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Letter to the Editor

IL-37 is an inhibitory cytokine that could be useful for treating infections

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KEYWORDS: *IL-37, inhibitory cytokine, inflammation, immune response, IL-1R8*

INTRODUCTION

Interleukin (IL)-37 is an anti-inflammatory cytokine that plays a crucial role in modulating the immune response. IL-37 acts by limiting excessive inflammation and protecting tissues from damage. IL-37 is a member of the IL-1 family and is a cytokine that inhibits both innate and adaptive immunity. When it binds to the IL-18 receptor (IL-1R5) (IL-18 is a proinflammatory protein), this cytokine has an anti-inflammatory effect.

DISCUSSION

IL-37 binds to IL-1R5, forming a complex with the IL-1R8 receptor that has anti-inflammatory properties (1). This complex dampens pro-inflammatory signaling pathways. The presence of IL-1R8 is essential, as the lack of this receptor does not allow IL-37 to carry out its anti-inflammatory effect. Among the biological effects of IL-37, there is the anti-tumor effect that it exerts on natural killer (NK) cells, on which IL-37 causes an increase in anti-tumor stimulation, a characteristic possessed by NK. These effects of IL-37 on NK cells also occur in the absence of the IL-1R8 receptor.

IL-37 is produced as an inactive precursor and requires processing by caspase-1 to become active. The active form of IL-37 can be secreted extracellularly or can function intracellularly. The effect of IL-37 on innate immunity occurs through the inhibition of the mammalian target of rapamycin (mTOR) signaling pathway, increased oxidative phosphorylation of the kinase, and reduction of succinate. IL-37 translocates to the nucleus, where it binds to SMAD3, a transcription factor involved in transforming growth factor-β (TGF-β) signaling.

IL-37 is produced by macrophage and dendritic cells, protagonists of innate immunity. IL-37 also plays a crucial role in acquired immune responses, acting on dendritic cells by causing them to produce high levels of the inhibitory cytokine IL-10 which participates in immune tolerance. IL-37 also has an inhibitory effect on antigen presentation by major histocompatibility complex Class II (MHCII). Mice with rheumatoid arthritis that were treated with this cytokine showed a reduction in joint inflammation (2). IL-37 has also been shown to be useful in the experimental treatment of mice with streptococcal infection, an effect that did not occur in mice in which the IL-1R8 receptor was suppressed (3). In addition, IL-37 can control inflammatory complications in viral diseases including influenza and COVID-19 (4), however, excessive IL-37 can potentially interfere with antiviral immunity.

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The anti-inflammatory action of IL-37 occurs mostly through its inhibition of IL-1, but also of tumor necrosis factor (TNF), IL-6, IL-17, and the chemokine CCL2. Subjects with deficient levels of IL-37 may be more likely to experience inflammatory diseases and also have more pronounced inflammation in infectious diseases (4). IL-37 mitigates the "cytokine storm" by reducing excessive inflammation. For example, in sepsis or viral infections, IL-37 limits tissue damage caused by overactive immune responses. T lymphocytes, which play an important role in infections, may be more activated in IL-37 deficiency, which contributes to the pathological damage.

CONCLUSIONS

Levels of IL-37 are increased in many inflammatory diseases, including psoriasis, arthritis, systemic lupus erythematosus, ankylosing spondylitis, allergic rhinitis, cancer, and periodontitis. The increased levels of IL-37 in inflammatory diseases are due to the organism's reaction in response to tissue inflammation, whereas decreased IL-37 seems to contribute to the severity of inflammation. Modulating IL-37 activity selectively during infections may offer novel therapeutic strategies for conditions characterized by immune dysregulation.

Conflict of interest

The author declares that they have no conflict of interest.

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ODONTOGENIC INFECTIONS: UPDATED RECOMMENDATIONS AND BEST PRACTICES

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ABSTRACT

Odontogenic infections stemming from the teeth or surrounding tissues are a prevalent source of discomfort and illness in oral health. It is imperative to treat these infections effectively because, if left untreated, they may have serious consequences. With the latest discoveries in pathogenic processes, antibiotic treatments, and integrated patient care techniques, this publication offers revised recommendations and best practices for managing odontogenic infections. Tooth caries, periodontal disease, tooth trauma, and invasive dental procedures are the main causes of odontogenic infections because they allow bacteria to invade and multiply. A comprehensive medical exam, complete records of affected patient, and proper imaging strategies are necessary for analysis. Prompt antibiotic usage is encouraged in updated guidelines, with first-line antibiotics like amoxicillin being chosen, unless contraindicated, to prevent resistance and limit side effects. In addition, particular dental processes like endodontic therapy, abscess drainage, and tooth extraction are used as part of the treatment program to remove the source of infection. Treatment for sepsis, osteomyelitis, Ludwig's angina, and cellulitis should be initiated quickly. Maintaining good oral hygiene, managing systemic illnesses appropriately, using antibiotics properly, and controlling infections in dental practices are all important aspects of prevention. This article includes case research highlighting the management of severe odontogenic infections, together with surgical interventions and antibiotic treatments. Moreover, it underscores the importance of early prognosis, targeted treatment, and preventive measures to control odontogenic infections correctly, improving patient outcomes and reducing the incidence of severe complications.

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KEYWORDS: *Odontogenic infection, antibiotic therapy, periodontal disease, microbial diagnosis, sepsis, Ludwig's angina, abscess drainage*

INTRODUCTION

Odontogenic infections are infections that start in the gums, alveolar bone, periodontal ligaments, or teeth themselves (1). They can range from localized abscesses to more serious systemic diseases, and they are among the most frequent causes of pain and illness in oral health (2). Odontogenic infections need to be managed carefully since they can spread to other anatomical tissues and, if left untreated, can result in serious side effects such mediastinitis, deep neck infections, or even potentially fatal sepsis (3).

The pathophysiology of odontogenic infections has been brought to light by recent advances in our understanding of these disorders, which have specifically focused on the involvement of polymicrobial communities and the interactions between aerobic and anaerobic bacteria (4). Traditional therapeutic approaches have also been called into question due to the advent of antibiotic-resistant bacteria, with a focus on the importance of accurate microbiological diagnosis and focused antimicrobial therapy (5). As a result of advancements in our knowledge of the pathogenic mechanisms underlying odontogenic infections, the development of novel antibiotic therapies, and the adoption of a more comprehensive patient care approach involving not only otolaryngologists and infectious disease specialists but also dentists, guidelines for the management of these infections have changed in recent years (6). In addition, the use of computer-aided surgery and 3D imaging has improved the diagnosis and surgical treatment of many infections by enabling less intrusive and more accurate procedures (7).

DISCUSSION

Causes and pathogenesis of odontogenic infections

Infections that start in the teeth or the supporting dental structures are referred to as odontogenic infections. Anaerobic bacteria like *Streptococcus*, *Peptostreptococcus*, and *Bacteroides* species are the most frequent causes of these illnesses, which are essentially bacterial in origin. Dental caries, or tooth decay, are frequently the first cause because they open a crack in the enamel that allows germs to enter the dental pulp. Bacteria can be introduced into dental tissues or their surrounding areas via invasive dental procedures, trauma, and periodontal disease, among other contributing factors. Bacteria can multiply and spread to the surrounding bone and soft tissues once they get to the pulp of the tooth (8). This bacterial invasion causes the host tissue to become inflamed, which may lead to the development of osteomyelitis, cellulitis, or abscesses. Odontogenic infections are caused by bacteria that produce toxins, break down natural tissue barriers, and activate the host's immune system. Serious pain, swelling, and even systemic problems may result from these infections if they are not treated right away (9). Antibiotic medication to suppress the infection and dental treatments such extractions, root canal therapy, or drainage to address the underlying cause are usually necessary for effective management.

Cavities, also referred to as dental caries, are a major source of odontogenic infections. The acidic byproducts of bacterial metabolism demineralize the enamel at the start of the process. Bacteria can easily enter deeper tissues through the carious lesion's direct progression into the dentin and eventual arrival at the tooth pulp. When an infection extends past the tip of the root into the surrounding bone, it can lead to the formation of a periapical abscess (10).

The gums, periodontal ligament, and alveolar bone are among the tissues that support the teeth that are chronically inflamed and infected by periodontal disease. Because of bone loss and gum recession, periodontal pockets emerge, which foster the growth of harmful germs. The breakdown of the alveolar bone and periodontal ligament as periodontal disease progresses can make it easier for bacteria to go from the gums to the surrounding tissues and circulation.

Tooth trauma, such fractures or severe cracks, can cut off blood flow to the pulp, which can result in pulp necrosis and open the door for bacterial growth. Due to their increased susceptibility to trauma, anterior teeth injuries are especially common. Bacteria can enter and grow in necrotic pulp, which increases the risk of an abscess or the infection spreading to other tissues (11).

Implant installation, endodontic treatments, and extractions are dental operations that, if not carried out under appropriate sterile conditions, might introduce bacteria into sterile areas. Also, by allowing germs to colonize surgical areas, poor oral hygiene and insufficient post-operative care might raise the risk of infection even further (12).

Due to the accumulation of plaque and tartar on teeth, poor oral hygiene practices play a major role in the development of odontogenic diseases in humans. Increased risk of bacterial invasion into deeper dental and periodontal tissues results from this build-up, which can cause both gum disease and tooth damage (13).

