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Biofilm aggravates antibiotic resistance: Molecular mechanisms behind

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***Abstract*---**It is possible for a variety of bacteria, including pathogens, to form biofilms, which serve as a mechanism for these organisms to defend themselves against antimicrobial agents in the environment. In order to explain this phenomenon of resistance within biofilms, several mechanisms have been proposed. These include delayed penetration of the antimicrobial into the biofilm extracellular matrix, slowing of the growth rate of organisms within the biofilm, and other physiologic changes brought about by interaction of the organisms with a surface. The existence of bacteria within a self-produced polymeric matrix, known as a biofilm, is another old survival strategy that is still used to this day. Biofilms, in a similar way, enable bacteria to adapt to their environment and promote the transfer of antibiotic resistance genes between different bacterial species. Because of its ability to spread antibiotic resistance genes as well as its innate phenotypic tolerance to antibiotics, biofilm must be considered synonymous with antibiotic resistance. Despite the fact that environmental biofilm does not fall under the current definition of antimicrobial stewardship, increased awareness of the existence, prevalence, and consequences of environmental biofilm among healthcare practitioners is critical to improving hygiene practises and preventing the emergence and spread of antibiotic resistance in healthcare facilities.

***Keywords*---**biofilm, planktonic cells, group behavior, drug resistance.

Introduction

Biofilm are microbial communities that attach to biotic or abiotic surfaces, with cells encapsulated in a self-produced matrix. Biofilms are crucial in medicine

since they've been linked to the development of a variety of bacterial diseases that are difficult to treat with medicines. Biofilm of *Pseudomonas aeruginosa*, for example, cause chronic lung infections in cystic fibrosis (CF) patients, while biofilms of *Staphylococcus aureus* can colonize indwelling medical equipment like pacemakers.

Bacteria can form biofilm on a variety of surfaces, including tissues, industrial surfaces, and artificial devices such as catheters, intrauterine contraceptive devices, and prosthetic medical devices, implants, cardiac valves, dental materials, and contact lenses, and can attach to inert or alive surfaces. Bacteria benefit from biofilm growth because it protects them from harmful environmental circumstances such osmotic stress, metal toxicity, and antibiotic exposure. [1] Biofilm cells are distinguished from planktonic cells by a number of fundamental traits. Biofilm cells are exposed to a gradient of nutrients and waste products, whereas planktonic cultures are subjected to relatively uniform environmental circumstances. As a result, biofilm subpopulations are physiologically varied, making biofilm research difficult because many experimental approaches, such as susceptibility testing and transcriptome profiling, examine the biofilm as a whole rather than individual biofilm subpopulations. Another significant distinction between the two lifestyles is that planktonic and biofilm cells do not have identical transcriptomes or proteomes, resulting in phenotypic discrepancies between both.

The fact that biofilm cells are substantially less vulnerable to antimicrobial treatments than their genetically identical planktonic counterparts is perhaps the most striking phenotypic difference between biofilms and planktonic cells. Biofilms of P. aeruginosa growing on urinary catheters, for example, are 1000 times more resistant to tobramycin than planktonic cells. Biofilm-based illnesses can persist indefinitely despite antibiotic treatment because to biofilm resistance to drugs. The basis for biofilm-specific antibiotic resistance and tolerance is widely considered to be multifactorial, with mechanisms of resistance and tolerance varying depending on the antimicrobial agent, bacterial strain and species, biofilm age and developmental stage, and biofilm growth circumstances. The increased antibiotic recalcitrance that is characteristic of biofilms cannot be explained by any one cause. However, when combined, these resistance and tolerance mechanisms significantly limit our capacity to treat biofilm-based infections effectively with the current antibacterial arsenal. Understanding the processes that underpin biofilm-specific antibiotic resistance and tolerance will aid in the development of medicines that disrupt these mechanisms and make biofilms more susceptible to antimicrobial therapy. The purpose of this paper is to provide an overview of the various processes that contribute to bacterial pathogens' biofilm-specific antibiotic resistance and tolerance [2]

