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IN BACTERIAL INFECTIONS, NEUTROPHIL RECEPTORS DETECT AND RESPOND TO PATHOGENS

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ABSTRACT

Neutrophils are the first immune cells that intervene after bacterial infection. These cells are the first line of defense in combatting infection by responding to and neutralizing pathogens. They have various receptors such as toll-like receptors (TLRs), NOD-like receptors (NLRs), Fc receptors (complement receptors (CRs)), pattern recognition receptors (PRRs), adhesion receptors, scavenger receptors, and chemokine/cytokine receptors, which are important for binding microorganisms. After neutrophil receptor binding, signaling cascades are activated which lead to gene expression changes that produce neutrophil activation. Then, reactive oxygen species (ROS) are produced which are toxic to bacteria. Additionally, neutrophils can produce proteases and antimicrobial peptides which break down bacterial cell walls and membranes, protecting the body from infection.

KEYWORDS: *infection, neutrophil, receptor, bacteria, pathogen, immunity, microbe*

INTRODUCTION

Bacterial infections occur when harmful bacteria invade and multiply within the host body, leading to a range of diseases. These infections can trigger immune responses, including the activation of neutrophils, which are a type of white blood cell and are among the first responders to microbial infection (1). They are part of the innate immune system and play a crucial role in defending against bacterial infections. Neutrophils are the first line of defense against infections and are highly effective at responding to and neutralizing pathogens (2).

DISCUSSION

Neutrophils perform various functions which include phagocytosis (the engulfment and digestion of pathogens and debris) (3), degranulation (the release of antimicrobial peptides and enzymes from granules to destroy pathogens) (4), the creation of neutrophil extracellular traps (NETs) (by expelling a web of DNA and antimicrobial proteins to trap and kill pathogens extracellularly) (4), and the production of cytokines that modulate the immune response and recruit other immune cells (5).

Receptors on the surface of neutrophils and other immune cells recognize and bind to specific molecules (ligands) on bacteria. This recognition is crucial for initiating an immune response. Neutrophils have various receptors on their surface that help them recognize, bind to, and respond to pathogens. Some key receptors that are found on neutrophils include

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toll-like receptors (TLRs), NOD-like receptors (NLRs), Fc receptors (complement receptors (CRs)), pattern recognition receptors (PRRs), adhesion receptors, scavenger receptors, and chemokine/cytokine receptors (6) (Table I).

Table I. *Some key neutrophil receptors that play a role in infection.*

Fcγ Receptors (FcγRs):	Bind IgG antibodies, leading to phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and release of inflammatory mediators.
Toll-like Receptors (TLRs):	Recognize components of microbial pathogens, such as lipopolysaccharides (TLR4) from Gram-negative bacteria or flagellin (TLR5).
NOD-like Receptors (NLRs):	Detect intracellular bacteria.
CR1 (CD35), CR3 (CD11b/CD18), CR4 (CD11c/CD18):	Bind to complement component C3b.
Fcγ Receptors (FcγRs):	Bind IgG antibodies, leading to phagocytosis, antibody-dependent cellular cytotoxicity (ADCC), and release of inflammatory mediators.
G-protein Coupled Receptors (GPCRs):	respond to chemokines, guiding neutrophils to infection sites.
Selectins:	E-selectin and P-selectin mediate the initial rolling of neutrophils on endothelial cells.
Integrins:	LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) mediate firm adhesion and transmigration.
Scavenger Receptors:	SR-A and CD36 involved in the recognition and phagocytosis of bacteria and apoptotic cells.
Formyl Peptide Receptors (FPRs):	Binds to N-formylmethionine-leucyl-phenylalanine (fMLP), a potent chemoattractant derived from bacteria.
C-type Lectin Receptors (CLRs):	recognize carbohydrate structures on pathogens.
Sialic acid-binding immunoglobulin-like lectins (Siglecs):	recognize sialic acid-containing structures on pathogens and host cells.
P-selectin glycoprotein ligand-1:	interacts with P-selectin and mediates rolling on activated endothelial cells.
CD14:	Acts as a co-receptor with TLR4 for the detection of bacterial lipopolysaccharide (LPS).

TLRs recognize pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharides (LPS) on bacterial surfaces (7). NLRs detect intracellular bacterial components, and Fc receptors bind to antibodies that are attached to bacteria, marking them for destruction (8).

Fc Receptors bind to the Fc region of antibodies that are attached to pathogens, facilitating phagocytosis and antibody-dependent cellular cytotoxicity (9). Fc gamma receptors (FcγR) bind to IgG antibodies and include subtypes like FcγRI, FcγRII, and FcγRIII, while Fc alpha receptors (FcαR) bind to IgA antibodies (10).

CRs recognize complement-coated pathogens, enhancing phagocytosis and inflammatory responses (11). CR1 (CD35) binds to C3b and C4b complement fragments. CR3 (CD11b/CD18, also known as Mac-1) binds to iC3b, a breakdown product of C3b. CR4 (CD11c/CD18) also interacts with iC3b and other complement fragments (12).

PRRs recognize PAMPs and damage-associated molecular patterns (DAMPs). TLRs recognize components of microbial pathogens, such as bacterial LPS (TLR4) and flagellin (TLR5) (13,14). NLRs detect intracellular pathogens and initiate inflammatory responses (7). C-type lectin receptors (CLRs) bind to carbohydrate structures on the surfaces of pathogens (15).

Adhesion receptors mediate the adhesion of neutrophils to the endothelium and their transmigration into tissues (16). Integrins, such as LFA-1 (CD11a/CD18) and Mac-1 (CD11b/CD18), interact with intercellular adhesion molecules (ICAMs) on endothelial cells (17,18). Selectins include L-selectin (CD62L), which mediates initial weak adhesion to the endothelium (19).

Scavenger receptors recognize and bind to a variety of ligands, including modified low-density lipoproteins (LDL) and microbial products. Scavenger receptor-A (SR-A) binds to a variety of polyanionic ligands, while CD36 binds to oxidized LDL and apoptotic cells (20).

Chemokine receptors guide neutrophils to the site of infection or inflammation by detecting chemokines. The receptors CXCR1 and CXCR2 bind to chemokines such as IL-8, which is crucial for neutrophil chemotaxis, and CCR1 and CCR2 respond to other chemokines involved in the recruitment of neutrophils (21).