Pathogenesis of Odontogenic Infections

The host's immune system and pathogenic microbes interact intricately throughout the pathogenesis of odontogenic infections. The principal bacteria implicated include facultative and anaerobic species, such as *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella spp.* and *Streptococcus mutans*.

Numerous pathways, including carious lesions, periodontal pockets, and traumatic trauma, allow bacteria to enter oral tissues. After they break through the barriers of soft tissue or enamel, bacteria avoid the body's defenses and start an infection (14).

Bacteria spread quickly throughout the infected tissues, triggering an immediate inflammatory reaction. The hallmark of this reaction is the inflow of neutrophils, which try to stop the infection but frequently cause tissue damage that leads to pus and the formation of abscesses. In the event that the infection is not adequately managed, it may progress via the head and neck's fascial planes and cause systemic side effects such as sepsis, cellulitis, or osteomyelitis. When virulent bacterial strains or an overtaxed local immune response are present, the likelihood of systemic involvement increases dramatically (15).

Diagnosis and Initial Evaluation

Compiling a full clinical examination, employing the right diagnostic instruments, and getting a detailed patient history are all necessary for a complete and accurate diagnosis of odontogenic infections (16).

When pain, swelling, fever, and pus leakage are present, clinicians should obtain a thorough history of the patient's symptoms. Any recent dental work, injuries, or adjustments to oral hygiene practices that may increase the risk of infection should also be noted (17).

Observing the oral cavity visually, palpating any uncomfortable or swollen areas, testing the movement of the teeth, and looking for purulent drainage or fistulas are all important components of the clinical examination. Determining the degree of periodontal disease, carious lesions, and periapical infections requires the use of radiographic imaging, such as panoramic and intraoral (periapical and bitewing) X-rays. Computed tomography (CT) scans can give precise information regarding the location and severity of an illness in more complicated cases (18).

Antibiotic Therapy

Antibiotics must be used carefully while treating odontogenic infections to reduce the chance of bacterial resistance and any negative side effects.

When there are indications of generalized cellulitis, fever, lymphadenopathy, or when local drainage is not possible, an antibiotic prescription should be made. Antibiotics might not be required for confined infections that can be successfully drained (19).

Because of their effectiveness against common oral bacteria, amoxicillin and amoxicillin with clavulanic acid are often prescribed as first-line antibiotics. Clindamycin or metronidazole are suitable substitutes for penicillin allergy sufferers. Depending on the severity and persistence of the infection, the course of antibiotic therapy typically lasts between five and seven days. If the infection worsens or does not go away, further treatments can be required (20).

Dental Interventions

In addition to medication, targeted dental procedures are necessary to address the infection's source.

The recommended treatment for infections of the tooth pulp is root canal therapy, including cases of acute pulpitis and periapical abscesses. Along with cleansing and closing the root canals to stop reinfection, this operation includes removing the affected pulp tissue. Surgical drainage becomes necessary to release pressure and remove pus in circumstances when an abscess has formed. Incision and drainage or root canal therapy can accomplish this. Extraction may be necessary to remove the source of infection from a tooth that is significantly damaged or irreparable. To remove any necrotic tissue and prevent additional infection, post-extraction care involves complete debridement of the site (21).

For infections originating from periodontal disease, deep cleaning procedures, such as scaling and root planing, are effective in removing plaque and tartar below the gum line, thereby reducing bacterial load and inflammation (22).

Management of complications

In dentistry and medicine, the care of odontogenic infection-related problems is essential since these infections can result in both local and systemic issues that call for quick and forceful intervention. These consequences can include potentially fatal illnesses, such as sepsis, as well as the spread of infection into soft tissues and bone structures (23).

1. Ludwig's Angina and Cellulitis

Serious side effects linked to odontogenic infections include cellulitis and Ludwig's angina, which are characterized by the infection spreading through the soft tissues of the face and neck. There is a strong chance of airway blockage and considerable swelling from this (24). The patient is managed with prompt intravenous antibiotic therapy, surgical drainage to remove pus and lower tissue pressure, and, in more serious situations, airway management procedures including tracheotomy or intubation to guarantee proper breathing (25).

2. Osteomyelitis

Dental infections that extend to the underlying bone can result in osteomyelitis, an infection of the jawbone. Prolonged intravenous antibiotic therapy is necessary for this situation in order to guarantee appropriate medication concentration at the infection site (26). Surgical intervention for debridement or removal of non-viable bone portions may be required if the infection results in bone tissue necrosis. To completely remove the infection and stop more problems, a combination of antibiotic medication and surgery is required (27).

3. Odontogenic Sinusitis

Odontogenic sinusitis, which is characterized by facial pain, nasal congestion, and perhaps purulent discharge, can result from infections affecting the upper teeth spreading to the maxillary sinuses (28). Decongestants are used to lessen sinus swelling and inflammation and antibiotics are used to treat the infection in the early stages of treatment. To restore proper sinus function, surgical drainage may be required if there is a sizable accumulation of pus or fluid in the sinuses (29).

4. Sepsis

Sepsis is a serious and sometimes fatal illness involving the systemic inflammatory response to infection which can occasionally result from odontogenic infections. Severe sepsis patients need to be admitted to an intensive care unit (ICU) immediately, where they should receive intravenous (IV) broad-spectrum antibiotics to fight the underlying infection (30,31). In order to sustain blood pressure and guarantee sufficient blood flow to essential organs, hemodynamic support could also be required (32,33). A multidisciplinary strategy is important to manage sepsis, and involves experts in infectious disease, critical care specialists, and, if required, maxillofacial surgeons to address the primary source of infection (34,35).

In conclusion, a variety of consequences can result from odontogenic infections, and each one calls for a unique and frequently intricate course of therapy. Effective patient recovery and the avoidance of unfavorable consequences depend heavily on prompt diagnosis and vigorous intervention (36,37).

Prevention and Best Practices

Maintaining a healthy mouth and general wellbeing prevents odontogenic infections. Practicing good oral hygiene is one of the best methods to lower the risk of this illness. This entails educating patients on the value of consistent brushing and flossing in addition to arranging for regular dental examinations (38,39). These habits aid in the prevention of odontogenic infections, which are frequently brought on by gum disease and tooth decay (40,41). Long-term oral health can be promoted, and the risk of infections can be greatly reduced by teaching patients these basic principles of dental care (42,43).

Keeping systemic health issues under control is just as vital as practicing basic oral hygiene (44,45). An individual may be more vulnerable to infections, particularly oral infections, if they have certain medical conditions such as diabetes (46,47). Patients with health conditions need to be closely monitored and managed in collaboration with their medical professionals to lower their risk of infection (48,49). When dental and medical providers coordinate care, patients are given all-encompassing care that considers all facets of their health, which reduces the risk of infection-related issues (50,51).

Another important element in preventing odontogenic infections is the appropriate use of antibiotics (52,53). Antibiotic resistance and other negative effects can result from the overuse or misuse of antibiotics, making it more difficult to treat diseases successfully (54,55). As a result, it's critical to adhere to tight standards for the use of antibiotics, making sure that they are only provided when necessary and at the appropriate dosage and duration (56,57). Dental practitioners can safeguard patient health and stop the growth of resistant germs by following these recommendations (58,59).

Maintaining current knowledge on infection prevention, diagnosis, and treatment is another essential aspect of continuing education for dental practitioners (60,61). Ensuring that the highest standards of care are upheld can be achieved by keeping up with the latest techniques (62,63). Furthermore, the incidence and severity of odontogenic infections can be decreased by teaching patients about infection prevention techniques, identifying warning symptoms, and realizing the significance of receiving healthcare promptly (64-66).

And lastly, two crucial strategies for infection control in dental clinics include keeping all dental treatments sterile and utilizing appropriately hygienized instruments (67,68). All patients will have a safer and healthier experience if dental practitioners adhere to these thorough precautions, which can effectively avoid odontogenic infections, reduce problems, and enhance patient outcomes (69,70).

CASE 1

A 70-year-old Caucasian male with a complex medical history including obesity, hypertension, type II diabetes, ischemic heart disease, chronic obstructive pulmonary disease, and a previous transient ischemic attack presented to the Bari Polyclinic in Italy with dyspnea, spontaneous pain, and swelling in the right mandible. The patient had been previously treated at another hospital with antibiotics for the mandibular edema but was later transferred to the ICU at Bari due to severe mediastinal involvement from a purulent phlegmon. A rectal swab revealed an infection with *Klebsiella Pneumoniae Carbapenemase* (KPC).

Initial blood tests showed no leukocytosis, but C-reactive protein was elevated. A non-contrast CT scan of the neck and chest revealed inhomogeneous tissue with air bubbles in the right sub-mandibular area, suggesting an abscess affecting the surrounding muscles, including the sternocleidomastoid muscle, the right thyroid lobe, and the right submandibular gland. The mediastinum and lung parenchyma also showed signs of infection and inflammation.

The patient underwent a complex surgical procedure, including intubation, tracheostomy, sialoadenectomy, and abscess drainage. The surgery involved extensive dissection to drain abscesses and protect vital structures. Post-operatively, the patient was treated with a combination of broad-spectrum antibiotics. Follow-up CT scans showed a reduction in the mediastinal and prevertebral abscesses, although the right submandibular area remained swollen.