Biofilm – A multicellular hazard

Biofilm production allows single-cell organisms to temporarily adopt a multicellular existence, where "group behavior" aids survival in harsh settings. What was originally thought to be the establishment of a colony of microbes adhered to a surface is now understood to be a complicated and dynamic developmental process. The transition from planktonic development to biofilm happens in reaction to environmental changes and is mediated by various

regulatory networks that convert signals into coordinated gene expression changes, allowing the bacterial cell to reorganize spatially and temporally. Bacteria are cocooned in a self-produced extracellular matrix that accounts for 90% of the biomass within the biofilm. Extracellular polymeric substances (EPS) serve as a stable scaffold for the three-dimensional biofilm structure, together with carbohydrate-binding proteins, pili, flagella, other sticky fibers, and extracellular DNA (eDNA). [3]

Nutrients are held in the matrix for the resident bacteria's metabolic use, while water is efficiently maintained through H-bond interactions with hydrophilic polysaccharides. Enzymes released by bacteria change the composition of EPS in response to food availability, allowing biofilm architecture to be tailored to the unique environment. As a result, the matrix's structural components produce a highly hydrated, robust structure with high tensile strength that keeps bacteria close together, allowing intimate cell-to-cell interactions and DNA exchange, while also protecting the biomass from desiccation, predation, oxidizing molecules, radiation, and other harmful agents.

The presence of environmental gradients within the biomass also contributes to biofilm resilience, resulting in community "division of labor" with subpopulations of bacteria displaying differential gene expression in response to local nutrition and oxygen availability. Despite being genetically similar to the rest of the bacterial population, studies have revealed the presence of metabolically dormant non-dividing persister cells within biofilms that are resistant to a variety of antibiotics. These are thought to be responsible for biofilm reseeding after antibiotic treatment is stopped in the clinical context. [4]

Mechanisms by which Biofilms Confer Antimicrobial Resistance

The emergence and spread of antimicrobial resistance among microorganisms (bacteria, fungi, viruses, and parasites) is one of the world's most pressing health concerns today. Antibiotic resistance is on the rise in both the community and the hospital setting, where strong selective pressure favors the selection, persistence, and maintenance of resistant, multidrug-resistant (MDR), and even pan-resistant strains (resistant to all current groups of antibiotics for therapeutic use), resulting in antibiotic treatment failure, increased mortality, and morbidity, and a significant cost impact [Figure 2] . The annual cost of antimicrobial-resistant Staphylococcus aureus infections is estimated to be around $4.6 billion. [5]

For both types of drugs, there are several examples of partial or full failure of standard antimicrobial therapies in the literature. Many hypotheses have been proposed and tested, many of which have fascinating implications. Biofilms are known to have increased antimicrobial resistance to most, if not all, antimicrobials. The mechanisms underlying such resistance are still being discovered, and they are expected to be complicated and basic. These processes can be divided into two types at first glance: constitutive and adaptive. [6] Factors Affecting Constitutive Resistance

Constitutive resistance elements are built into the biofilm mode of bacterial systems, which means that microorganisms acquire these resistance mechanisms

merely by adopting the biofilm phenotype. Many bacteria' "biofilm phenotype" has been discovered, and it has been discovered that protein expression, size, metabolism, and membrane proteins, to mention a few, all alter when a bacterium is in a biofilm (Costerton, et al. 1995). A biofilm might be thought of as a "reinvention" of the bacteria. This particular phenotype, together with the transportation challenges that develop with biofilms, may go a long way toward explaining a biofilm's antimicrobial resistance. [7]

