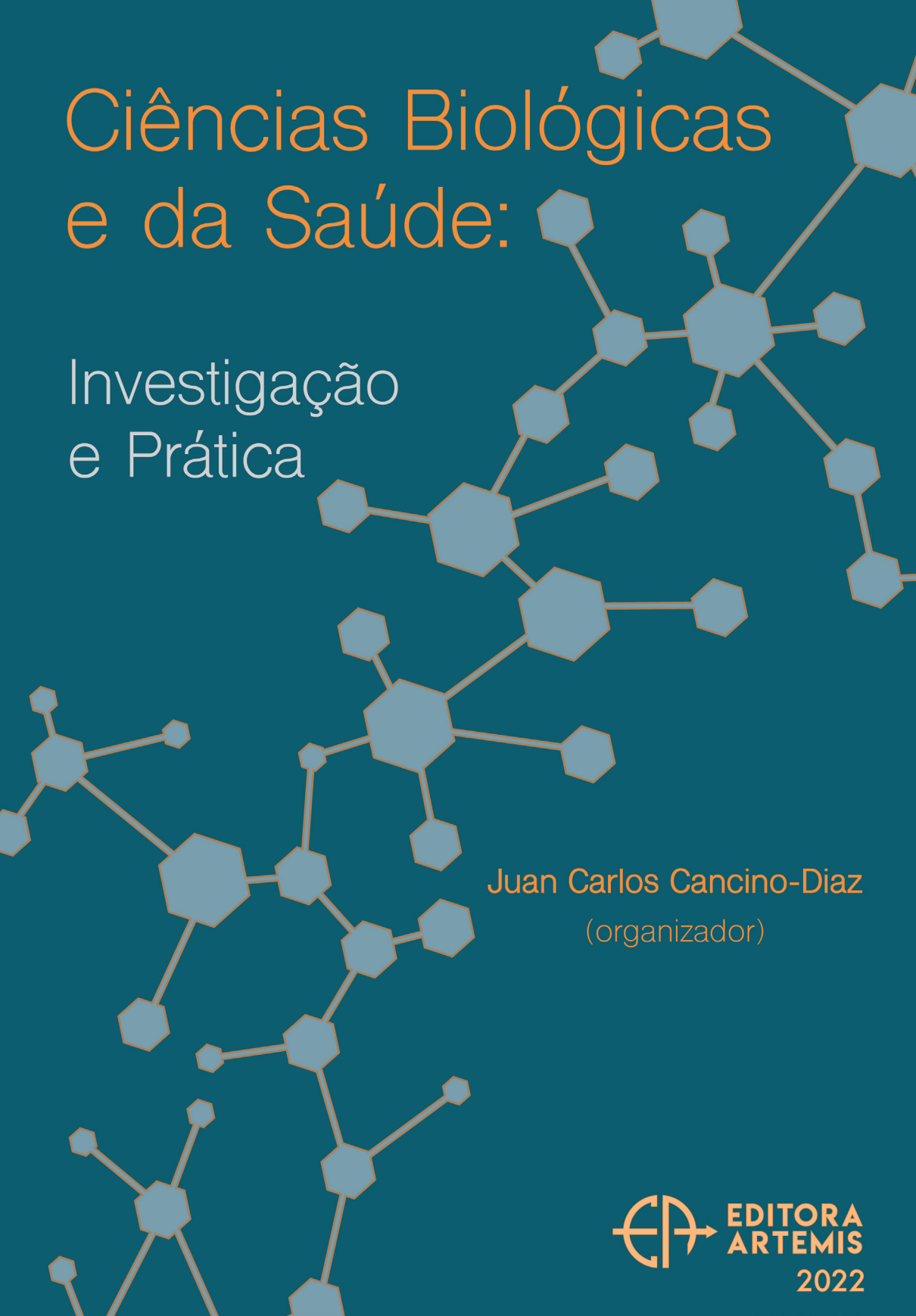
Ciências Biológicas e da Saúde:

