ; MIC: minimum inhibitory concentration; SCVs: small colony variants; QS: Quorum sensing; TCS: Two Component System

Mini Review

It is well known that biofilm infections are difficult to eradicate, adherent cells (bacteria and yeasts) exhibiting antimicrobial resistance increases of up to 200 times, as compared with planktonic counterparts [1,2]. These biofilms are thus the primary cause of failures in the implantation of medical devices, which generate high morbidity and mortality [3]. This resistance is actually more of a tolerance than a real resistance; indeed, it is essentially induced by an adaptation of the microorganisms, a reversible phenotype which switches back in the planktonic mode [4,5]. Resistance, on the other hand, generally involves an increase in the minimum inhibitory concentration (MIC) of the antimicrobial, due to an irreversible change in the microorganism through a mutation, or resistance acquired via horizontal gene trans-

fer. The low efficacy of antimicrobials on biofilms is clearly multiparametric [6] and implies both tolerance and resistance of adherent cells, in particular due to the high heterogeneity of the sessile cell physiology [7] due to gradients instauration within these structures [8].

Tolerance of Biofilms to Inhibitors

The mechanisms involved in the tolerance of biofilms are multiple [9-11] and include a low diffusivity of antimicrobials within the polymer matrix [12], a lower sensitivity to phagocytosis and other mechanisms put in place by the immune system of the host [13], a low growth rate of the microorganisms (dormancy), metabolic alterations, environmental gradients within the biofilm, and the presence of persister cells (Table 1).

Table 1: Main mechanisms involved in the tolerance of fungal and bacterial biofilms.

Mechanism Involved	Effect	References
Low penetration of the antimicrobial	Decrease of the local concentration of the antimicrobial	[15,16]
Low growth rate	Decrease of the efficacy of some antimicrobials (dormancy)	[19-21]
Metabolism alterations	Accumulation of proteins involved in adaptation, target modifications	[25,26]
Oxygen gradient	Decrease of the efficacy of some antimicrobials (intracellular penetration, dormancy)	[33-35]
Presence of persisters	Decrease of the efficacy of some antimicrobials (dormancy)	[37-38]
Quorum sensing	Activation of efflux pumps	[43]
Stress responses	Cross-resistance against antimicrobials	[50]

A Diffusional Resistance to Inhibitors

Due to its structural and mechanical properties, the polymer matrix constitutes the first defense against antimicrobial agents. It consists mainly of water, ions and ExoPolymers (EPS) in both fungal [11] and bacterial [14] biofilms. These EPS are essentially exopolysaccharides, protein lipids, but also extracellular DNA (eDNA). Due to their physico-chemical properties, EPS act as a filtering barrier, either by interaction with the compound (due to the presence of negative charges), or by trapping. Positively charged antibiotics, such as aminoglycosides, will thus bind to a negatively charged matrix, which will limit their diffusion within the biofilm [15]. Chlorine, commonly used as a disinfectant, penetrates weakly into a mixed biofilm of *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* [16]. Nevertheless, the limitation of the inhibitor diffusion in this gangue cannot alone explain the extraordinary resistance of biofilms. Thus, for example, an antibiotic such as the vancomycin, which diffuses correctly within the biofilm, is just as ineffective on sessile bacteria [17]. Likewise, fluoroquinolone antibiotics efficiently penetrate within *P. aeruginosa* biofilms [18,19].

A Low Growth Rate

Within biofilms, it exists heterogenous microenvironments corresponding to areas deficient in nutrients, oxygen or with extremely low local pH values [8,20]. Many studies show that microorganisms (yeasts [21] and bacteria [22]) display, within biofilms, a low growth rate and a phenotype close to, but different [23], from cells in the stationary phase of growth. This dormancy partially explains the ineffectiveness of antifungals [21] and antibiotics [22,24] on biofilm cells.