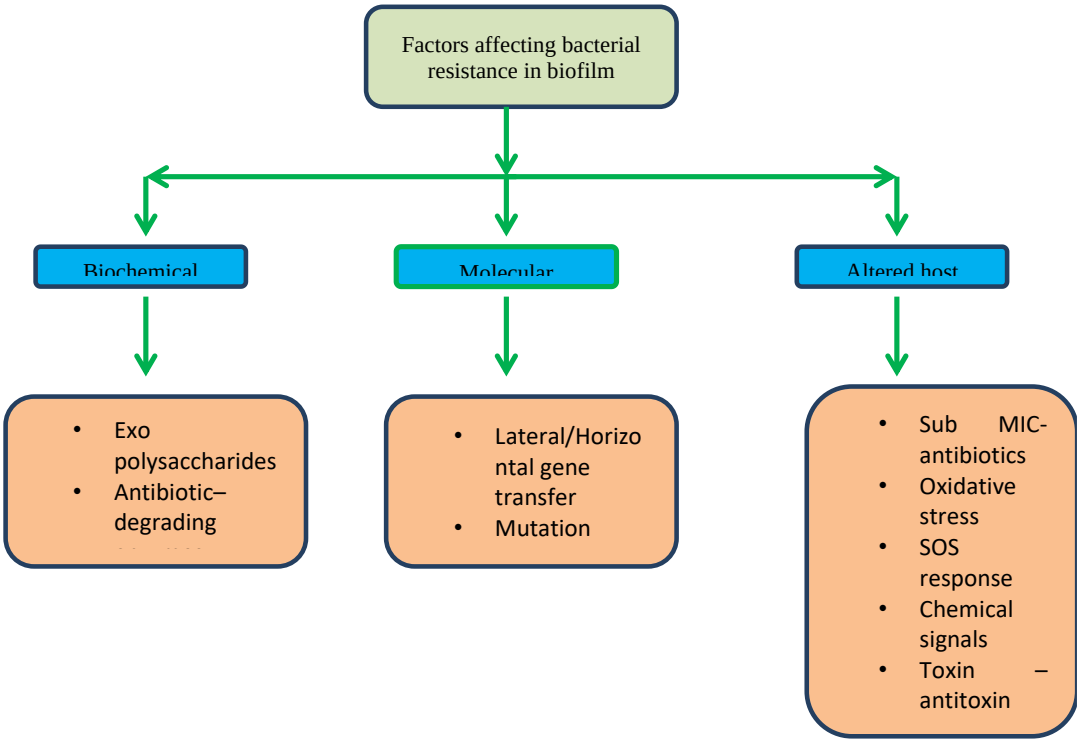

Figure 2. Mechanisms by which Biofilm Confer Antimicrobial Resistance

Antibiotic failure in biofilms: what causes it?

Antibiotic resistance is defined as a microorganism's acquired ability to withstand the effects of an antimicrobial agent, and it is linked to inheritable antibiotic resistance. Antibiotic tolerance, on the other hand, is a transitory and nonheritable characteristic determined by biofilm cell populations' physiological condition. Biofilm-specific properties that limit drug transport and action can also supply it. To operate on biofilm-forming microbes, an antimicrobial drug must overcome several obstacles, including a higher number of resistant mutations, high cell density, molecular exchanges, substance transport, efflux pump, and persistent cells. [8]

Antimicrobial penetration

Although decreased antibiotic penetration through the biofilm matrix is still occasionally cited as an important antimicrobial recalcitrance mechanism, it is

generally accepted in the literature that decreased antibiotic penetration through the biofilm matrix does not satisfactorily explain increased biofilm resistance or tolerance for most antimicrobial agents. Tetracycline, for example, reached all cells in uropathogenic Escherichia coli (UPEC) biofilms within 10 minutes of exposure without affecting cellular viability, and both ampicillin (in the absence of matrix -lactamase) and ciprofloxacin effectively penetrated Klebsiella pneumoniae biofilms at levels far exceeding the antibiotics' planktonic MICs. [9]