Investigação e Prática



Juan Carlos Cancino-Diaz
(organizador)

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PRÓLOGO

El estudio de las ciencias biológicas es tan amplio que abarca diferentes disciplinas, entre ellas la medicina, la inmunología, la microbiología y hasta el medio ambiente. La investigación en las ciencias biológicas aporta las bases científicas para el mejoramiento de las diferentes disciplinas. En la actualidad hay un gran interés sobre nuevas investigaciones en ciencias biológicas que ayudan a contestar diferentes inquietudes ocurridas en la vida cotidiana. En este libro constituido por 12 capítulos se enfoca en dos disciplinas de las ciencias biológicas, la disciplina médica y la disciplina inmunomicrobiología.

La disciplina médica está estructurada sobre aspectos comunes acontecidos en el área de la salud, como es el caso de las prácticas y experiencias de los enfermeros, investigación soportada con relevancia estadística sobre el impacto y los factores que influyen sobre los enfermeros al aplicar sus prácticas de salud hacia a los pacientes y a su vida personal. Estos trabajos son importantes porque demuestran que el bienestar del enfermo contribuye al mejoramiento del paciente y del entorno ambiental. Por otro lado, capítulos que abordan sobre el tópico neuromuscular están incluidos en esta área de salud. Esta investigación neuromuscular se inserta desde estudios sobre la relación y las necesidades de la familia con un miembro con enfermedad patológica neuromuscular, hasta investigación relacionada con aspectos de la asociación del tono muscular con la vista o la relación con el tipo de ejercicio o rutina ejercida por un individuo. Por último, en esta área de salud se adiciona un capítulo sobre COVID-19, un estudio interesante que establece el comportamiento y la experiencia de la población brasileña sobre la enfermedad del COVID-19, el estudio muestra como las diferentes poblaciones etarias presentaron su sentir de miedo de contraer COVID-19 en los diferentes períodos de la pandemia.

El libro tiene una sección de ciencias biológicas en la disciplina inmunomicrobiología. En esta parte es más diversa que incluye un capítulo que se enfoca sobre la utilización de la inmunología sobre el tratamiento del cáncer, la utilización de diferentes anticuerpos monoclonales dirigidos para reducir o inhibir el desarrollo del cáncer. Tres capítulos hablan sobre bacterias, uno de ellos sobre el efecto de la biopelícula de Staphylococcus epidermidis para evadir la respuesta inmune del neutrófilo, otro sobre la fermentación de Bacillus subtilis ANT01 sobre la actividad antifúngica y por último, la producción de ácidos orgánicos de origen fúngico para la aplicación en la lixiviación de metales.

El libro está dirigido a la comunidad médica y científica que aporta información relevante en el área de ciencias biológica; el lector puede tener una visión general de la investigación de esta área biológica y comprender la complejidad y diversidad de tópicos relacionados con esta área.

Dr. Juan Carlos Cancino Diaz

SUMÁRIO

SALUD Y PRÁCTICAS

CAPÍTULO 10

THE *Staphylococcus epidermidis* BIOFILM MAY EVADE THE NEUTROPHIL IMMUNOLOGICAL RESPONSE

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ABSTRACT: The complement system is a mechanism for bacteria opsonization, elimination, and neutrophils' recruitment. Neutrophils eliminate opsonized bacteria by phagocytosis, emptying their granules, releasing antimicrobial peptides (AMPs), or forming neutrophil extracellular traps (NETs). The *Staphylococcus epidermidis* biofilm can inactivate or evade the neutrophil death induction response. In addition, this biofilm can trap complement molecules or antibodies against *S. epidermidis*, preventing them from reaching the bacterial surface and inhibiting opsonization. Furthermore, the supramolecular size of the biofilm inhibits phagocytosis and prevents the AMPs from directly acting on the bacteria membrane. Neutrophil granules release cathepsin G, cathepsin B, metalloprotease-9, and proteinase 3 that can proteolytically process the accumulation-associated protein (Aap) from *S. epidermidis* inducing biofilm development. In parallel, NETs can be used as physical support for the biofilm. Then, *S. epidermidis* biofilm is considered a virulence factor that can help persist this microorganism by evading and controlling the neutrophil death response.
KEYWORDS: *Staphylococcus epidermidis*. Neutrophiles. Biofilm.

