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REVIEW

Biofilm: the invisible fortress of bacteria

Biofilm: la fortaleza invisible de las bacterias

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ABSTRACT

Introduction: Biofilm is an organized and multidimensional association of biological agents that are located within an extracellular matrix composed of polysaccharides (polymeric), as well as proteins, mineral salts and DNA. Together with cellular remains that represent 10 or 20 % of its composition.
Objective: characterize antimicrobial resistance from the point of view of the Biofilm.
Method: a bibliographic research was developed. Scielo, SCOPUS, and PubMed databases were used using the search terms and their English equivalents. After reviewing the title, summary and application of the inclusion criteria, we worked with 25 investigations.
Development: the composition of Bioflim is described as a complex organization, which gradually gains structure. The Biofilm compound is typical of gram-negative bacteria as a result of its high resistance capacity. The regulatory process for the formation of compound Biofilms is based on complex networks of regulators. One of the compounds demonstrated in this system is quorum sensing or autoinduction. For a Biofilm compound to be considered harmful or associated with antimicrobial resistance, a series of characteristics must be present.
Conclusions: Biofilm constitutes a biofilm made up of a heterogeneous group of molecules that give it similar characteristics, as well as peculiar ones for each of the bacteria. Its organization in structures, of greater complexity as the formation process progresses, allows it to respond to the adversities of the environment and a high capacity for antimicrobial resistance. Its composition and formation varies with each stage. For the most part, it is typical of gram-negative bacteria, which is the basis for their high capacity for resistance.

Keywords: Bacteria; Anaerobic Bacteria; Biofilms; Biofilm; Drug Resistance.

RESUMEN

Introducción: el Biofilm es una asociación dispuesta de forma organizada y multidimensaional de agentes biológicos que se ubican dentro de una matriz extracelular compuesta por polisacáridos (polimérica), además de proteínas, sales minerales y ADN. De conjunto con restos celulares que representa el 10 o 20 % de su composición.
Objetivo: caracterizar la resistencia antimicrobiana desde el punto de vista del Biofilm.
Método: Se desarrolló una investigación bibliográfica. Se utilizaron en las bases de datos Scielo, SCOPUS, PubMed mediante los términos de búsqueda y sus equivalentes en inglés. Tras la revisión del título, resumen y aplicación de los criterios de inclusión se trabajaron con 25 investigaciones.
Desarrollo: la composición del Bioflim se describe como una organización compleja, que va ganando en estructuración de forma paulatina. El compuesto de Biofilm es típico de las bacterias gramnegativas a consecuencia de su alta capacidad de resistencia. El proceso de regulación para la formación del compuesto

Biofilms se basa en complejas casadas de reguladores. Uno de los compuestos demostrados en este sistema se encuentra el quorum sensing o autoinducción. Para que un compuesto de Biofilm sea considerado como dañino o asociado a la resistencia antimicrobiana deben estar presente una serie de características.
Conclusiones: el Biofilm constituye una biopelicula integrada por un grupo heterogéneo de moléculas que le aportan características similares, a la par que peculiares para cada una de las bacterias. Su organización en estructuras, de mayor complejidad a medida que el proceso de formación avanza, le permite responder a las adversidades del medio y una alta capacidad de resistencia antimicorbiana. Su composición y formación varía con cada etapa. En su mayoría, es propia de las bacterias gramnegativas lo que fundamenta su alta capacidad de resistencia.

Palabras clave: Bacterias; Bacterias Anaerobias; Biopelículas; Biofilm; Resistencia a Medicamentos.