The interaction between bacterial components and neutrophil receptors involves complex biochemical pathways such as chemotaxis, phagocytosis, degranulation and NETosis. In chemotaxis, neutrophils migrate towards the site of infection in response to chemical signals (chemokines) (22). During phagocytosis, neutrophils engulf and digest bacteria through a process facilitated by receptors such as TLRs and Fc receptors (6). Following phagocytosis there is degranulation, in which antimicrobial substances that destroy bacteria are released from neutrophil granules. During the process of NETosis, NETs are released, which are networks of extracellular fibers composed of DNA and antimicrobial proteins that trap and kill bacteria (23).

Upon receptor binding, signaling cascades are activated (e.g., MAPK, NF-κB) that lead to gene expression changes necessary for neutrophil activation. An oxidative burst follows, with the production of reactive oxygen species (ROS) that are toxic to bacteria. Neutrophils can also produce proteases and antimicrobial peptides, enzymes and peptides that break down bacterial cell walls and membranes.

CONCLUSIONS

Neutrophils are equipped with a diverse array of receptors that enable them to detect and respond to pathogens effectively, thus they play a critical role in the body's defense mechanisms. In bacterial infections, neutrophils use various receptors to detect and respond to pathogens through intricate molecular and biochemical processes. These responses involve a coordinated effort to locate, identify, and destroy bacterial invaders.

Conflict of interest

The authors declare that they have no conflict of interest.

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MOLECULAR MECHANISMS OF CYTOKINE RECEPTOR SIGNALING IN INFECTION

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ABSTRACT

Cytokine receptor signaling is fundamental to the immune system's ability to respond to infections. The intricate signaling networks activated by cytokine-receptor interactions ensure a coordinated and effective immune response. The main families of cytokine receptors include: type I and type II cytokine receptors, which bind to ILs, interferons (IFNs), and colony-stimulating factors (CSFs) and signal through the Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway; tumor necrosis factor (TNF) receptors, which bind TNF cytokines and primarily signal through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways; interleukin (IL)-1 receptors, which bind IL-1 and signal through the MyD88-dependent pathway, leading to NF-κB activation; and G protein-coupled receptors (GPCRs), which bind chemokines and signal through G proteins, leading to changes in cellular calcium levels and activation of various kinases. Dysregulation of these pathways can lead to inadequate immune responses or chronic inflammatory diseases, highlighting the importance of understanding these mechanisms for developing targeted therapies.

KEYWORDS: *cytokine, receptor, signaling, infection, immunity*

INTRODUCTION

Cytokines are small proteins that are crucial for cell signaling in the immune system. They regulate various immune responses, including inflammation, infection control, and tissue repair. Cytokine receptors are present on the surface of immune cells and mediate the effects of cytokines. Understanding cytokine receptor signaling is essential for comprehending how the immune system responds to infections and maintains homeostasis.

Cytokines are secreted *in vitro* by immune cells, usually in response to a stimulus, and induce activities such as growth, differentiation, and cell death (1). Their action is usually local but can sometimes occur throughout the entire organism. Cytokines can have an autocrine effect, acting on the same cell that they were secreted from, or a paracrine effect by acting on adjacent cells. Some cytokines can also act in an endocrine manner, affecting cells very distant from them (2). They have a half-life of a few minutes and are non-antigen specific (3). These small protein molecules regulate different types of immune responses and tissue repair, but also the inflammatory process, aggravating the pathological state (1).

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Cytokine receptors are located on the surface of immune cells and can be activated by various protein substances, including cytokines themselves and microorganisms. These reactions are important for understanding how the immune system reacts to infectious agents.

Cytokine receptors are classified based on their structural features and the signaling pathways they activate. The major families include type I and type II cytokine receptors, tumor necrosis factor (TNF) receptors, interleukin (IL)-1 receptors, and G protein-coupled receptors (GPCRs).

DISCUSSION

Type I and type II cytokine receptors bind to cytokines such as ILs, interferons (IFNs), and colony-stimulating factors (CSFs) (4). They typically signal through the Janus kinase (JAK)-Signal Transducer and Activator of Transcription (STAT) pathway. TNF Receptors bind TNF cytokines and primarily signal through nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (5). IL-1 receptors bind IL-1 and signal through the MyD88-dependent pathway, leading to NF-κB activation (6) (Fig.1). GPCRs bind chemokines and signal through G proteins, leading to changes in cellular calcium levels and activation of various kinases (7).

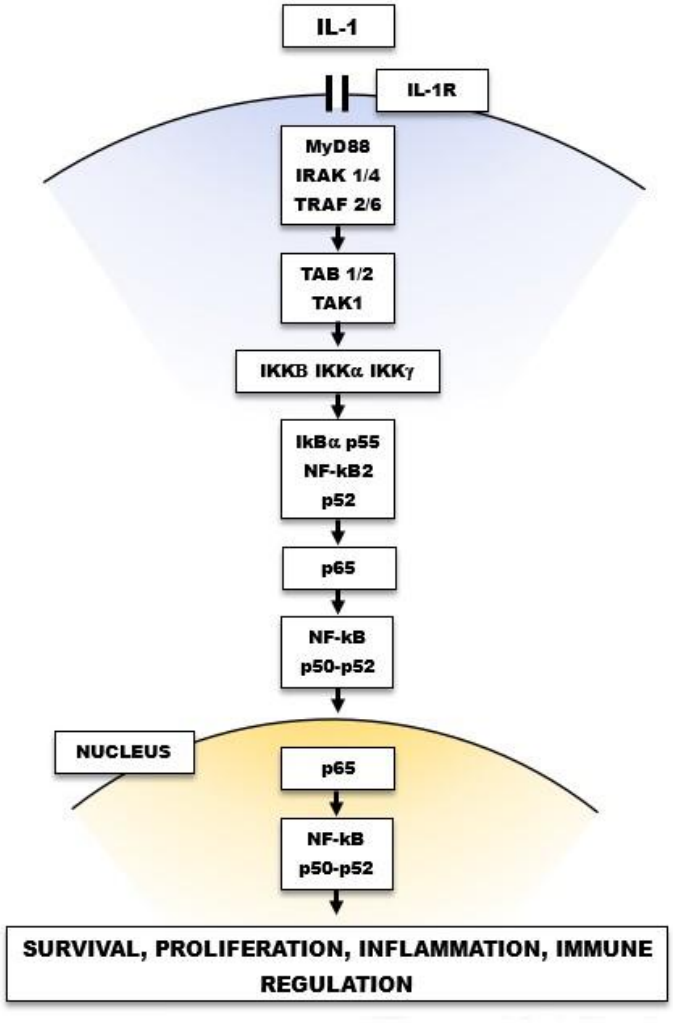

Fig. 1. *IL-1 is a cytokine which exerts multiple effects on cells by binding the IL-R. This activation leads to the generation of NF-kB and p50-p52, which causes the release of proteins in the nucleus that mediate inflammation, immune regulation, survival, and proliferation.*