An Alteration of the Cellular Metabolism

It is now well recognized that the “biofilm” phenotype reflects alterations in the gene expression of adherent cells, leading to the activation of some metabolic pathways, in particular in the deeper zones of the biofilm, whereas these alterations are weaker in the more peripheral regions [24,25]. These changes in metabolism reflect adaptations of the microorganisms to the environmental conditions they encounter and explain some tolerances to inhibitors. Thus, local deficiencies in amino acids, such as leucine, cysteine and lysine,

have been shown to be responsible for the tolerance of *Escherichia coli* biofilms to ofloxacin [26]. The development of so-called “post-genomic” approaches, such as transcriptomic (consisting of identifying and quantifying the mRNAs expressed) and proteomic (consisting of identifying and quantifying the proteins expressed by a cell at a given time), allowed, in the recent decades, to draw up an inventory of the differences in gene expression in bacteria [27,28] and fungi [29-31] organized in biofilm and in suspension. However, significant differences were observed at the quantitative level between the proteomic and transcriptomic approaches. Thus, while proteomics suggests that a large number of proteins are expressed differently in bacteria in biofilms, i.e. between 15 and 50% proteome modifications, the results obtained by transcriptomic suggest that a small proportion of the genome (between 1 and 15%) shows significant changes in expression. These differences can of course be explained by the weak correlation between the quantity of mRNA and protein, but could also indicate the existence of key proteins which would not yet be identified because modified qualitatively and not quantitatively, via post-translational modifications such as phosphorylations and/or acetylations, for example [32]. Thus, Massier, et al. [33] reported significant differences in the phosphorylation rates of extracellular proteins in planktonic and sessile *Acinetobacter baumannii* cells. These authors also demonstrated that some phosphosites were located in key regions of proteins involved in antibiotic resistance, such as in betalactamases [33].

Oxygen Gradients

The oxygen tension is low in deep zones of the biofilms. This property has been demonstrated by using microelectrodes a little 20 years ago [34]. Thus, it has been shown that oxygen penetrates the first 50 microns of biofilms [35]. These oxygen-deficient areas contribute to the ineffectiveness of some antibiotics on bacterial biofilm [36-38]. For example, these anaerobic microenvironments directly impact the efficacy of aminoglycosides, including intracellular transport, which requires the presence of a protomotive force [39].

A Presence of Persisters

Within biofilms, there is also a high proportion of persistent cells called persisters, corresponding to a subpopulation of dormant cells,

which do not divide, and that are highly adapted to resist against various stresses. These persisters are found in both bacterial [40] and fungal [41] biofilms. These cells represent less than 1% of the original population and their genome is identical to that of their congeners. Different mechanisms are involved in their formation [9 and cited references]. The slow metabolism of these cells makes them less sensitive to antibiotics compared to cells in the exponential or even stationary growth phase [42]. Persisters contribute significantly to the difficulty encountered in eradicating biofilm infections such as chronic urinary and pulmonary infections. The biofilm is in fact a very favorable protective niche for persisters [43]. When the antimicrobial treatment is stopped, the emergence of these bacteria from dormancy leads to the reformation of the biofilm and the recurrence of the infection [44]. These “persisters” differ from “small colony variants” (SCVs) which are found in high proportion within bacterial biofilms [40]. SCVs are adapted variants that grow poorly on standard culture media and therefore produce very small colonies. SCVs have been involved in the recurrence and persistence of chronic infections [43,44] and show a greater ability to adhere compared to “wild” bacteria in *Staphylococcus aureus* [40].

A Role of the Quorum Sensing

The Quorum sensing (QS) is a communication system between microorganisms, linked to cell density. It is based on the synthesis and accumulation in the extracellular medium of small molecules, called auto-inductors, playing the role of pheromones. QS is strongly involved in the formation and dispersion of bacterial [[45] and cited references] and fungal [[46] and cited references] biofilms, but less so in their resistance. However, it has been shown to play a role in the biofilm tolerance of *P. aeruginosa* through the activation of efflux pumps [47].

A Response to Stress

Many environmental stresses are known to induce resistance to antimicrobials in microorganisms [48]. The unfavorable environmental conditions prevailing within the biofilms will obviously cause significant stress on the sessile microorganisms. It has thus been shown that many genes involved in the stress response were strongly over-expressed in sessile bacteria [49] and yeasts [50]. In *Candida glabrata*, for example, the resistance of biofilms to oxidative stress has been correlated with the accumulation of proteins involved in the response to oxidative stress [51].