EL BIOFILM DE *Staphylococcus epidermidis* PUEDE EVADIR LA RESPUESTA INMUNOLÓGIA DEL NEUTRÓFILO

RESUMEN: El sistema del complemento es un mecanismo para la eliminación de bacterias y la opsonización de ellas, además para el

reclutamiento de los neutrófilos; los neutrófilos reconocen a las bacterias opsonizadas para eliminarlas por fagocitosis, o por el vaciado de sus gránulos, o por la liberación de péptidos antimicrobianos (AMPs) o por la formación de trapas extracelulares de neutrófilos (NETs). Sin embargo, la biopelícula de *Staphylococcus epidermidis* puede inactivar o evadir la respuesta de muerte por el neutrófilo. La biopelícula puede atrapar a las moléculas del complemento o a los anticuerpos contra *S. epidermidis* para evitar que lleguen a la superficie bacteriana e inhibir la opsonización. El tamaño supramolecular de la biopelícula hace que se inhiba el proceso de fagocitosis, además los componentes de la biopelícula impiden que los AMPs pueden actuar sobre la bacteria. El vaciado de los gránulos del neutrófilo libera catepsina G, catepsina B, metaloproteasa-9 y proteinasa 3 que pueden procesar proteolíticamente a la proteína Aap de *S. epidermidis* y como resultado inducir la biopelícula, además la formación de NETs puede ser utilizadas como una cama o soporte para incrementar la biopelícula. Todo esto demuestra que la biopelícula, como uno de los factores de virulencia de *S. epidermidis*, puede evadir y controlar la respuesta de muerte por el neutrófilo.
PALABRAS CLAVE: *Staphylococcus epidermidis*. Neutrófilos. Biopelícula.

1 INTRODUCTION

Staphylococci are Gram-positive bacteria forming clusters in the shape of bunches of grapes with a low content of guanines and cytokines in their genome. Staphylococci are halotolerant and classified into coagulase-positive staphylococci (i.e., *Staphylococcus aureus*) and coagulase-negative staphylococci (i.e., *Staphylococcus epidermidis*). From the point of view of human health, staphylococci are common nosocomial or healthcare-associated infections. The most frequent staphylococcal species associated with nosocomial infections are *S. aureus and S. epidermidis*. These two species can cause skin abscesses and sepsis and in acute infections can also cause chronic complications, such as in the case of medical implant-related infections (Lowy, 1998).

On the other hand, after *S. aureus* or *S. epidermidis* infects and colonizes a tissue, the immune system goes into action to control and eliminate bacteria. One of the first immune cells to participate in the early immune recognition are neutrophils, essential players in host defense against staphylococci. However, in the particular case of *S. aureus*, it is reasonably well known that this bacterium has many proteins and toxins that prevent neutrophils from functioning against them. In contrast, *S. epidermidis* has not yet been documented if it possesses an arsenal of proteins and toxins to evade the Neutrophil's action.

The prominent mechanism of infection of *S. epidermidis* is biofilm formation. Biofilm is a bacterial community attached to a biotic or abiotic surface with bacterial production of an extracellular polymeric substance (EPS) surrounding the resident bacteria. Biofilm infection is difficult to treat because the bacteria in the biofilm are protected against antimicrobial therapy and the action of the immune system (Otto, 2018). Furthermore, if

S. epidermidis lacks anti-host immune response proteins or toxins, the emerging question is, how does *S. epidermidis* evade the immune response mediated by neutrophils? This chapter presents different explanations for this question.