The JAK-STAT pathway is one of the signaling cytokine receptors. Its activation allows the binding of the cytokines IL-6, IL-10, and IFNs to their receptors and leads to the activation of associated JAKs (8). Activated JAKs lead to phosphorylation of tyrosine residues on the receptor, creating docking sites for STAT proteins (8,9). Phosphorylated STATs dimerize and translocate to the nucleus, where they regulate gene expression (10).

Lipopolysaccharide (LPS) is a gram-negative bacteria which activates immune cells that have CD14 receptors (11). The NF-kB activation pathway is implicated in the binding of cytokines, such as TNF to TNF receptors and IL-1 receptors to IL-1, which activates IkB kinase (IKK) (12). Subsequently, the degradation of IkB occurs with the phosphorylation of IKK in IkB with the release of NF-kB (13). Once activated, free NF-kB translocates into the nucleus and activates genes involved in inflammation and the immune response (12) (Fig.2).

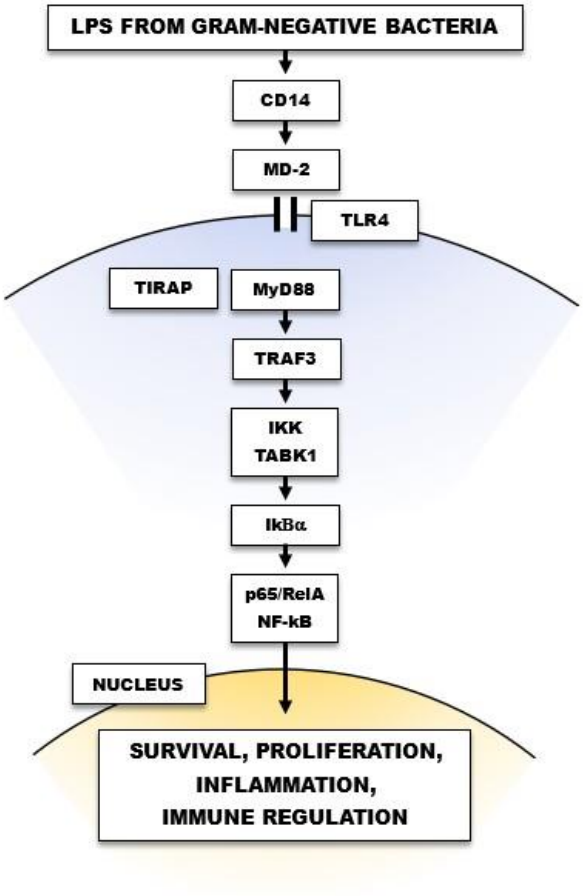

Fig. 2. *Lipopolysaccharide (LPS) activates the CD14 receptor and MD-2 to stimulate the toll-like receptor 4 (TLR4) on the cell membrane. This leads to a biochemical pathway cascade that activates NF-kB, which enters the nucleus and affects genes that code for proteins which mediate inflammation, immune regulation, survival, and proliferation.*

In the activation of the MAPK pathway, the binding of cytokines activates the kinases associated with the receptors that phosphorylate the MAPKs (14). The MAPK cascade involves three main kinases: MAPK kinase kinase (MAP3K), MAPK kinase (MAP2K), and MAPK. Activated MAPKs enter the nucleus and regulate the expression of genes involved in cell growth, differentiation, and the immune response (14).

In activation of the GPCR pathway, binding of chemokines to GPCRs activates heterotrimeric G proteins by exchanging GDP for GTP (15). Regarding signal transduction, G proteins dissociate into Gα and Gβγ subunits that activate downstream effectors such as adenylate cyclase, phospholipase C, and various kinases (16). All these pathways exert regulation of cellular responses, including activation, adhesion, and chemotaxis (17).

Cytokine receptor signaling is critical for orchestrating the immune response to infection (18). By binding to their receptors, cytokines exert important signals to enhance the immune response against infectious microorganisms (19). On the other hand, certain cytokines stimulate PIP3, activating Akt, which inhibits the cell cycle (20) (Fig.3).

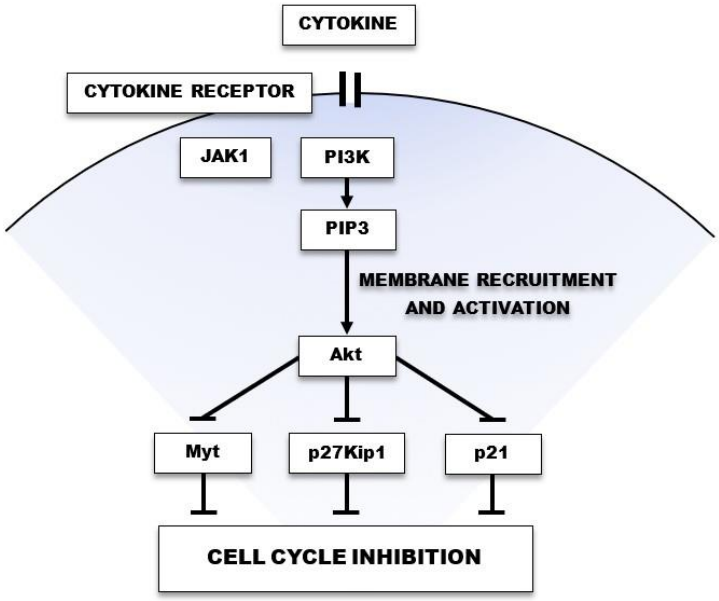

Fig. 3. *Activation of cytokine receptors may lead to Akt membrane recruitment and activation which inhibits Myt, p27Kip1, and p21, leading to inhibition of the cell cycle.*

Infection stimulates the innate immune response with the production of pro-inflammatory cytokines such as IL-1, TNF, IL-6 and IFN, which activate the NF-kB and MAPK metabolic pathways to initiate inflammation, recruit immune cells, and enhance the elimination of pathogens (1,21). In the adaptive immune response, cytokines such as IL-12, promote the differentiation of T cells into Th1 cells, which are crucial for fighting intracellular pathogens (22). IL-4 promotes the differentiation of Th2 cells, which are important for combating extracellular pathogens (23). IFNα and β activate the JAK-STAT pathway, inducing the expression of antiviral genes that inhibit viral replication and improve antigen presentation (24).