INTRODUCTION

Throughout history, many diseases have plagued humanity. Since then, man has tried to deal with each of these pandemics. With the emergence of antimicrobial drugs, an important turn has been made in the confrontation of the biological agents responsible for these affections, especially for bacteria. However, medical services face a more relevant phenomenon: antibacterial resistance. In the 1950s, a wide arsenal of antimicrobials was available, which led to the thought, later labeled as erroneous, that bacterial infections could be successfully treated and eliminated. However, along with the rapid advancement of new drugs, new bacterial strains emerged that were increasingly resistant. These include variants of Staphylococcus aureus, Streptococcus pneumoniae, Pseudomonas aeruginosa, and Mycobacterium tuberculosis.[1] The study of the different mechanisms of antimicrobial resistance began. In their research, Becerra et al.[1] assessed the different mechanisms of antimicrobial resistance used by bacteria. Among the different mechanisms or theories postulated about the development of antimicrobial resistance, intrinsic resistance can be mentioned. It is characterized by the generation or acquisition of new genetic material from resistant bacteria through transformation and transduction with traps that allow the implantation of this new material into the bacteria's genetic machinery. This mechanism is implemented by Staphylococcus aureus. Other mechanisms have been developed in conjunction with the above, such as using efflux excretion pumps. Other methods are related to adaptive drug resistance. Within this method, persistence mechanisms, drug indifference, and pellicule (biofilm) deployment can be cited. In the last century, the main bacteria requiring the attention of healthcare personnel, especially microbiologists, were those responsible for specific diseases. These biological agents, mostly specialized bacteria, stood out for their pathogenicity and specificity mechanisms. After developing antimicrobials, the causative agents of diphtheria, tuberculosis, cholera, pertussis, and others have considerably reduced the number of confirmed cases and the incidence, mortality, and morbidity rates.[2] Along with this phenomenon, a constant and gradual growth of ubiquitous bacterial infections has been observed. They are responsible for chronic infections characterized by poor response to antimicrobial treatment and poor response of the immune system. It is estimated that about 65 % of bacterial infections are of this type due to the development of antimicrobial resistance mechanisms, including biofilm.[2] In microbiology, biofilm or biofilms correspond to communities of microorganisms responsible for an aggregate growth of the extracellular matrix of bacteria. A matrix of proteins, extracellular deoxyribonucleic acid, and exopolysaccharides characterize them. This compound and the bacteria that produce them are the pathophysiological substrates for developing chronic infections such as acute otitis media, osteomyelitis, and infections related to medical devices (catheters, prostheses, especially joint or orthopedic prostheses).[3] In his study, Morón Araújo[4] presents two definitions of the Bioflim compound according to the evolution of the knowledge generated from its study. In the first moments, it was defined as a bacterial community that adhered to a solid plane immersed in a liquid medium. Subsequently, the structural definition of this compound was updated as a community of bacteria immersed in a liquid medium, attached to a surface or on top of each other, embedded from an extracellular matrix produced by them. They also show an altered phenotype about the multiplication or gene expression degree. Aspects that make it worthy of medical interest and its relationship with antibacterial resistance to pharmacological compounds.

Biofilm is an organized and multidimensionally arranged association of biological agents located within an extracellular matrix composed of polysaccharides (polymeric), proteins, mineral salts, and DNA, together with cellular debris representing 10 to 20 % of its composition. Important stages are involved in the production of this compound, such as conditioning, adhesion, matrix synthesis, maturation, and dispersion.[5,6] Regarding biofilm, theories or mechanisms have been postulated to describe or explain how this compound acts in antimicrobial resistance. In the first instance, they sustain the criterion that the synthesized matrix becomes more resistant to the passage of antibiotics, so the drugs cannot reach the site of action. Another theory states that bacteria

inside this compound do not replicate similarly, so their metabolism differs from those outside this compound; it has been related to a form of indifference to the drug.

On the other hand, the most accepted theory exposes the combination of several resistance factors, such as persistence and indifference.[1,5,7,8]

According to the study by Cueto-López et al.[9] concerning the behavior of infections diagnosed in surgeries where medical devices were used, an alarming growth of this complication can be observed. About breast implants, the infections oscillate between 2 %, a value that may increase if we talk about oncologic patients. For penile implants, the value is between 2 and 3 %, and it can reach 15 or 20 % if associated with comorbidities. The figures for surgical implants (meshes) and cochlear implants are 1 to 8 % and 1,6 to 10 %, respectively. The figures About medical devices increase due to the possibility of better and faster dissemination.