The patient's condition was complicated by the presence of *Klebsiella Pneumoniae* and *Staphylococcus hemolyticus*, confirmed by cultures from swabs and aspirates. Dental surgery was later performed to extract an infected tooth, which was identified as the source of the infection (Fig.1-4) (Fig.5-8).

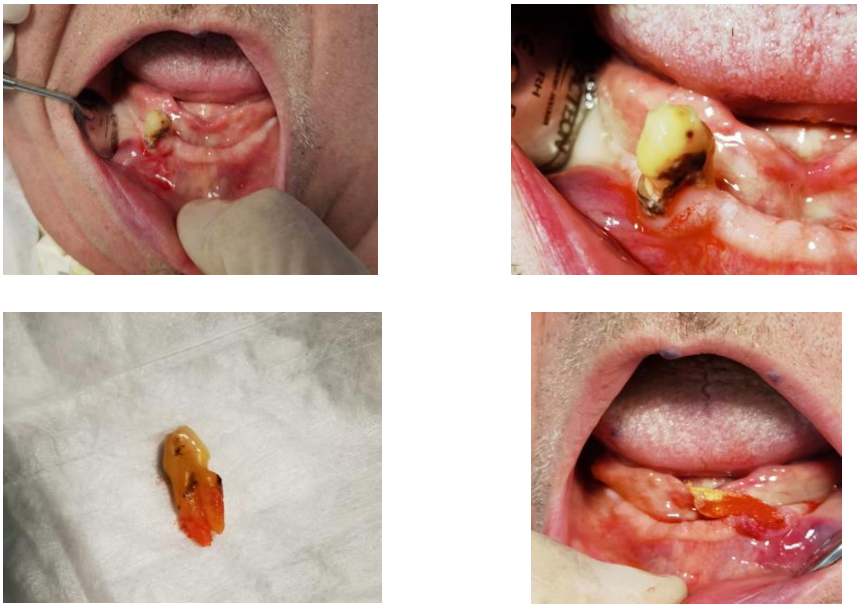


Fig. 1, 2, 3, 4. *Intraoral photo and a detail of the dental element 4.3 before the extraction; extracted 4.3 and intraoral photo after the extraction in which hemostasis with Tabotamp was performed.*

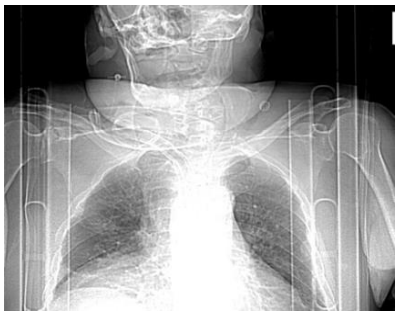
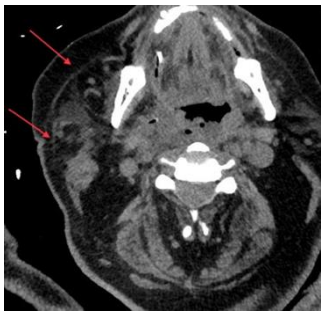
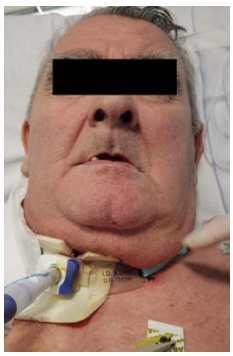
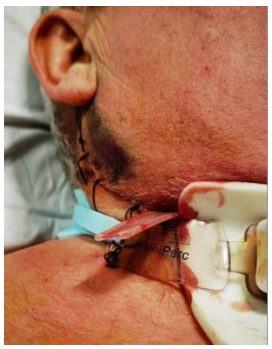





Fig. 5, 6, 7, 8. *Patient photos after the emergency surgery: front and right side. Evidence of the tracheotomy and of placement of cannula type Porte n. 9.*

This case highlights the serious risks associated with untreated odontogenic infections, which can spread to the neck and mediastinum, leading to life-threatening conditions such as deep neck abscesses, cellulitis, and necrotizing fasciitis. Early diagnosis and prompt surgical intervention are crucial to prevent fatal outcomes. Imaging techniques like CT scans play a vital role in assessing the extent of infection and guiding treatment. Despite the availability of antibiotics and advanced surgical techniques, deep-neck infections remain a significant clinical challenge due to their potential for rapid progression and severe complications.

CASE 2

This case report details the medical journey of a 59-year-old retired woman with decompensated type 2 diabetes mellitus and hypercholesterolemia. She was admitted during the COVID-19 pandemic with swelling in the right mandibular region, which worsened over seven days, leading to dysphonia and difficulty swallowing (Fig.9-11). Initial physical examination revealed a large abscess on the right side of her face, trismus (jaw muscle spasm), and edema in the tongue and mouth floor. Diagnostic tests, including a negative COVID-19 swab, blood tests, and imaging studies (X-ray, CT scans), were conducted. The scans revealed gas bubbles in the cavernous sinuses and a significant phlegmon (a type of inflammation) extending through the neck and face (Fig.12).

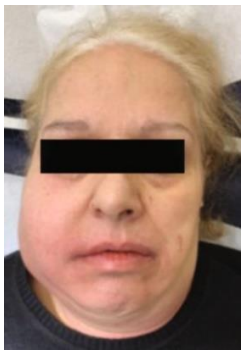
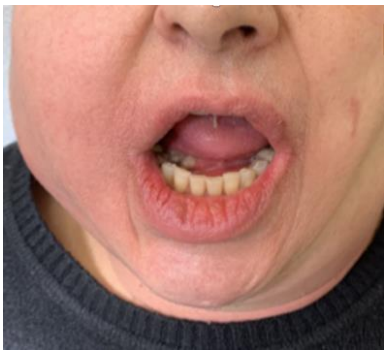
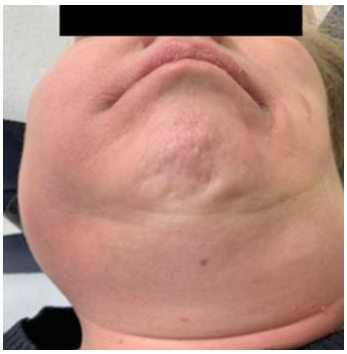




Fig. 9, 10, 11. *Evident swelling of the medial and inferior third of the right side of the face.*

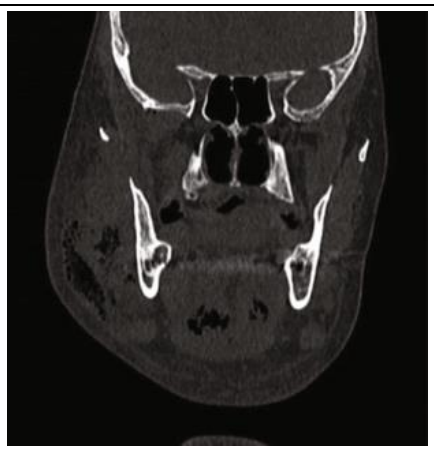


Fig. 12. *Neck-Chest CT that highlights presence of bilaterally gas bubbles in correspondence of the cavernous sinuses. At the level of the neck, a large phlegmonous collection with a considerable contextual air share located mainly in the right half face, the platysma and the ipsilateral parotid gland capsule. Medially it extends to the buccal floor to the left submandibular lodge and the sternocleidomastoid fascia.*

Given the severity of the infection, emergency surgery was performed to drain the abscess and remove the right submandibular gland. A tracheostomy was also conducted to secure the patient's airway. Post-surgery, the patient was prescribed a combination of antibiotics (Teicoplanin, Levofloxacin, Ceftriaxone) and was closely monitored.

Despite the surgery, the patient developed septic shock by the third day of hospitalization, necessitating admission to ICU and the administration of vasopressors to maintain blood pressure. Further imaging studies showed an increase in the phlegmonous collection, especially on the left side, and the continued presence of gas bubbles in the cavernous sinuses. However, no venous thrombosis was detected.

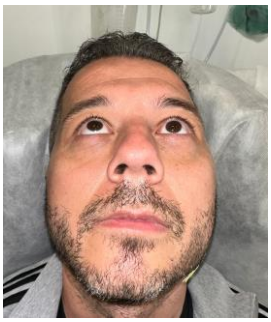
Subsequent surgeries included the extraction of teeth associated with the infection and additional drainage procedures. The patient remained under controlled mechanical ventilation and gradually improved, with the Sequential Organ Failure Assessment (SOFA) score dropping, indicating stabilization. Over the next few days, her condition continued to improve, leading to successful weaning from the ventilator on the ninth day.

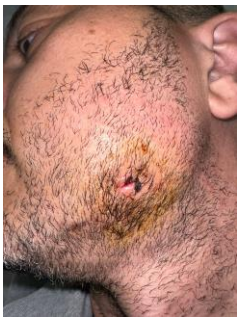
After further consultations, a new CT scan revealed stable conditions with no need for additional surgery. The patient remained stable for ten days post-surgery, showing good neurological orientation and gas exchange. She was discharged approximately one month later.

A follow-up three months after discharge showed no visible external swelling and good intraoral tissue healing. Control imaging revealed significant improvement, with almost complete reabsorption of the gas bubbles in the cavernous sinuses and a reduced phlegmon in the neck, with no further complications.