2 THE IMMUNE RESPONSE OF NEUTROPHILS AGAINST *S. epidermidis*

Several immune elements are needed to promote and amplify the neutrophil response. Immune elements such as the complement system can prime bacteria to facilitate neutrophil recognition. The purpose of the complement system is to enhance the uptake of bacteria by phagocytic immune cells, and they do this through opsonization with the C3b and iC3b molecules. In parallel, the complement system also attracts and activates leukocytes by releasing anaphylatoxin molecules C3a and C5a. There are three pathways for complement system activation: the classical pathway, the lectin pathway, and the alternative pathway. These pathways are activated depending on the individual's conditions; if a person has never been exposed to the pathogenic bacteria, then the complement can be activated through complement system members interacting with bacteria surface conserved molecules, like peptidoglycan and its components. The complement lectin pathway is involved in this direct recognition; this pathway occurs because lectins like the Mannose Binding Lectin (MBL) can bind to mannose carbohydrates motifs in pathogens.

In the case of the complement alternative pathway, no specific molecule is involved in the pathogen recognition, and it is triggered spontaneously by the C3 protein complement member autolysis in the bacterium surface. This pathway is recognized as positive feedback after the C3b molecule binds to the pathogen's surface, activated by the lectin or the classical pathway.

The other scenario is the activation of the classical complement pathway. When an immunocompetent individual has been exposed to the pathogenic bacteria and has generated antibodies against bacteria surface antigens, these antibodies, especially IgG and IgM, will bind to the bacteria surface. Then, the complement molecule C1 will recognize these antibody-antigen complexes. For example, the antibodies produced after *S. epidermidis* infection are mainly towards teichoic acid and peptidoglycan in its cell wall (Jung et al., 2012).

Complement activation (either of the indicated pathways) leads to the assembly of a C3 convertase on the surface of staphylococci, and this C3 convertase cleaves the C3 molecule deposited on the bacterial surface to produce C3a and C3b molecules. C3a is released into the environment, and C3b is covalently bound to the *Staphylococcus* surface; this bound C3b functions as an opsonin. Subsequently, a high density of C3b

on the bacterial surface interacts with the C3 convertase to form C5 convertase form. The C5 convertase breaks the C5 complement molecule to produce the C5a and C5b forms. C5a has the function of chemoattractant for phagocytic cells such as neutrophils, and C5b is deposited on the bacterial surface, beginning the formation of lethal pores in the bacterial cytoplasmic membrane, which causes the death of the bacteria; however, staphylococci such as *S. epidermidis* are reported to be resistant to direct killing by C5b due to their thick peptidoglycan layer (Berends et al., 2013).

Neutrophils recruiting through the activity of C5a causes the neutrophil to recognize either the antibodies or the complement components (C3a) on the bacterial surface (opsonization) and favors the phagocytic activity of neutrophils. Phagocytosis will generate the death and destruction of bacteria. However, neutrophils have other mechanisms of bacterial death than phagocytosis; these cells have an arsenal of effective antimicrobials stored in granules as antimicrobial peptides (AMPs), which are released when the neutrophil is activated. Another mechanism of death induction by neutrophils is forming extracellular traps (NETs). The most effective mechanism of killing staphylococci is intracellular killing in the phagolysosome after bacterial uptake. In this phagolysosome, the bacteria are in an environment of high presence of reactive oxygen species (ROS) and release of AMPs within the phagosome. These antimicrobial products effective against staphylococci in the neutrophil's granules include proteases such as cathepsin G, elastases, lactoferrin, lysozyme, and antimicrobial peptides (AMPs) such as LL-37. Neutrophil granules can also fuse with the cytoplasmic membrane and release to the microenvironment their contents to attack bacteria, but the drawback is that they also damage host tissue. Finally, in the formation of NETs, the neutrophil in adverse conditions is capable of releasing its DNA into the environment to form a network or mesh; in addition, AMPs derived from the granules can bind to the DNA network, and these NETs have as function to trap bacteria and together with AMPs cause bacterial death (Brinkmann et al., 2004).