Similarly, staphylococci biofilms were pierced by rifampin, daptomycin, amikacin, and ciprofloxacin without affecting cellular viability. Oxacillin, cefotaxime, and vancomycin, on the other hand, have difficulty diffusing through biofilms generated by Staphylococcus aureus and S. epidermidis, suggesting that a penetration barrier may play a role in biofilm sensitivity to antibiotics. [10] It appears that the impact of diffusion limitation varies depending on the experimental apparatus, bacterial strain, and biofilm formation conditions used. For example, Suci et al. (1994) discovered that ciprofloxacin diffusion through biofilms generated by Pseudomonas aeruginosa ERC-1 on a germanium substratum under flowing circumstances was hampered at early time periods following antibiotic exposure using infrared spectroscopy. However, ciprofloxacin was found to effectively penetrate P. aeruginosa ERC-1 biofilms established on a germanium substratum in flow chambers in another study conducted by Vrany, Stewart, and Suci, which also used infrared spectrometry to measure penetration of ciprofloxacin into P. aeruginosa ERC-1 biofilms established on a germanium substratum in flow chambers. Biofilms were much thinner in the latter study than in the first, possibly due to a lower amount of phosphate in the culture medium or a different cleaning method of the germanium substratum, highlighting the importance of culture conditions and biofilm thickness in antibiotic diffusion within biofilms. Microscopy was also used to show that fluorescently labeled ciprofloxacin penetrated P. aeruginosa PAO1 biofilms produced under flowing conditions on a glass coverslip quickly and effectively. [11]

Tobramycin and P. aeruginosa are a good example of limited antibiotic penetration being a factor of biofilm tolerance. Tobramycin diffusion was slowed by P. aeruginosa biofilms, but this barrier to penetration could be overcome by adding cations to the growing medium. These findings suggest that the positively charged tobramycin molecule interacts with matrix components including eDNA and phage particles, and that decreased penetration may explain P. aeruginosa biofilm tolerance to this aminoglycoside antibiotic. It's worth noting, though, that tobramycin can penetrate P. aeruginosa biofilms given enough time. [12]

These data imply that the significance of decreased antibiotic penetration is dependent on a number of factors, including the bacterial species or strain, the antimicrobial drug in question, and the biofilm formation conditions. However, since even antibiotics that penetrate the biofilm quickly do not cause considerable cell death, the significance of limited antibiotic penetration in increasing biofilm recalcitrance is unclear. Antibiotics that enter more slowly have been hypothesized as having the potential to develop tolerance by allowing time for an adaptive phenotypic response. [13]

Nutrients and antibacterial chemicals must pass through the biofilm matrix or slime created by and encasing the organisms to reach microbial cells within biofilms. The inability of antimicrobial molecules to diffuse through the polymer matrix or deactivation of the antimicrobial molecule by the matrix material could be the cause of this diffusional constraint. Antimicrobial resistance of organisms in biofilms has been proven in a number of studies due to delayed penetration processes. Suci et al looked examined ciprofloxacin penetration into P. aeruginosa biofilms. The biofilm greatly hampered antibiotic penetration, according to the researchers. They demonstrated that diffusion of 100 g/ml ciprofloxacin from the liquid phase of a sterile microbiologic medium to the liquid/solid interface of a sterile surface generally took 40 seconds using a continuous culture apparatus. After 21 minutes, significantly less medicines were delivered to the liquid/solid interface of a biofilm-containing surface. [14]