CASE 3

A 42-year-old male patient with a history of good oral health had recently developed a dental infection in tooth 3.7. The patient had always paid attention to his oral hygiene, but despite this, he began to experience acute pain and increasing sensitivity in the affected tooth. Initially, he attributed the pain to a simple trauma or cavity, but when the pain became unbearable, he decided to consult his trusted dentist (Fig.13-15).





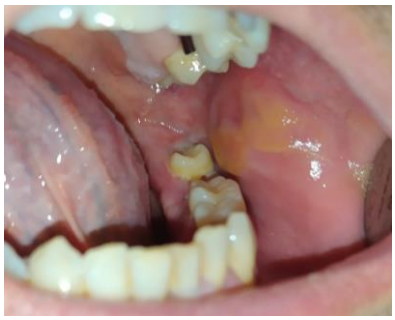


Fig. 13, 14, 15. *Evident swelling of the medial and inferior third of the left side of the face. Photograph showing a close view of the phlegmon on the internal side of the left cheek.*

During the visit, the dentist conducted a thorough examination and detected the presence of a periapical abscess which was confirmed by a dental X-ray. The abscess was the result of a bacterial infection that had developed around the tip of the tooth's root. Immediate treatment was essential to prevent the spread of the infection and to alleviate the patient's pain.

The treatment involved opening the tooth to drain the abscess, followed by cleaning and disinfection of the root canal. The dentist used endodontic techniques and external drainage to remove the infected tissue and to ensure that the root canal was thoroughly sterilized. After the cleaning, the canal was sealed to prevent further infection.

In addition to this treatment, the patient was prescribed a course of antibiotics to fight the infection. The patient was instructed on how to monitor the treatment site and what to look for in terms of signs of residual infection or post-operative complications.

After the treatment, the patient reported significant relief from the pain and expressed his gratitude for the timely and professional intervention by the dentist. The patient is now following a rigorous oral hygiene routine, which includes the use of dental floss and rinsing with an antibacterial mouthwash, to prevent future infections and maintain the health of his teeth and gums.

The case illustrates the importance of quick and effective intervention to avoid the serious risks associated with untreated odontogenic infections and shows that early diagnosis and intervention are crucial to prevent serious complications.

CONCLUSIONS

Odontogenic disorders pose a serious threat to both oral and general health and require a comprehensive approach to treatment. A combination of early diagnosis, targeted dental care, appropriate antibiotic medication, and other therapies should be employed in addition to effective preventive measures. By following the most recent recommendations and best practices, healthcare practitioners can significantly reduce the incidence of these illnesses and the associated damage. Such proactive measures not only improve clinical outcomes and patients' quality of life, but also ensure that they receive the best care possible. The wide-ranging impacts of odontogenic infections must be managed and prevented with an integrated approach.

Author Contributions

Conceptualization, A.D.I., F.I., A.M.I., G.I. and A.S.; methodology, A.D.I., D.C., P.M., G.D., G.I. and A.L. software, F.I., G.D., A.D.I., D.C. and A.S.; validation, F.I., A.M.I., G.D., A.L. and P.M. formal analysis, A.D.I., A.M.I., A.L., D.C. and G.S.; investigation, G.D., P.M., G.I., F.I. and A.S.; resources, A.M.I., A.S., A.D.I., F.I. and G.D.; data curation, G.D., D.C., P.M., A.S. and F.I.; writing original draft preparation, A.D.I., P.M., D.C. and G.I.; writing review and editing, F.I., A.L., D.C., A.M.I. and G.I.; visualization, D.C., A.S., A.D.I., A.L. and A.M.I.; supervision, G.D, F.I., A.D.I., A.M.I. and G.I.; project administration, P.M., D.C., F.I., A.M.I. and G.D.. All authors have read and agreed to the published version of the manuscript.

Informed Consent Statement

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Data is contained within the article.

Conflict of interest

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MAXILLOFACIAL INFECTION: FOCUS ON PERIODONTAL DISEASE

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ABSTRACT

Craniofacial structures, such as the mouth, teeth, and gums, can be subject to both acute and chronic infections. Management of maxillofacial infections, which activate immunity and inflammation, is very important since they can lead to serious complications. The most common pathogens responsible for these infection are viruses, bacteria, and fungi. Maxillofacial infections can be odontogenic, including dental abscesses, jawbone abscesses, and periodontitis, amongst others, and activate the immune system, generating inflammatory molecules. Lipopolysaccharide (LPS) present in Gram-negative bacteria is a large molecule capable of activating immunity and inflammation in the oropharygeal system. Bacterial infections, especially those mediated by Gram-negative bacteria, can cause periodontitis, where the immune response is triggered, resulting in chronic inflammation with gingival damage. Immune molecules, including metalloproteinases (MMPs) and cytokines, such as interleuking (IL)-1, tumor necrosis factor (TNF), and IL-6, are released and mediate inflammation and tissue damage. Upon stimulation, osteoclasts, the precursors of macrophages, lead to the activation of the receptor for nuclear factor kappa B (NF-kB), receptor activator of nuclear factor κ B-ligand (RANKL), and other proteins that contribute to osteoclastogenesis and therefore, bone loss. It can be concluded that bacterial infections can mediate periodontitis in chronic and severe cases.

KEYWORDS: *Infection, maxillofacial, periodontitis, immunity, inflammation, bacteria*

INTRODUCTION

Chronic infections can contribute to local and systemic inflammation and increase the risk of various disorders, including craniofacial diseases affecting the mouth, teeth, and gums (1). Maxillofacial infections involve the facial bones and soft tissues and can lead to significant complications if not properly managed (2). Understanding the mechanisms of infection, inflammation, and immunity in the maxillofacial region is crucial for effective treatment.

Infections begin with pathogens entering the oral mucosa, dental caries, or through spaces created by trauma (3). Infections can affect the face, lymphatic system, or bloodstream (4). The most common pathogens which are responsible for these infections include bacteria (such as *Staphylococcus aureus* and some species of *Streptococcus*), viruses (such as herpes simplex), and fungi (such as Candida) (5).

DISCUSSION

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Typical maxillofacial infections are odontogenic infections originating from dental structures (for example, dental abscesses) (6), but also from soft tissue infections such as cellulitis and abscesses, as well as infections of the jaw bones (osteomyelitis) (7). Neutrophils and macrophages are innate immune cells that constitute a physical barrier of the tissues and are the first immune cells that intervene in infections for the recognition of pathogens (8). Adaptive immunity involves the intervention of B cells that produce antibodies to try to neutralize the pathogen and facilitate its elimination (9). Helper T cells and cytotoxic T cells are part of cell-mediated immunity and target and kill infected cells, orchestrating the immune response (10). Pathogens defend themselves from the immune process by forming biofilms to resist phagocytosis and antibiotic treatment and can alter host immune responses to evade detection and destruction (11).

Tissue inflammation can be activated by bacterial products such as lipopolysaccharide (LPS) (12). LPS is a large molecule found in the outer membrane of Gram-negative bacteria that plays a key role in the development of inflammation. LPS triggers the immune response in the host by acting as an endotoxin. It causes inflammation and tissue damage, and stimulates the production of cytokines, prostaglandins, and other mediators involved in bone resorption. In addition, LPS can contribute to the progression of periodontitis (13).

Periodontal disease

Periodontitis is a gum infection that damages the soft tissue and can be serious (14). Bacteria are primarily responsible for causing this disease (15). Periodontitis is a chronic infection that occurs in 50% of the adult population in industrialized countries. Bacteria, particularly Gram-negative bacteria containing LPS, proliferate and release LPS, which triggers an immune response, causing chronic inflammation damages gum tissue and bone, which ultimately results in tooth loss if the infection is not treated (16).

In the mouth, certain bacteria can form plaque on the teeth that, if not removed, forms tartar which continues to host the bacteria (17). These bacteria stimulate molecules that attract immune cells and cause inflammation of the gums, i.e. gingivitis, the stage which occurs before periodontitis (18). Gingivitis is commonly caused by poor oral hygiene and leads to the accumulation of bacterial plaque on the gums that, without proper treatment, can destroy the bone that supports the teeth. In this disease, inflammatory molecules such as metalloproteinases (MMPs) are activated, along with others, and enter the inflammatory cascade (19). MMPs participate in the recruitment of migratory immune cells to the inflammatory site (20).

Several lines of experimental and clinical evidence indicate that inflammation in periodontal disease leads to bone loss (21). Periodontal disease is mediated by bacterial antigens that cause the activation of the immune system and inflammatory reactions. The first reaction is the activation of innate immunity with the generation of inflammatory cytokines and arachidonic acid products due to the activation of monocytes/macrophages, dendritic cells, and mast cells (22). The most important inflammatory cytokines that are secreted by the immune reaction are interleukin (IL)-1, tumor necrosis factor (TNF), and IL-6 (23). T and B lymphocytes stimulated by the antigen also activate the adaptive immune response and participate in the inflammatory reaction (24). In these reactions, which stimulate the differentiation of macrophage precursor cells into osteoclasts, there is activation of the receptor for nuclear factor kappa B (RANK) -ligand (RANKL) and other proteins that lead to osteoclastogenesis and thus bone loss (25). Therefore, stimulation of osteoclast maturation leads to bone loss. On osteoclast progenitors, inflammatory cytokines and other proteins participate in bone resorption and act through the RANK to RANKL binding reaction (26). Therefore, RANKL is critical for regulating bone metabolism.