On the other hand, Guamán Torres et al.[10] state that most infections in patients with medical devices may be due to biofilm generation by the bacteria involved. The behavior of antimicrobial resistance has hurt the development of medical care. As a result of the specialization of bacteria and the use of increasingly resistant methods, healthcare personnel require more effective therapeutic methods and means. For this reason, it is necessary to know the means of bacterial resistance used by biological agents. Based on the above, this study aimed to characterize antimicrobial resistance from the point of view of the biofilm.

METHOD

A bibliographic research on biofilm and its relationship with bacterial resistance was developed. In order to obtain the information, the following terms were used: Bacteria, Anaerobic Bacteria, Biofilms, Biofilm, Drug Resistance, and their equivalents in English. They were related from Boolean operators for a better relation between the terms. The databases Scielo, SCOPUS, PubMed, and the Google Scholar search engine were used. In the case of the SCOPUS database, the following search strategy was used: SUBAREA (medi OR dent OR heal) AND TITLE-ABS-KEY (biofilm) AND (bacteria)) AND (LIMIT-TO (EXACTKEYWORD, “Biofilm”) OR LIMIT-TO (EXACTKEYWORD, “Biofilms”) OR LIMIT-TO (EXACTKEYWORD, “Microbiology”) OR LIMIT-TO (EXACTKEYWORD, ‘Bacteria’)) AND (LIMIT-TO (SUBJAREA, ‘MEDI’)) AND (LIMIT-TO (DOCTYPE, ‘re’)) AND (LIMIT-TO (LANGUAGE, ‘Spanish’))).

Inclusion criteria were articles published in peer-reviewed journals, other sources (theses or others) deposited in institutional repositories, and related articles. Articles that did not meet these criteria were excluded. A total of 40 sources were found. After a review of the title, abstract, and application of the inclusion criteria, 25 research studies were included.

DEVELOPMENT

Biofilms compound contributes to the perpetuation of microbial resistance. However, this is only sometimes the case, as there are examples where this compound may be present in areas of the body that act as a defensive barrier. Biofilms of lactobacilli help in the fermentation of glycogen in the vagina and, therefore, in the maintenance of vaginal pH, a condition that contributes to the prevention of infections. Similarly, bacterial agents that contribute to biofilm formation in dental enamel prevent the formation and colonization of exogenous agents.[11] However, the condition of biofilm production is a characteristic of bacteria that is estimated to have been present since 3,5 billion years ago and in approximately 99 % of bacteria. This condition allows them to cope with the various adversities of the environment while responding and resisting the action of antimicrobials, which in turn provides them with a greater virulence capacity.[12]

Composition of Bioflim

The composition of Bioflim is described as a complex organization gradually gaining structure. Its components, despite having base substrates and similar in most bacteria, can be differentiated in certain compounds, which offer unique particularities for each infectious agent.[13] This compound begins to be generated when signals from the medium report adverse conditions. These conditions can range from deficits in nutrient availability, changes in osmolarity, pH of the medium, oxygen tensions, and temperature changes.[14] The biofilm was categorized as a composite in 1975 by defining it as a complex community of microorganisms living on diverse surfaces where multiple species may exist. Biofilm composition is varied and broad depending on the bacteria interacting in the medium. Its composition includes exopolysaccharides, extracellular ADNA, RNA, proteins, and lipids. The entire extracellular matrix generated from the union of these compounds creates an ideal environment for bacterial growth thanks to its antimicrobial, disinfectant, and protective qualities against the host’s immune system.[15] Several forms of organization are involved in the matrix arrangement. One of the most studied forms of organization is the flat structure with a homogeneous composition. It is characterized as a dense biofilm structure, with numerous microcolonies of similarly shaped bacteria within a dense structure with no water channels or pores running through it. A second form of organization corresponds to a heterogeneous mosaic, where the colonies presented a greater spatial organization on the substrate and were separated and delimited