An Overexpression of Efflux Pumps

Efflux pumps allow cells to expel inhibitors from their cytoplasm [50]. The involvement of efflux pumps in the tolerance of sessile microorganisms is relatively controversial. Thus, some studies have shown no correlation between the tolerance of biofilms of *P. aeruginosa* and the expression of efflux pumps [52,53]. By contrast, Liao et al. suggested a possible correlation between the expression of efflux

pumps and the decreased sensitivity of *P. aeruginosa* biofilms [54]. Similarly, overexpression of efflux pumps has been described as involved in the tolerance of *C. albicans* biofilms [[9] and references cited]. However, this involvement could be temporary and not concern mature biofilms [10], suggesting the role of other mechanisms such as genes and operons specifically involved in biofilm resistance. Few resistance mechanisms specifically set up by adherent bacteria have been described until now. Among these, it has been demonstrated in *P. aeruginosa* the production and accumulation in the periplasm of biofilm bacteria, of small cyclic sugar polymers able to trap aminoglycosides [55]. The production of these polymers is under the control of the *ndvB* gene which encodes a glucosyltransferase. This gene is specifically over-expressed from the first minutes following the bacterial adhesion. The PA0756-PA0757 proteins are the two elements of the first two component system (TCS) described as specifically involved in the biofilm resistance to antibiotics, in particular to ciprofloxacin [56] while these TCS were already strongly known to be involved in the biofilm formation [[57] and references cited] Similarly, still in *P. aeruginosa*, a cluster of 4 genes, called bac for *biofilm associated cluster*, has been identified, coding for proteins with unknown functions. This proteic system seems involved in the biofilm formation, in the sessile bacteria virulence but also in the resistance to tobramycin [58].

Polymicrobial Biofilms

In nature, biofilms are often polymicrobial [59]. In the medical field, chronic infections are also frequently caused by multispecies biofilms, sitting in different sites [see [59] and references therein], Emerging evidence suggests that a lot of interspecies interactions occur in these complex communities, leading to therapeutic failures [60]. In all these communities, the biological interactions are complex and are most often defined according to the result of the interaction on each of the two participating species: they can be commensal type or, on the contrary, parasitic or even mutualistic. Regardless of the consequences for each species, these interactions can lead to an acceleration and aggravation of the disease [61,62]. We can then speak of synergy between bacterial species, which can result, for example, by an increase in the production of virulence factors or even by an increase in the tolerance of species to certain antibiotics [62]. This antimicrobial tolerance can be developed by different mechanisms [63], e.g., horizontal gene transfer [64], production of β -lactamases [65], of primary metabolites [66,67] and/or of QS molecules [68] which protect neighbors, even against environmental stresses [69]. In a contradictory way, it has been shown that *P. aeruginosa* became more susceptible to ampicillin when in the presence of a drug-sensitive anaerobic community than in monoculture [70], pointing out that polymicrobial interactions can produce different antibiotic sensitivity profiles. Though polymicrobial biofilms may associate eukaryotic and prokaryotic organisms, it is clear that most studies are still today performed on bacterial pathogens. Nevertheless, it has been reported

that the biofilm matrix produced by *C. albicans* modify the structure of polymicrobial biofilms and lead to altered sensitivity of bacterial species to antibiotics [71,72]. The farnesol, a quorum sensing molecule produced by *C. albicans*, has also been shown to be able to protect *S. aureus* from vancomycin within a polymicrobial biofilm [73].

Conclusion

The resistance of microorganisms in biofilms is obviously complex and multiparametric, even if one can consider the existence of different stresses encountered by sessile cells as a common denominator. The massive doses of antimicrobial agents that would be required to eradicate them are incompatible with environmental requirements and medical reality. The fight against biofilms therefore requires new antibacterial control strategies. Among these, we can cite the search for new molecules that are more effective on adherent bacteria. This approach requires upstream a better knowledge of the molecular mechanisms specifically mobilized in this resistance, which would constitute new therapeutic targets. It is also clear that interspecies interactions modulate the sensitivity of polymicrobial communities in unpredictable ways, data obtained on monospecies cultures being not able to be extrapolated to polymicrobial structures. Better understanding these interactions is obviously an important challenge in the near future in order to better fight against polymicrobial biofilm infections.

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