To prevent periodontitis, proper dental hygiene is crucial to avoid the buildup of plaque, and when necessary, antibiotic therapy is important to eliminate bacteria (27). In addition, severe cases of periodontitis may require surgery to clean deeply infected pockets and repair damaged tissue (28).

CONCLUSIONS

Infectious diseases caused by bacteria are treated with antibiotics specifically selected based on the involved pathogens. Surgical interventions are also very common for drainage of abscesses, removal of necrotic tissue, and management of the source of infection. Anti-inflammatory drugs are used against pain and swelling.

In maxillofacial infections, there are complex interactions between pathogens, host immune responses, and inflammatory processes. These reactions are still not fully elucidated and continued research is vital to shed light on mechanisms which could help generate new effective treatment strategies to manage infections and prevent disease. Understanding the role of bacteria in periodontitis is important to prevent the onset and progression of this oral disease.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

ROLE OF IL-4 AND IL-31 IN MASTOCYTOSIS

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KEYWORDS: *IL-4, IL-31, mastocytosis, immunity, infection, mast cell*

INTRODUCTION

Mast cells (MCs) are immune cells that originate in the bone marrow and are present in all tissues, especially around small vessels and nerve endings (1). Mastocytosis is a disease characterized by an abnormal increase in MCs in various tissues or organs (2). Interleukin (IL)-4 and IL-31 are immune mediators which are involved in many diseases including allergic diseases (allergic rhinitis and eczema), autoimmune diseases (systemic lupus erythematosus and rheumatoid arthritis), and infectious diseases.

DISCUSSION

IL-4 is a cytokine that functions primarily as a regulator of IgE-mediated immune reactions, MCs, and eosinophils. After activation by IL-4, Th2 cells subsequently produce IL-4, which is important for activating B cells. The T cell that initially produces IL-4, thus inducing differentiation toward Th2, has not been identified, but recent studies suggest that basophils may be the effector cell.

IL-31 is a cytokine encoded by a gene located on chromosome 12 in humans. IL-31 binds to its specific receptor that is expressed mainly on the cell surface of T helper lymphocytes and, to a lesser extent, on dendritic cells.

The binding of interleukin to its receptor, which is expressed on the surface of some neurons on which the TRPV1 receptor is also expressed, is responsible for some biological effects including the sensation of itching. Both IL-4 and IL-31 are cytokines that play a significant role in the immune response and are associated with the symptoms and pathophysiology of mastocytosis (3).

In mastocytosis, IL-4 is produced primarily by T cells and MCs. It plays a key role in the immune response by promoting the differentiation of naive T cells into Th2 cells, enhancing IgE production by B cells, and suppressing Th1-mediated inflammatory responses. Elevated levels of IL-4 can increase IgE production, which contributes to MC activation and degranulation. IL-4 can exacerbate the allergic symptoms and hypersensitivity reactions commonly seen in patients with mastocytosis. Therefore, IL-4 influences MC behavior and may support their survival, further contributing to disease progression.

IL-31 is a cytokine produced primarily by Th2 cells and MCs. It is a crucial molecule involved in the sensation of itch and the pathology of skin diseases such as atopic dermatitis. In mastocytosis, IL-31 is directly associated with the severe itch that patients with this disease often experience. IL-31 binds to the IL-31 receptor (IL-31R) on sensory neurons to mediate the sensation of itch. High levels of IL-31 contribute to the dermatological manifestations of mastocytosis, such

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as urticaria pigmentosa with itchy, pigmented skin lesions. IL-31 can also increase inflammation, worsening systemic symptoms. In mastocytosis, dysregulated production of IL-4, IL-31, and other cytokines amplifies the severity of the disease by perpetuating a cycle of MC activation, immune response, and symptom manifestation.

Biological therapies targeting IL-4 or IL-31 are being studied to manage symptoms such as pruritus and allergic reactions in mastocytosis and other MC-related diseases. Systemic mastocytosis occurs primarily in adults and is characterized by multifocal lesions of the bone marrow and it often involves other organs, usually the skin, lymph nodes, liver, spleen, and/or gastrointestinal tract (Table I).

Table I. *Classification of systemic mastocytosis.*

- Asymptomatic mastocytosis presents no organ dysfunction and a benign prognosis.
- Mastocytosis associated with other hematologic disorders (eg, myeloproliferative disorders, myelodysplasia, lymphoma).
- Progressive mastocytosis is characterized by impaired organ function.
- Mast cell (MC) leukemia presents with > 20% MCs in bone marrow, multiorgan failure, and a poor prognosis (with no skin lesions).

Blockade of IL-4 receptors can suppress the activity of both IL-4 and IL-13, providing a broad-spectrum immunomodulatory effect (4).

CONCLUSIONS

Studies of IL-4 and IL-31 in mastocytosis are critical for developing new, more targeted therapies and improving symptom management in patients with this disease.

Conflict of interest

The author declares that they have no conflict of interest.

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MYOCARDITIS: INFLAMMATION OF THE HEART MUSCLE CAUSED BY INFECTIONS

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ABSTRACT

Myocarditis is a disease of the heart muscle that may also affect young people. Myocarditis is an inflammation of the myocardium that often heals spontaneously, but can also occur in mild and severe forms. In severe forms, there is an alteration of the electrocardiogram, heart failure, low blood pressure, chest pain, and shortness of breath. In addition, some protein levels are elevated, such as Troponin. Myocarditis can be caused by infection with viruses, bacteria, fungi, and parasites that induce inflammation of the myocardium. Both the innate and acquired immune systems are involved in this disease. Microorganisms can reach the heart through circulation, the respiratory tract, the gastrointestinal tract, or other routes. Viral myocarditis is one of the most common forms and occurs when viruses infect cardiomyocytes through specific receptors such as the coxsackie-adenovirus receptor (CAR), Toll-like receptor (TLR), or the ICAM-1 receptor. Receptor activation leads to NF-kB signaling with production of inflammatory cytokines (IL-1β, IL-6, TNF). Various T cells are activated, including CD8+ cells that target and destroy infected cardiomyocytes with activation of NLRP3 that triggers caspase-1, causing the synthesis of inflammatory cytokines. The virus enters the cell and uses viral proteases such as 2A and 3C to perform cytopathic effects, while bacteria can release superantigens that trigger excessive immune activation. These infections interfere with mitochondrial metabolism, induce inflammation, and can cause fibrosis.

KEYWORDS: *Myocarditis, heart, muscle, cardiomyocyte, microorganism, infection*

INTRODUCTION

Myocarditis is inflammation that specifically affects the heart muscle, the myocardium. It is a disease that tends to affect young people and can occur almost completely without symptoms, often healing without sequelae, even if it can present itself in a very serious form. Since it is life-threatening in severe forms, diagnosing this disease early and formulating an adequate treatment plan is very important.

The symptoms of myocarditis are very variable in severity and type. In the mild form, there may be only a slight fever and tiredness, while in the severe form, there may be heart failure, low blood pressure, chest pain, shortness of breath and loss of appetite. In severe forms, tachycardia or heart block may also occur, with a significant drop in blood pressure and shock that requires hospitalization in intensive care. The patient affected by severe myocarditis presents alterations in the electrocardiogram, with the presence of high levels of some proteins in the bloodstream, including Troponine, a protein normally contained in myocardial cells.

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The defining diagnostic test for this pathology is myocardial tissue biopsy, which is an invasive test that is rarely performed. More often, in myocarditis, a frequent and routine diagnostic test uses magnetic resonance imaging (MRI), which is not invasive and detects the possible presence of inflammation of the myocardium.

DISCUSSION

Myocarditis can have many causes, including infections (1). Other forms of myocarditis may be induced by certain drugs, exposure to toxins, hypersensitivity, autoimmunity, or the presence of systemic diseases. Infectious myocarditis is an inflammatory disease of the myocardial muscle caused by infectious agents such as viruses, bacteria, fungi, and parasites (2,3). The biological and biochemical mechanisms of infectious myocarditis involve several complex processes, including pathogen invasion, immune system activation, and tissue damage.

Molecular and biochemical pathways involved in myocarditis lead to immune responses, oxidative stress, and damage caused by microorganisms including viruses (Coxsackievirus B, adenovirus, influenza virus, cytomegalovirus, and SARS-CoV-2), bacteria (Streptococcus pyogenes, Corynebacterium diphtheriae, and Borrelia burgdorferi), fungi (Aspergillus and Candida), and parasites (Trypanosoma cruzi and Toxoplasma gondii) (4).

The infection begins with the entry of infectious agents, which enter the body through the respiratory tract, gastrointestinal system, or other routes. These infectious agents reach the heart through the ematic circulation. For example, one of the most common forms of myocarditis is the viral form, which occurs when viruses infect cardiomyocytes through specific receptors such as the coxsackie-adenovirus receptor (CAR) (5). Normally, the virus enters cardiac cells using cellular receptors, including ICAM-1, and replicates. The intracellular virus changes the physiological condition of the cell, causing cytotoxic effects, cell lysis, and the release of damage-associated molecular patterns (DAMPs) (6). The pathogenic virus activates the innate immune response that recognizes viral RNA/DNA or bacterial components via pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) (7). These effects activate signaling pathways, including NF-κB, which lead to the release of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF (8) (Fig.1). The response to microorganisms activates immune and inflammatory pathways with the involvement of PRRs. TLRs recognize microbial components including viral RNAs and bacterial lipopolysaccharides (LPS). In particular, TLR3, TLR4, and TLR7 play an important role in recognizing viral and bacterial infections in myocarditis (9).