Neutrophil's activation by the complement occurs against any bacterium; in the case of *S. epidermidis*, this process occurs the same. Nevertheless, staphylococci can form biofilms, which confers protection to the bacteria embedded in it; however, it is not known in detail how the biofilm can evade the neutrophil response. In the following topic, some examples of this evasion by the *S. epidermidis* biofilm will be mentioned.

3 EVASION OF THE NEUTROPHIL RESPONSE BY *S. epidermidis* BIOFILM

An evasion mechanism of the neutrophil response towards *S. epidermidis*, independently of the bacteria, is that the infected individual has deficiencies in the complement C3 molecule, which leads to neutrophils malfunctioning against staphylococcal

infections (Reis et al., 2006). In addition, mice deficient in complement C5 cannot eliminate systemic infection by *S. aureus*; the same should happen with *S. epidermidis*.

Although *S. epidermidis* lacks an extensive repertoire of virulence factors compared to *S. aureus*, this species is isolated with high frequency in infections associated with medical implants, suggesting that biofilm formation is an essential mechanism of immune evasion (Le et al ., 2018). The biofilm, both structurally and its components, could be involved in the evasion of the neutrophil response.

Phagocytosis is a very effective strategy of the neutrophil to eliminate planktonic bacteria (not biofilm developing bacteria) and even in small aggregates of bacteria; however, the response of the neutrophil towards staphylococci under biofilm conditions is not very effective. Some studies indicate that neutrophils can bind, infiltrate and phagocytize staphylococci in biofilm in the presence and absence of opsonins. However, bacteria in biofilm are more resistant to killing by neutrophils than planktonic bacteria, and in mature biofilms, the efficiency of phagocytosis decreases considerably (Gunther et al., 2009). It has also been shown that *S. epidermidis* biofilm is more resistant to neutrophil killing than *S. aureus* biofilm (Gunther et al., 2009), indicating that *S. epidermidis* has a neutrophil evasion mechanism mediated by its biofilm-specific components. Neutrophils can phagocytose particles similar to the neutrophil cell size (approximately 10 μm). When neutrophils are exposed to polystyrene spheres larger than 11 μm, neutrophils cannot phagocytose them; thus, biofilms of sizes larger than 10 μm will not be able to be phagocytosed by these cells. Nevertheless, neutrophils could fragment the biofilm by releasing its granules since they contain proteases such as elastase, cathepsin G, proteinase 3, DNases, and enzymes such as lysozyme (Cassatella et al., 2019). To our knowledge, neutrophils do not have enzymes that degrade the main component of a carbohydrate-type biofilm consisting of the polymer N-acetyl glucosamine (PNAG), which could explain the *S. epidermidis* biofilm resistance towards phagocytosis.

The staphylococci biofilm's extracellular polymeric substance (EPS) comprises extracellular DNA, proteins, and polysaccharides. The biofilm of *S. epidermidis* can be of two types, one of carbohydrate made up of PNAG and the other type of protein that consists of the protein Aap. PNAG is an essential component of the biofilm with qualities of immune evasion since this polymer provides mechanical protection against phagocytosis and cationic AMPs; in addition, the physicochemical properties of PNAG prevent antibodies from penetrating the surface of bacteria, thus avoiding immune activation.

Protection against AMPs is usually due to negatively charged biofilm components, but PNAG is positively charged, and PNAG has been shown to protect against cationic AMPs such as LL-37 by charge repulsion (Vuong et al., 2004). PNAG also protects against

anionic AMPs by sequestering these molecules and keeping them away from the bacteria. In addition, *S. epidermidis* secretes the protease SepA, and this protease cleaves AMPs produced by neutrophils.