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from their neighbors.[16] The third form of organization corresponds to the spatial composition of a tulip or mushroom, where the different compounds are organized so that there is communication between them for the normal flow of liquids. These channels act as means of communication and sending signals.[16] Each of these forms of organization is superior to the previous one, an aspect that speaks in favor of the resistance capacity that the Bioflim can provide to bacteria, as well as its capacity to respond to the conditions of the environment. Likewise, there is a series of polysaccharides of importance in the formation and composition of the biofilm. One of the most studied is the one produced by S. aureus, being the icaADBC locus essential for its production and secretion. It is considered one of the main components of the extracellular matrix.[17]

Biofilm compound formation

Biofilm compounds are typical of gram-negative bacteria due to their high resistance capacity. Its formation begins with the period of adhesion to the surface where the compound will be synthesized. One of the particularities of this stage is the participation of the mobile elements of the bacteria (flagella, fimbriae, among others) to achieve their attachment to the surfaces. However, this is optional for the success of the stage since gram-positive bacteria such as staphylococci can use surface proteins. Once fixation is achieved, the bacteria divide gradually and form microcolonies with the daughter cells.[11] In general, this stage requires the presence of surfaces of an inflammatory or necrotic nature to achieve adequate fixation of the bacteria. [16] The presence of lesions or juries in the tissue, together with the different phases of healing, including neovascularization, make the affected area ideal for bacterial proliferation due to the constant supply of nutrients for the normal reconstruction process. In turn, losing the integrity of the protective tissue (skin or mucosa) is a determining factor for the inoculation of bacteria. At a later stage, the bacteria begin to secrete an exopolysaccharide that forms the matrix of the Biofilm and forms mushroom-like structures (mushrooms) between which the presence of canals can be observed. The composition of this compound is unique for each bacterium: alginate for Pseudomonas aeruginosa, cellulose, a compound rich in glucose and galactose or poly-N-acetylglucosamine for S. Typhimurium, V. cholerae and S. aureus respectively.[11,18] This peculiarity of bacteria to synthesize a different compound, in consideration of the authors, provides additional and unique elements in bacterial resistance that should be analyzed to achieve the optimal treatment for each infectious agent. The matrix that is formed not only achieves a consolidation of the structure of the Biofilm but also allows the attraction of a greater number of bacteria, which in turn contributes to the formation of greater amounts of this compound. According to authors such as Jaime Romero[16] in his study on the formation of the composite and its role in dental infections, Fusobacterium nucleatum is one of the key bacteria for the adhesion phase as it is cataloged as the bridge bacteria that attracts others such as Streptococcus intermedius necessary for the formation of the composite. To conclude the formation process, some bacteria are released from the biofilm matrix to colonize new structures. There are still aspects to investigate about this process because it is the stage considered less known. Some theories have been postulated that forming biofilms with different characteristics and variable composition in some areas where bacteria exit occurs stands out. At the same time migrations occur, the inflammatory process spreads, thus achieving the chronic nature of the infection. It is estimated that at this stage, the conformation of the matrix has only 15 % of bacteria distributed in about 300 overlapping layers.[11,16] The regulatory process for forming the biofilm compound is based on complex cascades of regulators. One of the compounds demonstrated in this system is quorum sensing or autoinduction. This compound, acyl-homoserine lactone for Gram-positive bacteria and peptides for Gram-positive bacteria, induces compound formation upon environmental changes based on bacterial population density. In addition to quorum sensing, other global regulators, such as CsrA in E. coli and CytR of V. cholerae, are important determinants for the biofilm development of these bacteria.[18]

Biofilm-generated antimicrobial resistance

A series of characteristics must be present for a biofilm compound to be considered harmful or associated with antimicrobial resistance, such as colonization of substrates by bacteria with adherent capacity and biofilm producers. There must also be a damaged material or tissue lesion that conditions the proliferation of this type of bacteria. In turn, infection must be achieved due to small bacterial compounds, usually Staphylococcus aureus, Staphylococcus epidermidis, and Pseudomonas aeruginosa, which are resistant to treatment with antimicrobials.[11] The clinical responses generated from the action of the Biofilm vary according to the phase of production and consolidation of the compound. In the first instance, a low response to the action of the antimicrobial compound is observed. As the infectious process progresses, there is a constant and increasing release of toxins by the causative agents; in this state, the organism's response capacity decreases.[14]