P. aeruginosa mucoid exopolysaccharide (MEP) was tested for its capacity to bind tobramycin by Hoyle et al. They discovered that bacterial cells were distributed from biofilms due to tobramycin diffusion across the biofilm-fluid interface and into the biofilms, and that these dispersed cells were 15 times more vulnerable to tobramycin than cells in intact biofilms. However, Nichols et al. discovered that tobramycin's efficacy against biofilm cells could not be explained purely by a reduction in biofilm diffusion. They speculated that the effect could be owing to bacteria's extraordinarily slow growth rates within the biofilm's depths due to a lack of organic nutrients, inorganic ions, and oxygen. S. epidermidis susceptibility to tobramycin was investigated by DuGuid et al. [15]. They came to the conclusion that the structure of cells within biofilms was at least partly responsible for the organisms' resistance to this antibiotic. Gordon et al. looked studied the capacity of three beta lactam antibiotics (ceftazidime, cefsulodin, and piperacillin) and two aminoglycoside antibiotics (gentamicin and tobramycin) to diffuse through alginate gels. They discovered that beta lactams diffused into the matrix significantly faster than aminoglycosides, using both synthetic and bacterially generated alginates. The aminoglycosides, on the other hand, initially adhered to the alginates, and diffusion rose significantly after an 80–100 minute lag period.

EPS as a main hindrance for antibiotic penetration

To affect the coated cells, antibiotic molecules must enter the biofilm matrix. The amount of molecule that is transmitted to the inner layer of biofilm and interacts with an antibiotic agent is influenced by the extracellular polymeric matrix, which functions as an anti-spread barrier for an antimicrobial agent [Figure 1]. Biofilm EPS creates a physical barrier with various anionic and cationic molecules such proteins, glycoproteins, and glycolipids that can bind charged antimicrobial drugs and provide bacteria with a safe haven. Pel exopolysaccharides, for example, are able to distribute cationic antibiotics like as aminoglycosides and hence provide resistance to these compounds in Pseudomonas aeruginosa biofilms. [16] The matrix's adsorption sites also impede antibacterial substance movement. Glycocalyx layer, a component of EPS, can hold up to 25% of its weight in antibacterial molecules and act as an exoenzyme adherent.

It is well agreed that decreased antibiotic penetration into the EPS layer in printed materials does not fully explain the increased resistance of bacteria forming biofilms to most antimicrobial drugs. Because even antibiotics that swiftly disperse the biofilm do not cause significant cell death, the act of reduced antibiotic penetration in growing biofilm is unclear. It's been proposed that reducing antibiotic penetration allows time for an adaptive phenotypic response, which would likely lessen susceptibility. [17]