Purified free PNAG is a complement activator (release C3a and C5a). However, PNAG in the structure of the *S. epidermidis* biofilm behaves differently as it protects against IgG and C3b deposition, neutrophil phagocytosis, and biofilm opsonization (Fredheim et al., 2011); this indicates that the complement system is highly activated by PNAG but does not indicate that complement components are deposited on or near the bacterial surface. On the other hand, *in vitro* experiments reveal that IgG can penetrate the biofilm, but these antibodies do not reach the surface of the bacteria since they are retained by the PNAG, preventing opsonization and death by the neutrophil; indicating that the excess of PNAG in the biofilm works as an antibody capturer or filter and prevents antibodies binding to the bacteria surface. In this way, biofilm EPS functions as a trap for complement and antibodies to prevent reaching the surface of the bacteria and being killed by neutrophils.

Concerning biofilms made of protein, the *S. epidermidis* accumulation protein Aap is the main element involved in the protein-type biofilm formation. The Aap protein needs to be proteolytically processed between its A domain and B domain to expose the B domain; two B domains interact with each other to bind the bacteria and produce a cell aggregate for biofilm production (Rohde et al., 2005). Proteases that can cleave Aap are either *S. epidermidis*-specific proteases or external proteases; SepA protease from *S. epidermidis* proteolytically processes Aap to produce biofilm (Paharik et al., 2017); external proteases such as trypsin, elastase and cathepsin G also do the same (Rohde et al., 2005). In a study carried out by our research group, it was shown that trypsin is a biofilm inducer in *S. epidermidis* commensal skin isolates that cannot form biofilm (Martínez-García et al., 2019). In addition, another study showed that cathepsin G, cathepsin B, metalloproteinase 9, and neutrophil proteinase 3 induce biofilm formation in *S. epidermidis* isolates with a non-biofilm-producing phenotype. It was also shown that *S. epidermidis* with a non-biofilm-producing phenotype in the presence of neutrophil, the biofilm is induced by the release of the proteases mentioned above (Gómez-Alonso et al., 2022). These observations strongly suggest that *S. epidermidis* has taken advantage of releasing neutrophil granule contents as neutrophil proteases cleave Aap protein for biofilm formation.

On the other hand, the mechanism of NETs by neutrophils may be beneficial for the bacterium since the release of neutrophil DNA can be used as a bed or support to improve biofilm formation, as has been the case for *Pseudomonas aeruginosa* and *S. epidermidis* in contact lens infections (Patel et al., 2018).

All this indicates that the adaptive evolution of *S. epidermidis* towards the neutrophil has generated a beneficial interaction for *S. epidermidis*, in which its biofilm is the central strategy to evade the innate immune response.

4 CONCLUSION

The neutrophil can kill bacteria, but *S. epidermidis* can evade the neutrophil's action. Also, *S. epidermidis* can benefit from the neutrophil activation since releasing proteases or DNA from these immunological cells can stimulate biofilm formation. The *S. epidermidis* biofilm, as one of the main virulence factors, inactivates the different strategies that the neutrophil possesses to eliminate or kill the bacteria. *S. epidermidis* has evolved from its normal skin-bacteria relationship, allowing *S. epidermidis* to recognize and respond against the immune response of neutrophils.

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SOBRE O ORGANIZADOR

Dr. Juan Carlos Cancino Diaz - Egresado de la Escuela Nacional de Ciencias Biológicas (ENCB) del Instituto Politécnico Nacional (IPN), México, con la licenciatura en Ingeniero Bioquímico. Estudios de posgrado en la misma institución con la especialidad de maestría en Bioquímica y doctorado en Inmunología. Actualmente es profesor e investigador de la ENCB-IPN impartiendo la catedra de Microbiología veterinaria para los Químicos Bacteriólogos Parasitólogos. El área de investigación es sobre el estudio de la biología de *Staphylococcus epidermidis*, con una alta producción de artículos científicos en revistas científicas de prestigio. Ha desempeñado como director de tesis de licenciatura, maestría y doctorado. Tiene una patente otorgada por el instituto mexicano de la propiedad intelectual y cuatro en curso de aprobación. Es miembro del sistema nacional de investigadores de México nivel II. Es editor de un libro sobre *Staphylococcus epidermidis* que está en curso de publicación y cinco capítulos de libro sobre su área de investigación.

ÍNDICE REMISSIVO

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Símbolos