CONCLUSIONS

Cytokine receptor signaling is important for the development of the immune system against infectious pathogen antigens. The different signals of activation of cytokines linked to their receptors can lead to an effective immune response against infectious microorganisms but can also lead to hyperinflammation due to the release of pro-inflammatory cytokines. The study of these mechanisms can lead to improvements in the treatment of inflammatory and autoimmune diseases.

Conflict of interest

The authors declare that they have no conflict of interest.

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IL-1 INDUCES NF-kB IN INFECTIOUS DISEASES

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ABSTRACT

Cytokines are proteins that mediate the immune response and act as signaling molecules in inflammatory processes. Pathogens activate the immune and inflammatory response which is mediated by cytokines. The most studied cytokines in the inflammatory response are interleukin (IL)-1, tumor necrosis factor (TNF), and interferon (IFN)-γ. These cytokines intervene to attack pathogens but their overexpression causes inflammation. In bacterial infections, IL-1β is secreted and induces nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation with subsequent release of other pro-inflammatory cytokines, such as TNF. This cascade of inflammatory cytokines can be very harmful and can even lead to death. Sepsis is a severe systemic infection with IL-1-mediated NF-kB activation that leads to dysregulation of inflammatory mediators, contributing to the disease. In sepsis, NF-kB activation is crucial for the host defense mechanism, but can also induce a "cytokine storm" that leads to multiorgan failure and death. Viral infection activates NF-kB to control virus replication and spread, but excessive activation can contribute to inflammation and lung damage. In conclusion, understanding the mechanisms of IL-1 in NF-kB activation in infections is important for more effective therapy.

KEYWORDS: *IL-1, NF-kB, infection, cytokine, immunity, inflammation, signal pathway*

INTRODUCTION

Cytokines are small proteins released by cells, particularly those of the immune system, that act as signaling molecules to regulate immunity, inflammation, and hematopoiesis. Infections can trigger a wide range of immune responses, among which the production of cytokines is crucial.

In infections, cytokines are activated after pathogen recognition (1). When a pathogen (such as bacteria, viruses, fungi, or parasites) enters the body, immune cells recognize it through pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) (1). These receptors detect pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (2).

The recognition of pathogens leads to the activation of immune cells, which then release cytokines. Cytokines, such as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), and chemokines, play vital roles in orchestrating the immune response and, when they are overexpressed, induce inflammation (3).

Pro-inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ promote inflammation to help eliminate pathogens (4,5). Anti-inflammatory cytokines, such as IL-10 and TGF-β, regulate and suppress the inflammatory response to prevent excessive damage to the host (6).

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A severe, uncontrolled release of pro-inflammatory cytokines can lead to a "cytokine storm," which can cause systemic inflammation, multi-organ failure, and even death (7,8). This condition is observed in severe infections like COVID-19, influenza, sepsis, and certain autoimmune diseases (9).

Rheumatoid arthritis is mediated by the excessive production of TNF-α and IL-6 which leads to chronic inflammation in the joints (10). In inflammatory bowel disease (IBD), there is dysregulated cytokine production involving TNF, IL-12, and IL-23, which causes chronic inflammation in the gastrointestinal tract (11). In systemic lupus erythematosus (SLE), the overproduction of IFN-α and other cytokines contributes to systemic inflammation and organ damage (12).

Immunodeficiency disorders also involve the dysregulation of cytokines and other immunoproteins, including antibodies. Disorders like Severe Combined Immunodeficiency (SCID) involve deficiencies in cytokine signaling pathways, leading to a severely compromised immune response (13).

Additionally, certain cytokines can promote tumor growth and metastasis. For instance, IL-6 and IL-8 are associated with tumor progression in various cancers (14). Conversely, cytokine-based therapies (like IFN-α and IL-2) are used to treat some cancers by enhancing the immune response against tumor cells (15). However, this treatment is still being investigated and further studies are needed to improve this therapy.

Understanding the role of cytokines in infections and related disorders is critical for developing therapeutic strategies. Targeted therapies that modulate cytokine activity (e.g., monoclonal antibodies against specific cytokines) have been developed to treat various inflammatory and autoimmune diseases, showcasing the importance of cytokines in both health and disease.

DISCUSSION

IL-1 is a key pro-inflammatory cytokine involved in various immune responses and is a potent inducer of inflammation. It exists in two forms: IL-1α and IL-1β, with IL-1β being the most extensively studied due to its role in inflammatory processes. IL-1β is produced primarily by activated macrophages and plays a critical role in host defense against infections (16). It acts by binding to the IL-1 receptor (IL-1R) on target cells, initiating a cascade of signaling events that lead to inflammation and immune activation (17).

Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) is a family of transcription factors that regulate the expression of genes involved in immune and inflammatory responses, cell proliferation, and survival, and it is a central regulator of the immune response (18). NF-κB is activated in response to various stimuli, including cytokines such as IL-1, microbial products, and stress (19). The NF-κB family consists of several proteins, including RelA (p65), RelB, c-Rel, p50, and p52, which can form various dimeric complexes to modulate gene expression (18).

IL-1 induces NF-κB activation by binding to IL-1R, causing the recruitment of adapter proteins and the activation of TAK1 and IκB Kinase (IKK), which leads to NF-κB translocation (20). IL-1β binds to the IL-1 receptor type I (IL-1RI) on the cell surface. This receptor complex also includes the accessory protein IL-1 receptor accessory protein (IL-1RAcP). Upon IL-1 binding, the receptor complex recruits adapter proteins such as myeloid differentiation primary response (88MyD88) and IL-1 receptor-associated kinase (IRAK) (21). These adapters facilitate the downstream signaling cascade. The formation of the receptor complex leads to the activation of transforming growth factor-beta-activated kinase 1 (TAK1). TAK1 plays a crucial role in transmitting signals from the IL-1 receptor to downstream effectors. TAK1 activates the IκB kinase (IKK) complex, which consists of IKKα, IKKβ, and NF-κB essential modulator (NEMO) (22). The IKK complex phosphorylates the inhibitor of NF-κB (IκB), leading to its ubiquitination and subsequent degradation by the proteasome (23). The degradation of IκB releases NF-κB dimers, predominantly the p65/p50 complex, allowing them to translocate into the nucleus (24). Once in the nucleus, NF-κB binds to specific DNA sequences in the promoters of target genes, initiating their transcription.