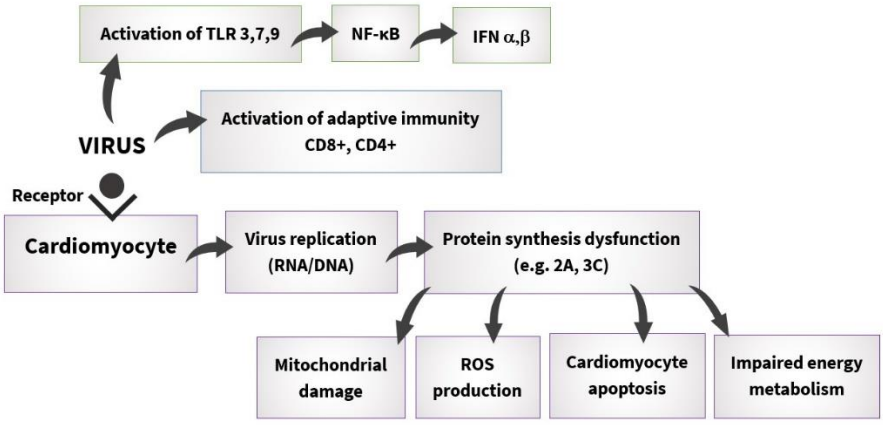

Fig. 1. *The virus binds the cardiomyocyte receptor which induces several biological effects including virus replication and impaired protein synthesis (2A and 3C) which can result in mitochondrial damage, the production of reactive oxygen species (ROS), cardiomyocyte apoptosis, and impaired energy metabolism. In addition, the virus activates adaptive immune responses involving CD8+ and CD4+ cells and also activates Toll-like receptors (TLRs) 3, 7, and 9, inducing NF-kB that promotes interferon (IFN) α and β generation which reacts against the virus.*

Virus-infected cardiomyocytes are recognized as non-self and attacked by immune cells, including natural killer (NK) cells and macrophages, causing cellular damage and tissue inflammation (10). Microorganisms can activate the adaptive immune response, where antigen-presenting cells (APCs) activate T cells and B cells. A subclass of T cells, CD8+ cytotoxic T cells, target and destroy infected cardiomyocytes, while helper T cells generate and release pro- inflammatory cytokines that feed the immune and inflammatory network. In some cases, autoimmune reactions can occur with antibodies that attack self-antigens such as cardiac myosin, leading to chronic inflammation.

While cytokines IL-1 and TNF promote inflammation and cardiac dysfunction, interferon (IFN)-α, -β, and -γ help in viral clearance, but can also cause tissue damage. In inflammation, there is activation of NLRP3 which triggers caspase-1, causing the synthesis of IL-1 and IL-18 and increasing the inflammatory response (11). The adaptive immune response involves cytotoxic T cells that directly attack infected cardiomyocytes, while CD4+ helper T cells (Th17) release pro-inflammatory cytokines such as IFN-γ and IL-17 (12). However, in this immune and inflammatory network, regulatory T cells (Tregs) are also produced that counteract excessive inflammation.

In viral pathogenesis, certain viruses, such as Coxsackievirus B, use the Coxsackievirus and Adenovirus Receptor (CAR) to enter cardiomyocytes. Once the virus has entered the cell, it uses viral proteases such as 2A and 3C to carry out cytopathic effects, apoptosis, and cell death. The antiviral response is mediated by IFN via JAK-STAT signaling.

Bacteria carry out pathogenic effects through toxins by inhibiting protein synthesis in cardiomyocytes. Some bacteria such as Streptococcus pyogenes release superantigens that trigger excessive immune activation, while lipopolysaccharide (LPS) from Gram-negative bacteria activates TLR4, triggering inflammatory cascades and NF-κB (13). Bacterial infections increase oxidative stress and produce reactive oxygen species (ROS) and nitric oxide (NO), impairing mitochondrial function and leading to cardiac dysfunction (11).

Furthermore, parasitic infections can infect cardiac cells and disrupt mitochondrial metabolism (14). All these different types of infections that affect cardiomyocytes may induce chronic inflammation that can lead to cardiomyopathy and fibrosis (15).

CONCLUSIONS

Microbial myocarditis is a direct infection of microbes in cardiomyocytes that causes an immune and inflammatory response with oxidative stress and fibrosis. The immune response involves both innate and adaptive cells. Specific inflammatory and molecular pathways are targeted in myocarditis with activation of inflammatory cytokines, binding of TLRs, and production of ROS. A better understanding of these reactions may provide more specific therapeutic strategies for the treatment of myocarditis.

Conflict of interest

The authors declare that they have no conflict of interest.

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UNDERSTANDING THE ROLE OF FUNGI IN THE LARGER ECOSYSTEM: ANTIMICROBIAL RESISTANCE OF FUNGAL PATHOGENS

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ABSTRACT

Fungal spores are responsible for both seasonal and perennial allergic symptoms. Due to an increase in the use of broad-spectrum antifungals, antimicrobial resistance, including antifungal resistance, is a major concern in medical microbiology. *Candida auris* is a yeast that survives very well in the environment, and is a newcomer to the pathogenic world. The identified gene sequence of *C. auris* has allowed for better understanding of its pathogenicity and resistance. Despite the new treatments used in recent years, antifungal therapy is still limited, and therefore, the study, isolation, and resistance of fungi is very complex and requires more global attention to avoid future infections that are currently increasing.

KEYWORDS: *Fungi, Candida, antimicrobial resistance, fungal pathogen, infection*

INTRODUCTION

Fungi need moisture to grow and flower and stagnate when the soil dries up. When the fungi stop growing and become dry, the wind carries their spores to different areas, where the spores remain above the ground and can survive for years. In this way, fungi spread from warm to cold places. Research has shown that fungal spores can become airborne at any time in dirty environments, causing particular susceptibility in exposed populations (1). Dusty and humid environments may indicate the presence of spores in the air where they can persist like other atmospheric particulates (2).

Fungal infection can present with diverse symptoms that affect different parts of the body and range in severity (Table I). Individuals affected by fungi are often unaware of the tests for detection, as there is a lack of awareness about the diseases that the spores can cause, and the symptoms can be confused with other infections, as often happens in the diagnosis of respiratory diseases such as pneumonia (3).

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Table I. *Possible complications from fungal infection.*

Severe forms of pneumonia	Disseminated infection
	Rupture of lung nodules, resulting in difficulty breathing and chest pain
Chronic infection	Cough
	Nodules in the lungs
	Low fever
	Weight loss
	Chest pain
	Blood in the sputum
Systemic infection	Joint pain and swelling, especially in the knees and hips
	Nodules, ulcers, or skin lesions
	Painful lesions of the skull, spine, or other bones
	Meningitis

Patients often resort to antibiotics, which is not useful or necessary because these drugs are utilized for bacterial infections and not for fungi (4). In these situations, the use of antibiotics can often favor the growth of fungi (5).

The peak of spore circulation occurs around mid-summer and then decreases in the winter period with the first frost. Spores are also transported by dry air that peaks in the early afternoon in conditions of low humidity, circulating *Alternaria, Cladosporium*, and *Epinococcum* species. The spores transported by humid air peak in the early hours of dawn when there is a high percentage of humidity, and these include ascospores, the sexual spores of Ascomycetes, and basidium spools (6).

Alternaria is the most common genus of fungi in places with dry and hot climates (7). It is commonly found in soil or on seeds and plants. This fungus produces a type of mold that is prevalent in southern Europe, which grows on decaying fruit and vegetables in particularly humid environments characterized by a temperature that varies between 18 and 32 degrees Celsius and a humidity rate greater than 65%. *Alternaria* commonly releases its spores on walls, carpets, and soil. Several studies have shown associations between *Alternaria* and severe asthma, conjunctivitis, rhinitis, and dermatitis (8). Sensitivity to *Alternaria* is considered a risk factor for severe asthma attacks and asthmatic epidemics (9).

Cladosporium is the most widespread spore in temperate regions and is the most commonly found fungus in outdoor environments where it is found on dead plants or vegetal substances (10).

Aspergillus is a genus that includes about 200 molds that is often isolated from house dust but is also found in compost piles and dead vegetation (11). The species belonging to this genus are strongly aerobic and grow in almost all oxygen-rich environments. Many species develop on starchy foods, especially if not vacuum-packed, such as cereals and potatoes. Several species also show the phenomenon of oligotrophy, meaning that they can grow in environments that are poor or even devoid of essential nutrients, such as *Aspergillus niger*, which can grow on damp walls (12). *Aspergillus fumigatus* and *Aspergillus clavatus* are the main species capable of causing allergies (13).

Penicillium is found in soil, food, cereals, and house dust. It grows in the water of old damaged buildings, on walls, and in decaying fabrics where it presents as a greenish color (14).

Exposure to allergens plays a significant role in the morbidity of asthma and can promote allergic sensitization in genetically susceptible individuals (15). It can therefore be confirmed that environmental factors play just as important a role as genetic factors in the development of asthma. An effective environmental allergen remediation must include a global approach that aims to prevent exposure to all allergens to which the subject is sensitized. A global prevention plan must also include a significant commitment from public health agencies (16). The current challenge is to find effective public health interventions capable of reducing the impact of atopic diseases.