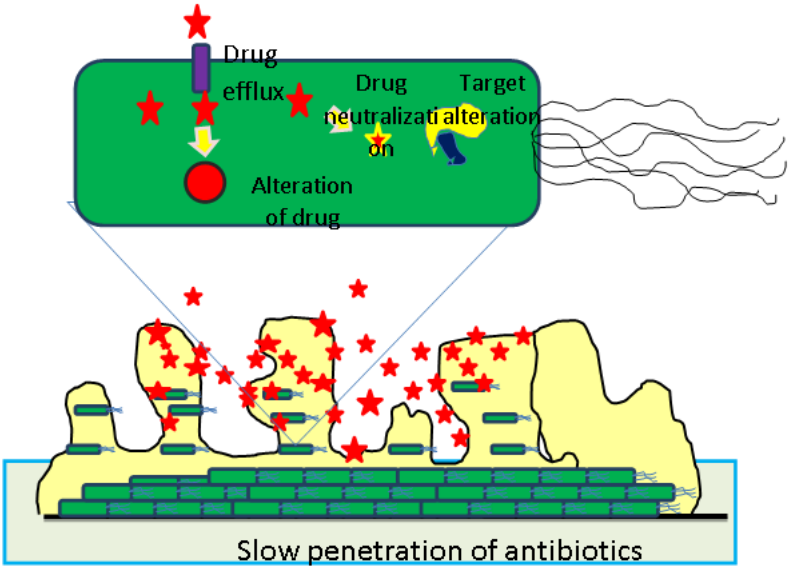

Figure 1 – Antibiotic resistance mechanism of biofilm

Alteration of the Cellular Growth Rate

An alternate hypothesized explanation for biofilm associated cells (sessile organisms) resistance to antimicrobials is that their growth rate is substantially slower than that of planktonic (biofilm free) cells, resulting in less antimicrobial molecule uptake. This question has been explored in a number of studies. Apart from other biofilm activities, Evans et al. [18] devised a cell culture approach to test the effect of growth rate. They investigated the effect of a quaternary ammonium chemical (cetrimide) on E. coli biofilms using this method. At the slowest growth rates, the organisms were the most resistant. Sessile and planktonic cultures were also sensitive at growth rates exceeding 0.3 per hour. Using a similar test approach, Evans et al. investigated the effect of ciprofloxacin on biofilms of P. aeruginosa and E. coli. They discovered that intact biofilm cells were more resistant to P. aeruginosa than biofilm cells extracted from the surface and examined in suspension. However, the pace of biofilm formation had no effect on susceptibility. The ciprofloxacin activity was regulated by the bacterial cell cycle, as newly generated daughter cells, those that had recently detached from the biofilms, were more sensitive than other populations.

The effect of ciprofloxacin on *S. epidermidis* biofilms was investigated by DuGuid et al. An increase in growth rate resulted in an increase in vulnerability in all

cases. Their findings backed up Evans et al findings.'s that the phase of the cell division cycle has a significant impact on an organism's susceptibility to antimicrobials. Desai et al. investigated Burkholderia cepacia susceptibility to ciprofloxacin and ceftazidime in the stationary phase and at various stages of exponential development. During the exponential phase, bacteria (both planktonic and biofilm) improved their resistance by a factor of 150; during the stationary phase, bacteria (both planktonic and biofilm) demonstrated the maximum level of resistance to both antibiotics. P. aeruginosa cells in older biofilms were considerably more resistant to tobramycin and piperacillin than cells in younger biofilms of the same culture, according to Anwar et al. Chuard et al. also discovered that older S. aureus biofilms (four or twenty-four hours) were less sensitive than biofilms that were only two hours old. Fleroxacin susceptibility was moderately reduced, oxacillin and vancomycin susceptibility was increased, and gentamicin susceptibility was highest. [19]

Amorena et al. also discovered that younger (6-hour) S. aureus biofilms were more sensitive to a variety of antibiotics than older biofilms. Biofilm age may be essential because as the biofilm ages, more extracellular polymeric compounds are produced, resulting in less nutrition and oxygen penetration into the biofilm matrix. All of these investigations show that cell growth rate and, in some situations, growth phase influence antimicrobial susceptibility.

Gram-negative bacteria synthesize sigma factors in response to environmental challenges like nutritional constraint. Sigma factors that are regulated by the rpoS regulon in E. coli regulate the transcription of genes whose products help to ameliorate the effects of stress. Adams and McLean tested strains with and without the rpoS gene in chemostats to study E. coli biofilm development. During the slow growth of these organisms, the rpoS gene is active. They discovered that knocking down the rpoS gene lowered E. coli's ability to grow in biofilms considerably, while having no effect on the same organisms growing planktonically. [20]

Biofilms with higher cell densities and a greater number of viable organisms were formed by the rpoS+ species. These findings strongly suggest that, at least for this organism, factors that cause bacterial growth to slow, such as nutritional constraint or the accumulation of toxic metabolites, are conducive to the creation of biofilms. This is especially important for species living deep within biofilms, where nutrition and oxygen deficiency can be severe. A slower pace of growth would not harm cell metabolism and would actually help organisms by lowering antibiotic absorption. [21]

Antibiotic-modifying enzymes in the matrix

Antimicrobials can be degraded by enzymes found in the biofilm matrix, such as secreted-lactamases, preventing them from reaching their biological targets. K. pneumoniae biofilms, for example, develop a secreted -lactamase that has been shown to effectively digest ampicillin and prevent it from reaching biofilm cells. K. pneumoniae biofilm cells, on the other hand, had other mechanisms that limit their susceptibility to ampicillin, since they were still more resistant to ampicillin

than their planktonic counterparts even in the absence of -lactamase in the matrix. [22]