The role of NF-kB in infection

In bacterial infections, IL-1β-induced NF-κB activation plays a critical role in orchestrating the host immune response (25). For example, during infection with Escherichia coli or Staphylococcus aureus, the activation of NF-κB leads to the production of pro-inflammatory cytokines, chemokines, and adhesion molecules (26). These mediators enhance the recruitment and activation of neutrophils and macrophages to the site of infection, facilitating the clearance of bacteria.

Sepsis is a severe systemic inflammatory response to bacterial infection that is characterized by excessive cytokine production, including IL-1β (27). NF-κB activation in sepsis leads to the upregulation of inflammatory mediators like TNF and IL-6, contributing to the pathophysiology of the disease (27). Dysregulated NF-κB activation can result in a cytokine storm, leading to multi-organ failure and high mortality rates.

In viral infections, NF-κB activation is crucial for the host defense mechanism. Viruses such as influenza and HIV exploit the NF-κB pathway to enhance their replication and evade the immune system (28).

Influenza virus infection activates NF-κB, leading to the production of type I IFNs and pro-inflammatory cytokines (29). While NF-κB activation is essential for controlling viral replication and spreading, excessive activation can contribute to lung inflammation and damage.

HIV-1 utilizes NF-κB to promote its replication. The virus activates NF-κB to enhance the transcription of its genome, integrated into the host cell DNA (30). Persistent NF-κB activation in HIV infection is associated with chronic inflammation and immune activation, contributing to disease progression and co-morbidities (31).

In COVID-19, severe cases are often characterized by the hyperactivation of NF-κB, leading to a cytokine storm (32). Elevated levels of IL-1β, IL-6, and TNF are observed in critically ill patients, contributing to acute respiratory distress syndrome (ARDS) and systemic inflammation (33).

NF-κB activation also plays a role in the immune response to fungal and parasitic infections (34). Infections caused by Candida species trigger NF-κB activation, leading to the production of pro-inflammatory cytokines that are essential for fungal clearance (35). However, excessive inflammation can result in tissue damage and contribute to disease severity.

In malaria, caused by Plasmodium species, NF-κB activation in response to parasitic infection leads to the production of inflammatory cytokines (36). While this response is necessary for controlling parasite replication, dysregulated NF-κB activation can contribute to severe malaria pathology, including cerebral malaria (37).

Targeting the IL-1/NF-κB signaling pathway holds therapeutic potential for managing infectious diseases that are characterized by excessive inflammation. Several strategies are being explored including IL-1 blockade, NF-κB inhibitors, and cytokine modulation.

Agents such as Anakinra (IL-1 receptor antagonist) and Canakinumab (anti-IL-1β monoclonal antibody) have shown efficacy in reducing inflammation in conditions like sepsis and COVID-19. By inhibiting IL-1 signaling, these therapies can attenuate NF-κB activation and its downstream inflammatory effects.

Direct inhibitors of NF-κB signaling are also under investigation. These include small molecules that inhibit IKK activation or NF-κB translocation. However, due to the broad role of NF-κB in immune responses, careful consideration of potential immunosuppressive effects is necessary.

Modulating the balance of pro- and anti-inflammatory cytokines can help control excessive NF-κB activation. For example, enhancing IL-10 production or signaling can provide an anti-inflammatory counterbalance to IL-1β-induced NF-κB activation.

CONCLUSIONS

IL-1-induced NF-κB activation plays a critical role in the immune response to infections. While this pathway is essential for pathogen clearance and immune activation, its dysregulation can lead to excessive inflammation and tissue damage, contributing to the pathology of various infectious diseases. Understanding the intricate mechanisms of IL-1/NF-κB signaling and its impact on infectious diseases opens avenues for targeted therapeutic interventions aimed at modulating inflammation and improving clinical outcomes.

Conflict of interest

The author declares that they have no conflict of interest.

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RESPIRATORY INFECTION AND ANTIMICROBIAL RESISTANCE

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ABSTRACT

Antimicrobial resistance to the effects of antibiotics has caused a significant public health problem with reduced effectiveness of standard treatments. Resistance occurs through various mechanisms such as genetic mutations, horizontal gene transfer, and selective pressure from the widespread use of antimicrobials. Antibiotic resistance requires genomic insights, new technologies, and innovative solutions. In the treatment of respiratory infections, mainly caused by *Streptococcus pneumoniae*, *Hemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus piogenes* and *Moraxella catarralis*, inappropriate use of antibiotics leads to the development of resistant bacteria. Pathogens can develop different specific mechanisms to avoid the effect of the antibiotic. Continuous therapeutic treatments with the same antibiotics can induce resistance, and therefore, research for developing new antibiotics is necessary to address pathogen resistance and ensure effective treatment.

KEYWORDS: *infection, antimicrobial resistance, microorganism, bacteria, antibiotic*

INTRODUCTION

Antimicrobial resistance refers to the ability of microorganisms, such as bacteria, viruses, fungi, and parasites, to withstand the effects of medications that once effectively treated them. This phenomenon is a significant public health concern as it leads to the reduced efficacy of standard treatments, prolonged illnesses, increased mortality, and the need for more potent and potentially toxic medications. Resistance arises through various mechanisms, including genetic mutations, horizontal gene transfer, and selective pressure from the widespread use of antimicrobials. Understanding and addressing pathogen resistance is critical for maintaining the effectiveness of current treatments and for the development of new therapeutic strategies.

Antimicrobial resistance is a dynamic and evolving challenge in modern medicine (1,2). Recent advancements and emerging trends highlight the complexity of this issue and the need for innovative solutions. Several new methods to combat resistance that are gaining attention in the scientific community include genomic insights and clustered regularly interspaced short palindromic repeats (CRISPR) technology, antibiotic stewardship programs, phage therapy, antimicrobial peptides (AMPs) and novel compounds, microbiome modulation, and global surveillance and big data (3-7).