People who spend a lot of time outside in dusty environments should be vaccinated against that particular fungus to stay uninfected (17). However, there are no vaccines available for any fungal disease to date. There are medications to treat fungi, but patients are often misdiagnosed (18). Fungal vaccines are currently being tested in many laboratories and have so far attracted much enthusiasm as they have produced a positive immune reaction in the body (19).

DISCUSSION

Continuous antimicrobic treatment of infections leads to an increase in antimicrobial resistance for both bacteria and fungi (20). The threat of antifungal resistance is a major global health concern. The World Health Organization (WHO) has published the first list of fungal "priority pathogens," a catalogue of 19 fungi that pose a risk to public health, including *Candida auris* (21).

Resistance has been reported in both *Candida* species and *Aspergillus* and *Trichophyton* molds (22). This is due to an increase in the use of broad-spectrum antifungals, especially in hospitals and in environments where antifungals are frequently used, such as in agriculture. New diagnostic methods and treatment options for the emergence of resistant fungal pathogens (such as *C. auris*, Azole-resistant and *Aspergillus* species) should be studied more thoroughly (23).

C. auris is a yeast that survives very well in the environment and is a newcomer to the pathogenic world (*C. auris* is so named because it was first identified in 2009 in the ear of a Japanese woman). *C. auris* infection can be acquired in the hospital, is difficult to eradicate, and is also more resistant to disinfectants than other fungi. Due to their level of resistance, *Candida* species, including *C. auris*, require prompt treatment (24).

In recent years, the Centre for Disease Control (CDC) has reported that there has been a significant increase in fungal resistance to *Candida* species that has caused thousands of deaths in the United States (25). *C. auris* cases have increased exponentially in the last two years.

Fungi isolated from non-sterile bodies are often non-pathogenic. Yeasts are part of the human microbiome and their presence in the body is considered normal, especially in the gastrointestinal and genitourinary tracts. Yeasts can also be found in the upper respiratory tract but are rarely associated with influenza. Molds are not associated with the human microbiota; however, they are ubiquitous in nature and may play a pathological role (26).

Fungal spores can be isolated from affected respiratory tracts and grown in cultures for further study (27). They can be grown on agar plates during or before incubation, where antifungal-resistant can also be tested. Most laboratories are able to identify most yeasts. However, *C. auris* is difficult to routinely identify in many clinical tests (28). In fact, morphological and biochemical tests alone are not able to identify *C. auris*. Molecular and mass spectroscopy tests are the only reliable ones. The entire gene sequence identified has allowed to evaluate the photogenetic of the isolated material causing the infections. Invasive infections of *Candida* species are often associated with antifungal resistance; this is very important (29).

Some molecular microarray panels have been approved by the FDA and are used in many laboratories. These can rapidly and accurately detect commonly resistant yeast such as *C. glabrata*, *C. krusei* and most importantly, *C. auris* (30). However, with these microarray panels, no resistant markers were found. Pathogen identification is important because it allows for targeted antifungal therapy. Some kits allow the processing of blood cultures to create pellets of microorganisms that can be analyzed and identified rapidly. The accuracy of the methods used depends on the quality of the protein extracted and the instrument utilized. Note that these tests can identify *Candida* species associated with resistance, but they cannot detect resistance genes or provide data regarding antimicrobial susceptibility (31).

C. auris normally colonizes the skin and mucocutaneous tissue and swab analysis is done from the axilla and inguinal region. Often, patients with *C. auris* are asymptomatic if the skin infection is superficial, but they are predisposed to a more invasive infectious disease (32).

There are several types of screening, but the molecular test is very accurate and fast, and therefore, saves time. There are also other tests available that can identify not only *C. auris*, but also other potentially antimicrobial-resistant organisms including other *Candida* species. Mold diagnostic laboratories still rely on morphological characteristics. This process can take several weeks, depending on the growth characteristics of the organism being tested. Some tests for filamentous mold can shorten the identification time and often provide more informative details, such as species level determination, than morphological characteristics alone (33).

Mold diagnoses are non-invasive, as the spores of these organisms often do not infect blood (*Fusarium* species are an exception). In the case of *Fusarium* infection, diagnosis is made by collecting cultures of blood samples, but these have a low yield of detecting the invasive infectious fungus. The presence of specific fungal antigens in blood and body fluids may be useful in certain clinical cases. In the last 5 years, there has been an increase in genomic studies to identify invasive mold infections in high-risk patients, but specificity, cost and time limit the development of metagenomics (34).

The detection of resistance in mold isolates is often determined by the susceptibility of invasive tests or by the recruitment of treated resistant infections. The use of polymerase chain reaction (PCR) on formalin-fixed, paraffin-embedded tissues may be useful for rapid identification of invasive mold infections. Common resistance mechanisms can be identified with PCR (35).

C. auris is a multidrug-resistant isolate that has been identified globally. This strain is difficult to treat because it is resistant to various classes of anti-fungal therapy (36). Some of these strains also show resistance to anti-metabolite classes. There are 4 classes of *C. auris*, each possessing a different resistance (37).

For example, Azole resistance seems to be associated with the ERG11 and CDR1 genetic mutation (38). The ERG11 mutation is a member of the cytochrome P450 family and causes structural alterations and a decrease in the binding affinity of the enzyme with Azole (39). However, there are other mutations associated with Azole resistance. In the last

10 years, several novel anti-fungal agents have been discovered for the treatment of highly resistant fungi, but in many cases, the treatment is still limited.

CONCLUSIONS

The increase in antimicrobial resistance of fungal pathogens, including *C. auris*, is a global concern. Rapid and accurate identification of fungi is essential for the therapy of infections. The use of molecular methods for identification has replaced the now obsolete morphological method which is slow and less accurate. The new anti-fungal agents can provide more specific treatments for current and future invasive infections caused by highly resistant mold and yeast.

Conflict of interest

The authors declare that they have no conflict of interest.

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THE IMMUNOLOGICAL ROLE OF MICROBIOTA IN THE HUMAN INTESTINE AND THE BIDIRECTIONAL COMMUNICATION OF THE GUT-BRAIN AXIS

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ABSTRACT

A group of microorganisms, such as bacteria, viruses, and fungi, located in the same specific environment is called microbiota. These microorganisms have biological effects and regulate the human body, especially at the intestinal level. Microbiota is ubiquitous in the soil, and in humans, it is mainly found in the intestine, particularly in the colon. It controls almost all biological functions and has adapted to live in symbiosis with the human body without causing damage. The microbiota maintains human health and plays an important role in metabolism and regulation of immune functions. The concentration of microorganisms in the intestine is influenced by various factors such as diet, age, genetics, and health conditions and varies from individual to individual. The intestinal microbiota plays a key role in the digestion of complex carbohydrates, proteins, and other nutrients. The microbiota synthesizes essential vitamins such as vitamin K and B which are important for energy metabolism, red blood cell formation, and DNA synthesis. Through hydrolysis, the microbiota can influence xenobiotic metabolism with the modification of environmental toxins and plays a crucial role in the production of mucus. In addition, the bacteria of the microbiota promote the secretion of antimicrobial peptides such as defensins and cathelicidins that inhibit pathogenic microorganisms. The microorganisms that make up the microbiota have an effect on the modulation of both the innate and adaptive immune system. Gut microbes can influence the maturation and activity of antigen-presenting dendritic cells, and in the adaptive response, they can differentiate T cells. The human microbiota is a good example of symbiosis and cooperation between different types of organisms that provide an advantage to the parties.

KEYWORDS: *Microbiota, intestine, immunology, gut-brain axis, microorganism*

INTRODUCTION

The microbiota is a collection of microorganisms such as bacteria, viruses, and fungi that have adapted to living in a specific environment where they have evolved and are specialised in carrying out specific biological effects (1). The microbiota also includes the virome, the genetic material of viruses (2). However, here in this article, we will mainly discuss bacteria because there are more advanced techniques available for their study. Most of the bacteria are

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extremophiles and anaerobes so they live in the dark and without oxygen; and today we know that bacteria are 60/80% Gram-positive, 20/40% Gram-negative, and 60/80% anaerobic.

Microbiota are found in nutrient-rich and nutrient-poor soils where they ferment, break down organic matter, and fix nitrogen, converting atmospheric nitrogen into a form that plants can use (7). Microbiota are found in marine environments where they have adapted to photosynthesize efficiently in low-light conditions near the ocean surface. Microbiota found in deep waters derive energy from chemicals such as hydrogen sulfide, which are emitted from the Earth's crust rather than from sunlight (8). In addition to being found almost ubiquitously in soil, microbiota is also found in the human gut.

Microbiota largely regulate the human body, especially at the intestinal level (3). In the last 10 years, there has been much discussion about microbiota because new technologies have allowed the knowledge and discovery of these microorganisms. The internal surface of the gastrointestinal tract is about 200-300 square meters. In human feces, it is believed that there are 109 virus-like particles per gram, of which bacteriophages are the prevalent enteric viruses. For every human cell, there are at least 10 microbial cells. The gut microbiota is made up of 1,014 microbes, approximately 3 million genes, and 300-1,000 species of bacteria (this is a vague number because there is ongoing research on this topic), and has control over almost all functions of the body, both at the metabolic and physiological levels (4). The remarkable quantity of bacteria present together with our eukaryotic cells has allowed us to define man as a "superorganism", whose genomic structure includes both its genome and the genome of all resident microorganisms (5).