AmpC -lactamase, which is chromosomally encoded and released into the matrix of P. aeruginosa biofilms, is a key determinant of -lactam antibiotic resistance in this bacterium. Bagge et al. (2004) demonstrated that in the absence of ceftazidime and imipenem, which can stimulate ampC expression in *P. aeruginosa* biofilms, ampC expression was insignificant in P. aeruginosa biofilms using a translational fusion of ampC with an unstable green-fluorescent protein reporter. Even though the cells in the biofilm center and base were physiologically active, ampC expression was limited to the biofilm periphery in the presence of a low dose of imipenem; however, an increased concentration of imipenem resulted in full induction of the reporter throughout the biofilm, implying that at high doses, imipenem can overwhelm the degradative ability of -lactamase in more superficial zones and continue to diffuse deeper into the biofilm. Due to a higher quantity of -lactamase in the matrix, mature P. aeruginosa biofilms are more resistant to ceftazidime and meropenem than younger biofilms. [23]

As a defense strategy, biofilm-forming microbes can amass large numbers of -lactamases in the biofilm matrix. When -lactamases concentrate in the P. aeruginosa biofilm matrix, medicines like imipenem and ceftazidime are hydrolyzed more quickly. P. aeruginosa PAO1-J32 biofilms have been reported to have strong promoter (ampC-lactamases) activity, as measured by scanning confocal laser photomicrographs. Furthermore, while ampicillin cannot reach the deeper levels of biofilms associated with -lactamase activity, deletion of -lactamase increases the quantity of ampicillin that reaches the deep layer. [24]

Growth rate, stress response, and persistent cells are all factors to consider. Physiological heterogeneity occurs during biofilm growth due to the presence of oxygen and other nutrients gradients in biofilms. This gradient is formed when cells at the biofilm's surface absorb available food sources and oxygen before the nutrients diffuse deeper into the biofilm. Bacterial communities with varied growth rates arise as a result of nutrient and oxygen concentration gradients. Many antibiotics have a growth-dependent impact. Because most antibiotics target the production of some kind of macromolecule, it's unlikely that they'll have much of an effect on the microorganisms in biofilm that limit macromolecular production, so conventional antibiotics are usually less effective against metabolically inactive or slow-growing cells. [25]

A limited subset of bacteria can be reversibly converted into slowly developing cells in biofilms. Persistent or dormant cells are the term for these cells. Persistent cells are highly resistant to antibiotics and are formed stochastically or under endogenous stress (e.g., oxidative stress and antibiotic exposure). When opposed to active and rapidly developing bacteria, these cells have a lower metabolism rate, making them less sensitive to antibiotics. Chronic urinary tract infections and the lungs of cystic fibrosis patients have high quantities of persistent cells, especially when immune system components penetrate poorly. Downregulation of processes such as energy production and biosynthesis characterizes the dormant phenotype. [26]

Toxin/antitoxin (TA) systems produced by environmental stimuli or DNA damage increase persistent development. TA systems inhibit protein synthesis by phosphorylating the elongation factor Ef-Tu (e.g., HipBA), resulting in translation inhibition and antibiotic tolerance; (ii) expressing the TA modules (e.g., TisB toxin forming an anion channel in the membrane), resulting in a decrease in PMF and ATP levels; and (iii) breaking down mRNA (e.g., RelE and MazF toxins) Long-term treatment with aminoglycosides and the RNA polymerase inhibitor rifampicin, in combination with TA systems, may prevent persistent resuscitation. Fluoroquinolones are thought to induce TisB toxin in Escherichia coli through causing DNA damage. Many TA systems are linked to multidrug-tolerant persistent cells in biofilms. This tolerance, however, is restricted to a few antibiotics and TA. [27]