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DISCUSSION

The inappropriate use of antibiotics for treating respiratory infections, in which they are not necessarily required leads to the development of resistant bacterial strains, as well as unnecessarily exposing the patient to the adverse reactions of the pharmacological treatment and leading to a waste of economic resources. The most common etiological agents in bacterial respiratory infections are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Streptococcus piogenes*, and *Moraxella catarralis*.

S. pneumoniae is a gram-positive bacterium and a leading cause of pneumonia, meningitis, otitis media, and bacteremia, particularly in children and the elderly (8). It is encapsulated, which helps it evade the host's immune system. *S. pneumoniae* has developed resistance primarily through alterations in penicillin-binding proteins (PBPs), reducing the efficacy of beta-lactam antibiotics (9). Additionally, resistance to macrolides occurs via modification of the ribosomal target site or efflux mechanisms that expel the antibiotic from the bacterial cell (10). The emergence of multi-drug-resistant strains complicates treatment and highlights the need for ongoing surveillance and development of new antibiotics or vaccines (11).

Numerous studies have been conducted on the distribution of resistance of *S. pneumoniae*, the most common etiological agent of community-acquired pneumonia (CAP), to the most widely used antibiotics (beta-lactams and macrolides) (12-14). Pneumococci are germs that are highly sensitive to penicillin, both the natural versions, such as penicillin G, and the semi-synthetic versions, such as aminopenicillins (amoxocillin), with a minimum inhibitory concentration (MIC) of 0.01 μm/ml and 0.03 μm/ml respectively. However, the chemo-sensitivity of pneumococci to beta-lactams has undergone a notable change over the years due to the development of new local resistance (15).

Penicillin was produced in 1940 and was the first antibiotic used in infectious diseases (16), but penicillin-resistant strains of *S. pneumoniae* already appeared in 1970 with structural modifications of the PBPs of the bacterium preventing inhibition by the antibiotic of bacterial peptidoglycan synthesis (17). Macrolides were therefore used to treat pneumococcal infections. However, the frequent use of these drugs led to the appearance of *S. pneumoniae* species that were also resistant to macrolides.

The most common mechanisms of macrolide resistance are ribosomal methylation mediated by the erm(B) gene and efflux pump synthesis mediated by the mef(A) gene (18). Penicillum-resistant *S. pneumoniae* strains can be distinguished into intermediate-resistant strains and highly resistant strains based on MICs (19). The Clinical and Laboratory Standard Institute (CLSI) has defined the MIC breakpoints, for example, the threshold concentrations (micrograms per milliliter) to express the sensitivity and resistance of microorganisms to penicillin (20). Values between 0.12 and 1 μg/ml indicate intermediate resistance. Values greater than 2 μg/ml indicate high resistance.

Penicillin resistance has been on the increase over recent years, with distribution that varies considerably in different geographical areas. *S. pneumococcus* resistance to penicillin can reach approximately 44% in some regions of the United States (21,22), 22% in Brazil (23), as much as 70% in some European countries such as Spain, Hungary, and France (24,25), and levels as high as 70-78% in Asian countries such as South Korea, Hong Kong, and Taiwan (26,27).

In cases of respiratory infections caused by penicillin-resistant *S. pneumoniae* strains, high-dose amoxocillin clavulanate of 80-90 mg/kg per day should be administered, thus achieving antibiotic sensitivity rates of 99%. The MIC breakpoints used to distinguish macrolide-resistant *S. pneumoniae* strains are 1 μg/ml for azithromycin and 0.5 μg/ml for erythromycin (28). Erythromycin-resistant strains are particularly high in South America, Europe, South Africa, and Asia, and high numbers of azithromycin-resistant strains have been seen in North America and Saudi Arabia. In cases of resistance to macrolides, a third-generation cephalosporin is recommended and, as a second choice, one of the most recent antibiotics: fluoroquinolones (levofloxacin, moxifloxacin, etc.), ketolides (telithromycin), and oxazilodones (linezolide). Resistance to new-generation antibiotics is very low or absent (29).

H. influenzae is a gram-negative bacterium that can cause a range of infections, including respiratory tract infections, meningitis, and septicemia (30). It is especially known for causing serious infections in children before the advent of the *Haemophilus influenzae* serotype b (Hib) vaccine (31). *H. influenzae* has developed resistance through the production of beta-lactamase enzymes that degrade beta-lactam antibiotics, rendering them ineffective (32). Some strains have also acquired mutations in penicillin-binding proteins, contributing to beta-lactam resistance (33). Resistance to other antibiotics, such as macrolides and tetracyclines, often arises through efflux pumps and ribosomal protection proteins (34). Increasing resistance necessitates careful selection of antibiotics and consideration of combination therapies to overcome these mechanisms.

M. pneumoniae is a unique, small bacterium lacking a cell wall, a trait which makes it inherently resistant to beta-lactam antibiotics (35). It is a common cause of atypical pneumonia, especially in children and young adults, and is also associated with other respiratory infections. This bacterium exhibits resistance primarily to macrolides, the preferred

treatment option, through mutations in the 23S rRNA of the 50S ribosomal subunit, which reduce drug binding (36). This resistance can lead to treatment failures and the need for alternative antibiotics such as tetracyclines or fluoroquinolones. The absence of a cell wall and the bacterium's intrinsic resistance to certain antibiotics pose challenges for treatment and highlight the need for new therapeutic approaches and monitoring resistance patterns.

Recent advances to combat pathogen resistance

Recent advances in genomics have revolutionized our understanding of antimicrobial resistance. High-throughput sequencing technologies allow for rapid and detailed analysis of microbial genomes, revealing resistance genes and their mechanisms. CRISPR technology is being explored not only for gene editing but also as a tool to combat antibiotic resistance (37,38). By targeting and inactivating resistance genes, CRISPR-based strategies offer a promising approach to restore the efficacy of existing antibiotics.

Antibiotic stewardship programs aim to optimize the use of antibiotics to combat resistance. These programs involve coordinated efforts to prescribe antibiotics at the right dose and duration (39). New aspects of these programs include integrating advanced diagnostic tools and real-time data analytics to guide clinical decisions. For example, rapid diagnostic tests can quickly identify pathogens and their resistance profiles, allowing for more targeted therapy and reducing the misuse of broad-spectrum antibiotics.