In the past, the intestine was not given this great importance. Other organs were considered more noble and the intestine was considered a peripheral organ of secondary importance. Today, it is considered just as important as other systems because it contributes to the state of health.

DISCUSSION

The microbiota is a group of living microorganisms in a specific location which forms a community that has adapted to living in a specialized environment. In the human body, these microorganisms coexist in natural symbiosis with the human host without causing damage (6), particularly in the colon, where they are adapted to efficiently ferment dietary fiber to produce short-chain fatty acids, which are important for host health. The species and number of microorganisms in the microbiota can vary greatly.

The microbiota plays an important role in maintaining human health by influencing various physiological functions, especially metabolism and immune regulation (9). The human gut microbiota is composed of a diverse population of bacteria, viruses, fungi, and protozoa. The most common bacteria are:

- Firmicutes (e.g., *Lactobacillus, Clostridium*)
- Bacteroidetes (e.g., Bacteroides, Prevotella)
- Actinobacteria (e.g., Bifidobacterium)
- Proteobacteria (e.g., *Escherichia coli*)

This microbial composition is influenced by various factors such as diet, age, genetics, and health conditions, and varies from individual to individual (10).

The gut microbiota contributes significantly to the digestion of complex carbohydrates, proteins, and other nutrients, which the human host cannot fully break down on its own (11). Microbes ferment indigestible polysaccharides, such as cellulose and resistant starch, into short-chain fatty acids like butyrate, propionate, and acetate. Butyrate is an important energy source and promotes intestinal barrier integrity (12). Propionate affects hepatic gluconeogenesis and reduces cholesterol synthesis, and acetate enters the systemic circulation and serves as a substrate for lipogenesis (12).

Gut bacteria metabolize dietary proteins into bioactive molecules such as branched-chain amino acids, amines, and phenolic compounds. However, excessive protein fermentation can also produce toxic metabolites such as ammonia and hydrogen sulfide (13). The microbiota synthesizes essential vitamins such as vitamins K and B (B12, biotin, folate), which are essential for energy metabolism, red blood cell formation, and DNA synthesis (14). Some strains of bacteria also produce cofactors such as bile acids, which aid in lipid digestion and cholesterol metabolism (15).

The gut microbiota also plays a crucial role in drug metabolism and detoxification. Microbes in the gut can activate or inactivate drugs through enzymatic transformations, such as hydrolysis, reduction, or conjugation; they can influence xenobiotic metabolism, modifying environmental toxins, food additives, and drugs, which can affect drug efficacy and toxicity (16).

Microbial fermentation of dietary fiber produces short-chain fatty acids (SCFAs) such as butyrate, propionate, and acetate, which regulate immune functions by influencing T regulatory (Treg) cells, dendritic cells, and macrophages (17). For example, butyrate has anti-inflammatory properties and promotes Treg cells that control immune homeostasis (18). The microbiota is involved in the function of the intestinal barrier, a critical interface between the external environment

and the immune system (19). The intestinal microbiota enhances this barrier by strengthening tight junctions by enhancing the expression of proteins that maintain tight junctions between epithelial cells. Additionally, the microbiota mediates the production of the mucus layer. Microbes stimulate goblet cells to secrete mucus, which forms a physical barrier that protects epithelial cells from pathogens. Furthermore, commensal bacteria promote the secretion of antimicrobial peptides such as defensins and cathelicidins, which inhibit pathogen colonization (20).

The microbiota modulates the intestinal immune system, having a profound effect on both the innate and adaptive immune systems. In the host innate immune response, pattern recognition receptors (PRRs) detect molecular patterns associated with microbes via receptors, such as Toll-like receptors (TLRs), on epithelial and immune cells (21). This recognition triggers immune responses to eliminate pathogens while maintaining tolerance to commensals. Gut microbes can influence the maturation and activity of dendritic cells, which are key cells that present antigens and educate the adaptive immune system.

In the adaptive immune response mediated by Treg cells, the differentiation of Tregs is induced by some bacterial species such as Bacteroides fragilis, which helps maintain tolerance to commensal bacteria and prevent excessive immune responses that could lead to inflammation (22). Moreover, the gut microbiota stimulates B cells to produce secretory IgA, an antibody that coats the intestinal mucosa and prevents pathogens from adhering to the intestinal lining (23).

The gut microbiota helps the immune system distinguish between harmful pathogens and harmless commensals. This process is essential for preventing autoimmune diseases and allergies. Commensal bacteria outcompete pathogenic bacteria for nutrients and attachment sites, a phenomenon known as colonization resistance. They also produce antimicrobial substances that inhibit the growth of pathogens. When the gut microbiota is out of balance (dysbiosis), it can lead to several diseases such as inflammatory bowel disease (IBD), metabolic disorders, and immune-related diseases (24).

Dysbiosis in patients with IBD is characterized by reduced diversity and overgrowth of pro-inflammatory bacteria such as Enterobacteriaceae. Dysbiosis in metabolic processes is linked to obesity, type 1 diabetes, and non-alcoholic fatty liver disease, through mechanisms involving endotoxin release. Immune-related dysbiosis has been implicated in the development of autoimmune diseases such as rheumatoid arthritis and allergies due to impaired immune tolerance (25).

The gut microbiota interacts with the brain through the gut-brain axis, influencing mental health. Dysbiosis is associated with mood disorders, such as depression and anxiety, potentially through altered production of neurotransmitters (e.g. serotonin) and immune activation (26).

Probiotics are live beneficial bacteria, such as strains of Lactobacillus and Bifidobacterium, that are used to restore a healthy microbial balance. Prebiotics are non-digestible fibers, such as inulin and fructooligosaccharides, that promote the growth of beneficial bacteria. Fecal microbiota transplantation involves the transfer of fecal matter from a healthy donor to a patient with dysbiosis (27). This approach is successful in treating conditions such as Clostridioides difficile infections and is being studied for other disorders such as IBD and metabolic syndromes (28). Diets rich in fiber and polyphenols are associated with greater microbial diversity and better health outcomes. In contrast, diets high in fat and sugar can lead to dysbiosis. (29).

The microbiota is made up of millions of genes. In a human gene, there are about 100 microbial genes (it is thought to be as many as 150 as of today). The techniques in use today promote a better understanding of bacteria, but there is also a virome, the set of viruses and their genetic heritage. It is believed that there are 109 virus-like particles per gram in human feces and bacteriophages are the prevalent enteric viruses. So, we are in the presence of a numerically very large group of microorganisms (30). What is important in this symbiotic relationship is that we welcome them, allowing them to recover everything they need for their metabolism (darkness, anaerobic conditions, etc.) and they are able to offer us many advantages. These microorganisms have the sole interest of surviving and they transform into pathogens when something changes this balance, so this environment must be protected (31).

Role of the Microbiota in the Gut-Brain Axis

The gut-brain axis is a complex bidirectional communication network that connects the central nervous system (CNS) with the enteric nervous system and the gastrointestinal tract (32). The gut microbiota influences this axis and plays an important role in various neurological, psychological, and metabolic conditions. Gut microbes produce a variety of bioactive molecules that influence brain function and behavior (33). Short-chain fatty acids such as acetate, propionate, and butyrate are produced by bacterial fermentation of dietary fiber. These metabolites modulate the immune system by interacting with G-protein-coupled receptors on immune cells and influence neurotransmitter systems by crossing the blood-brain barrier (BBB) or by acting on vagal afferents. They also regulate processes such as mood, cognition, and inflammation (34) and regulate the integrity of the gut barrier, thereby, influencing systemic inflammation, which may indirectly impact brain function.

Gut bacteria can synthesize several key neurotransmitters, such as serotonin (5-HT) (about 90%) produced in the gut by enterochromaffin cells. Serotonin is critical for regulating mood, sleep, and digestion (35). Some bacteria such as Lactobacillus and Bifidobacterium can produce gamma-aminobutyric acid (GABA), an important inhibitory neurotransmitter that calms neuronal excitability, and dopamine, which affects reward and motivation (36). The gut microbiota influences the availability of tryptophan, which is a precursor to serotonin and kynurenine, which influence pathways linked to mood disorders such as depression.

Furthermore, the gut microbiota can modulate the production of pro-inflammatory (e.g., IL-6, TNF) and anti-inflammatory (e.g., IL-10) cytokines (37). These cytokines can cross the BBB and directly influence brain regions associated with mood and behavior, such as the hippocampus and hypothalamus.

CONCLUSIONS

The microbiota is found in many natural environments where it has adapted to photosynthesize efficiently in low-light conditions. The human intestinal microbiota is essential for the biochemical and immunological homeostasis of the human body. It plays a central role in nutrient metabolism, immune modulation, and protection against pathogens. The interaction between the gut microbiota and the brain is crucial because it involves a variety of molecular and biochemical pathways, with significant implications for neurological, psychological, and immune health. Future studies on the human intestinal microbiota and its interaction with the brain could improve the understanding of pathogenetic mechanisms and open therapeutic possibilities with new drugs for the treatment of many diseases associated with microbiota imbalance.

Conflict of interest

The authors declare that they have no conflict of interest.

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