Bacterial biofilm releases antigens and stimulates antibody production, inhibiting the proliferation of T lymphocytes and peripheral monocytes by inducing prostaglandin E2 and interfering with B cell blastogenesis and coagulation. It also appears to affect opsonization and phagocytosis by inhibiting chemotaxis adversely, inducing degradation, and inhibiting the oxygen-dependent metabolic activities of PMN leukocytes, leading to

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intracellular death.[14] One of the bacteria with the greatest role in developing Bioflim as antimicrobial resistance mechanisms is Pseudomonas aeruginosa. This opportunistic, ubiquitous bacterium has the particularity of adapting to the environment in which it is found and to the availability of nutrients.[19] This aspect undoubtedly gives it an important characteristic in antimicrobial resistance and a special interest in health care. The different treatments used to manage this agent are based on a series of mechanisms of action that affect the cell wall, protein synthesis, and DNA and RNA processes. However, studies such as the one generated by Bolivar-Vargas et al.[19] recognize the resistance mechanisms generated from the DNA and its relation with the Biofilm, one of the qualities of Pseudomonas aeruginosa as a consequence of the union to plasmids due to its high DNA content, which provides an evolutionary adaptation. According to this author,[19] this agent generates two types of biofilms. A flat or initial one that integrates a confluence of bacteria. As opposed to a structured one where channels separate bacteria. This mechanism is involved in a series of highly resistant processes such as pneumonia and other pathologies such as secondary infections or in the bacterial endowment of cystic fibrosis, chronic wounds, otitis media, and urinary tract infections, among other pathologies. According to international data, it is estimated that infections caused by this agent exceed 8,9 % of cases due to resistance. A study by García-Mariño et al.[20] showed the presence of Staphylococcus epidermidis as a producer of Biofilm as a complication of urethritis in the male sex. In the study, 48 samples of patients diagnosed with urethritis were analyzed, of which more than 50 % were resistant to drugs such as penicillin, oxacillin, and ampicillin, among others. In turn, Champi Merino et al.[21] expose the antimicrobial resistance generated from the Biofilm by Staphylococcus aureus to different drugs such as beta-lactams, aminoglycosides, macrolides, lincosamides, chloramphenicol, tetracyclines, sulfa trimethoprim, rifampicin, quinolones, and glycopeptides. On the other hand, in their research, Zavala Castillo et al.[22] expose the relationship between the Biofilm generated by this bacterium and the resistance generated to oxacillin. Janampa Bautista et al.[23] showed that biofilm-producing bacteria were isolated in a health institution where Klebsiella pneumonia was predominant. On the other hand, Rodriguez Sevilla et al.[24] analyzed the response capacity of Mycobacterium abscessus to some antimicrobials, including amikacin, which proved to be resistant. Regarding the treatment that could be used against bacteria that use these compounds, metallic nanoparticles can be mentioned, especially those of copper, in addition to their combination with known antimicrobials such as fosfomycin, where copper can be included in the increase of the response capacity of the drug, as expressed by Gonzalez Machado.[25] In the same way, other compounds, such as the enzymatic treatment, can cause damage to the composition of the biopalicula and allow the entrance of the antimicrobial agent.

CONCLUSIONS

A biofilm comprises a heterogeneous group of molecules that provide similar characteristics and are peculiar to each bacteria. Its organization in structures, of greater complexity as the formation process progresses, allows it to respond to the adversities of the environment and a high capacity for antimicrobial resistance. Its composition and formation varies with each stage. For the most part, it is characteristic of gram-negative bacteria, which is the basis for its high resistance capacity.

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The authors declare that there is no conflict of interest.

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Research: Nairobi Hernández Bridon.
Drafting - original draft: Nairobi Hernández Bridon.
Writing - proofreading and editing: Nairobi Hernández Bridon.