Bacteriophage therapy, which uses viruses that specifically infect bacteria, is being revisited as a potential alternative to antibiotics. Phages can be engineered to target multi-drug-resistant bacteria, and their specificity reduces the risk of disrupting the normal microbiota (40). Advances in synthetic biology have enhanced the ability to design phages with improved efficacy and safety profiles. Clinical trials and case studies have demonstrated phage therapy's potential in treating infections resistant to conventional antibiotics (41).

The discovery and development of AMPs and other novel compounds offers new avenues for tackling resistant pathogens. AMPs are part of the innate immune system and exhibit broad-spectrum activity against bacteria, viruses, and fungi (42). Research into synthetic and natural AMPs is progressing, with several candidates showing promise in preclinical and clinical studies (43). Additionally, the exploration of novel chemical scaffolds and drug repurposing efforts are uncovering new antimicrobial agents that could circumvent existing resistance mechanisms (44).

The human microbiome plays a critical role in health and disease, including the development and spread of antibiotic resistance. New research is focusing on microbiome modulation as a strategy to combat resistance (45). Probiotics, prebiotics, and fecal microbiota transplantation (FMT) are being investigated for their potential to restore healthy microbial communities and outcompete resistant pathogens. Understanding the interactions between the microbiome and pathogenic bacteria can lead to innovative treatments that support the natural defenses of the human body.

Global surveillance systems and the use of big data are crucial for tracking the emergence and spread of resistance. Enhanced surveillance involves not only the monitoring of resistance patterns but also the collection of data on antibiotic use and outcomes (46). Integrating big data analytics and machine learning algorithms allows for the identification of trends, the prediction of resistance hotspots, and the development of targeted interventions (47). International collaborations and data-sharing initiatives are essential for a coordinated global response to antibiotic resistance.

CONCLUSIONS

In conclusion, antimicrobial resistance, exemplified by organisms such as *S. pneumoniae*, *H. influenzae*, and *M. pneumoniae*, underscores the complex challenges in treating bacterial infections. Each pathogen has developed specific mechanisms to evade antimicrobial action, necessitating vigilant monitoring, judicious use of antibiotics, and continuous research into novel therapeutic strategies. Addressing pathogen resistance is crucial for ensuring effective treatment and controlling the spread of resistant infections.

The landscape of antimicrobial resistance is continuously evolving, presenting new challenges and opportunities. Advances in genomics, innovative therapeutic approaches, and enhanced surveillance efforts are at the forefront of combating resistance. By leveraging these new aspects, the scientific and medical communities can develop more effective strategies to preserve the efficacy of existing antibiotics and discover new treatments, ultimately improving patient outcomes and public health. Addressing antimicrobial resistance requires a multifaceted approach, integrating cutting-edge research, clinical practice, and global cooperation.

Conflict of interest

The authors declare that they have no conflict of interest.

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TRICHINELLA SPIRALIS MUST INHIBIT THE IMMUNE SYSTEM TO SURVIVE

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ABSTRACT

Trichinella spiralis is a parasitic nematode that infects various mammals, including humans. This tissue-dwelling parasite plays its pathological role by affecting the immune system and causes the disease trichinellosis. T. spiralis generates a variety of proteins that protect it from the host's immune system and it releases inhibitory proteins such as proteases, antioxidant enzymes, and immunomodulatory molecules. T. spiralis modulates T-cell and macrophage responses, reducing the immunological response launched against it by the organism. By producing proteases, the parasite inhibits the infiltration of immune cells that would help fight the infection. These anti-immune effects help T. spiralis survive. In addition, this parasite helps the response shift from Th1 to Th2, an effect that is less effective in eliminating infections. Recently, it has been reported that antigens secreted by T. spiralis can interact with immune cells by binding to the toll-like receptor (TLR), reducing the inflammatory response. It can be concluded that T. spiralis affects the immune system to survive and carry out its pathological action, but it can also produce immunity-stimulating antigens, an effect that could be useful to fight certain autoimmune diseases that are currently incurable.

KEYWORDS: *Trichinella spiralis, helminth, parasite, nematode, immunity*

INTRODUCTION

Helminths are pathological parasites that act on the host's immune system by activating and modulating it. Trichinella spiralis is a parasitic nematode that infects various mammals, including humans, and causes trichinellosis (or trichinosis) when organisms consume raw meat containing its larvae.

T. spiralis includes many species such as T. native, T. nelsoni, T. britovi, T. murrelli, and the new species, T. chanchalensis (1), and is present in many low income and industrialized countries. Some species of T. spiralis, such as T. pseudospiralis, T. papuae, and T. zimbabwensis are not encapsulated (2). The biological cycle is immediate; eggs are released into the external environment and the larva develops. When the climatic conditions are mild, the parasite remains infectious for 5-8 years (3). To establish and maintain infection, it must evade and manipulate the host immune system (4).

T. spiralis is very effective at evading the immune system. Trichinellosis, the infection caused by this parasite, is a disease where there is immune stimulation due to antigen molecules of the parasite. The molecular mechanisms by which T. spiralis achieves this are diverse and sophisticated, involving both evasion and active suppression of immune responses.

The parasite can induce both pro-inflammatory and anti-inflammatory cytokines, which can have varying effects on the immune system (5,6). The acute phase of infection is associated with a strong pro-inflammatory Th1 response (7),

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while the chronic phase often involves a shift toward an anti-inflammatory Th2 response, characterized by the production of cytokines like IL-4, IL-10, and TGF-β (8).

It has been reported that T. spiralis might have a protective effect against certain autoimmune diseases (9). However, the relationship between T. spiralis and autoimmunity is complex and has multifaceted aspects.

DISCUSSION

T. Spiralis modulates host immune responses in different ways. The parasite secretes a variety of proteins that help it avoid detection and destruction by the host immune system (10). These proteins can interfere with antigen presentation and reduce the host's ability to mount an effective immune response (11). Furthermore, the parasite can directly suppress immune cell function. For example, T. spiralis can modulate the activity of T cells and macrophages to reduce their ability to attack the parasite (12,13).

When activated, T. spiralis releases excretory and secretory products such as protease inhibitors, antioxidant enzymes, immunomodulatory molecules, and other enzymes. Protease inhibitors are molecules that can inhibit host proteases, which are part of the host's immune defense mechanisms (14). By inhibiting these enzymes, T. spiralis can prevent tissue damage and immune cell infiltration that would otherwise help clear the infection (7).