Bacteria have a variety of stress responses that enable them to cope with environmental changes such as oxidative stress, temperature changes that are unexpected, low water activity, deprivation, and DNA damage. These adaptive reactions help the bacteria survive longer. Antimicrobial susceptibility can be influenced by adaptive stress responses because they affect many of the same cellular components and processes that antimicrobials target. One of the causes of the stress response is heterogeneity in the biofilm. The metabolic activity of cells in hypoxic zones is reduced, and they appear to be in a standstill phase. Many stress responses are known to cause bacterial cells to enter the stationary phase. [28]

Nutrient deprivation also causes the creation of (p)ppGpp, which mediates the stringent response, a global stress response. Multidrug tolerance in P. aeruginosa biofilms is aided by the stringent response and (p)ppGpp signaling. When the stringent response was inactivated, the killing of ofloxacin, gentamicin, meropenem, and colistin increased. Through mechanisms involving the stringent and SOS responses, nutrient deprivation also produced ofloxacin tolerance in E. coli K-12 biofilm. [29]

Efflux pumps in biofilms

Efflux pumps are membrane proteins involved in the export of hazardous chemicals from the inside of the bacterial cell to the outside world. Efflux pump genes can be found in bacterial chromosomes or mobile genetic components like plasmids, and they are found in all species of bacteria. Efflux pumps extrude a wide range of substrates, including medicines, detergents, colors, poisons, and waste metabolites. [30] The main facilitator superfamily (MF), the small multidrug resistance family (SMR), the ATP-binding cassette family (ABC), the resistance nodulation-division family (RND), and the multidrug and toxic compound extrusion family are the five recognized kinds of bacterial efflux pumps (MATE). The ABC family system hydrolyzes ATP to carry out the antimicrobial agent flow, while the MF, MATE, and RND families operate as secondary carriers and catalyze the drug ion antiproton. [31]

Efflux pumps are involved in some bacteria' inherent resistance to antibiotics. Overexpression of these pumps causes acquired resistance and contributes to other resistance mechanisms. Multidrug resistance can result from

overproduction of the efflux pump. Multidrug resistance (MDR) is a trait of bacterial efflux pumps. The efflux pump reduces the transmembrane diffusion of lipophilic solutes by slowing the diffusion of hydrophilic solutes by downregulating "porin" synthesis in pathogenic bacteria such E. coli, Enterobacter aerogenes, and Klebsiella pneumonia. [32] Some multidrug efflux pumps play an important role in biofilm development, and this process can be leveraged to assist bacteria resist antibiotic attacks from a variety of classes. Mutant E. coli lacking the several genes related with efflux pumps has been shown to have significantly reduced biofilm formation.

In the presence of azithromycin, upregulation of certain efflux pumps (MexAB-OprM and MexCD-OprJ) has been reported in resistant P. aeruginosa biofilms. It has been discovered that flow pump PA 1874-1877 is linked to antibiotic resistance in biofilms. In biofilm settings, decreased resistance to aminoglycosides and fluoroquinolones is shown when these genes are altered. [33] Efflux of EPSs and QS molecules to assist biofilm matrix formation and control QS, respectively, leads to indirect regulation of genes involved in biofilm formation and influences aggregation by boosting or blocking adherence to surfaces and other cells, according to various studies.[34]

Conclusion

Specific antimicrobials that have been found to be more efficient in either killing biofilm organisms or blocking their adhesion may be used in treatments to control or attenuate biofilms. Other biofilm therapies concentrate on specific biofilm components, such as the extracellular polymer matrix. Standard and established approaches for microbiologic control with antimicrobials are clearly insufficient for the treatment of infections involving biofilms. It is necessary to gain a better knowledge of the role of biofilms in infection. Reid and Bailey 39, for example, wondered why some patients who had been colonized by biofilms do not display symptoms of infection. How does a doctor know whether or not asymptomatic biofilm growth needs to be treated with antibiotics? To validate laboratory findings, more research into how in vivo biofilms respond to antibiotic treatment is needed. The findings of these types of investigations are expected to lead to more effective treatment techniques. However, for this to happen, the medical community as a whole must recognize the relevance of biofilms. It's time for a paradigm shift.

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