The parasite also produces antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, which neutralize reactive oxygen species (ROS) produced by immune cells (15). This helps the parasite survive the oxidative burst that is part of the host's immune response.

T. spiralis can secrete immunomodulatory molecules that mimic host cytokines or interfere with cytokine signaling (12). This can skew the immune response towards a Th2 type response, which is less effective at clearing helminth infections compared to a Th1 type response (16). Excretory and secretory antigens are specific proteins secreted by T. spiralis that can directly interact with immune cells to alter their function. For example, some excretory/secretory antigens can bind to toll-like receptors (TLRs) on immune cells, altering their signaling pathways and reducing inflammatory responses (12,17).

T. spiralis infection can lead to the induction of regulatory T cells (Tregs), expanding these immune cells that suppress other immune responses. This helps create an environment that is more permissive for the parasite's survival. T. spiralis can also modify host tissues and affect cells they are in contact with (18). T. spiralis larvae form cysts within host muscle tissues, creating a physical barrier that protects them from immune cells (19). The cyst wall is also immunologically inert, meaning it does not provoke a strong immune response.

T. spiralis also modulates gene expression, affecting microRNAs (miRNAs) (20). This helminth can release miRNAs that are taken up by host cells, leading to changes in the host gene expression profile (21). This can downregulate genes involved in the immune response and create a more favorable environment for the parasite (21,22).

Specific molecules and pathways are affected by T. Spiralis. The T. spiralis serine protease TsSerp is involved in degrading host proteins and modulating immune responses by interfering with cytokine production and immune cell signaling pathways (24). T. spiralis excretory/secretory (Ts-ES) antigens include a variety of proteins and glycoproteins that interact with host immune cells (12). They can modulate dendritic cell function, inhibit T cell proliferation, and alter cytokine production (18, 23).

T. spiralis can induce the production of vascular endothelial growth factor (VEGF), which helps in creating a favorable environment for the larvae in the host muscle by promoting angiogenesis and tissue repair processes that may help in cyst formation and maintenance (25).

The antigenic molecules expressed by this parasite can activate innate immunity with consequent stimulation of adaptive immunity. The antigens act on antigen presenting cells (APCs) such as macrophages and dendritic cells which downregulate adaptive immune cells, such as Tregs and regulatory B cells, activating a sort of immunosuppression (18). This immunosuppression is induced by inhibitory cytokines such as IL-10, IL-17, and TGF-β, and this reaction is exerted by T. spiralis to avoid the immune response and allow its survival (12,26). This mechanism could be useful for suppressing the overstimulated immune system in chronic inflammatory diseases such as autoimmune diseases, transplant rejection, and allergic diseases such as asthma (27-29).

T. spiralis larvae can invade the intestine and activate epithelial cells with the secretion of cytokines IL-25 and IL-33 (also called alarmin). These cytokines activate type 2 innate lymphoid cells (ILC2), which in turn produce IL-5 and IL-13 cytokines that act on the precursors of epithelial cells to increase the production of immunosuppressive cytokines (30).

The type 2 immune response induced by the antigenic molecules causes the stimulation of IgE, IgG1, and IgG4 antibodies and anti-inflammatory cytokines including IL-4, IL-13, and IL-33 (31,32). These cytokines facilitate the proliferation of basophils, eosinophils, and macrophages, increasing allergic phenomena and mucus secretion, which are elements of the parasitic immune defense (16).

By implementing these strategies, T. spiralis escapes the host's immune system and survives. The infection causes an increase in eosinophilic granulocytes, which is a hallmark characteristic of parasitic infections that protects the parasite (33). Proteins derived from T. spiralis larvae are phagocytosed by macrophages, altering their ability to present antigen and activate T cells, a reaction which is mediated by STAT4 (6). The negative regulation of STAT4 and the cytokine IL-12 causes an inhibition of interferon-gamma (IFN-γ) that allows the T. spiralis to evade the immune response (34).

CONCLUSIONS

Understanding the biology and the mechanisms by which T. spiralis evades the immune response and affects host tissue is crucial for developing strategies to combat the infection and for designing new therapeutic approaches that can overcome the parasite's immune evasion tactics. In addition, immune system activation by helminths is currently being studied for its application in the treatment of diverse pathologies, including autoimmune diseases, that have a poor response to treatment.

Conflict of interest

The authors declare that they have no conflict of interest.

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APPROACHING HIV-ASSOCIATED DEMENTIA: SYMPTOMS, NEUROLOGICAL AND LABORATORY EXAMINATION, AND TREATMENT

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ABSTRACT

HIV-associated dementia (HAD) is a severe mental disease caused by HIV-1 infection that usually occurs in the the advanced stages of AIDS. HAD affects cognitive, motor, and behavioral functions, and the symptoms have a varying range of severity, which is assessed by the use of neurological examination, laboratory testing, and imaging studies. Some electroencephalographic anomalies are considered an early marker of the disease. Widespread cerebral atrophy is seen in approximately half of HAD cases and is often present in the advanced stages, although this is not indicative of the severity of cognitive deficits. Studies have also demonstrated neuropsychological abnormalitis, especially regarding memory and language, and testing is necessary in order to assess the cognitive impact of HAD. Treatment is focused on managing the HIV-1 infection and alleviating the symptoms of HAD.

KEYWORDS: *HIV, HIV-associated dementia, virus, treatment, laboratory examination*

INTRODUCTION

HIV-associated dementia (HAD), also known as AIDS Dementia Complex (ADC), is a severe neurological complication of HIV-1 infection (1). In most patients, HIV-1 infection is already known before the onset of dementia symptoms but HAD can sometimes appear before other signs or symptoms of the infection (2). In the latter case, the onset of the disease is usually insidious and one of the first signs, psychomotor slowing, can be attributed to depressed mood. The onset is usually more abrupt in the later stages of HIV-1 infection.

HAD typically occurs in advanced stages of AIDS and can significantly impact cognitive, motor, and behavioral functions (3). HAD symptoms can vary in severity and may progress over time. They are generally categorized into cognitive, motor, and behavioral symptoms (Table I).

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Table I. *Typical symptoms that present in HIV-associated dementia (HAD).*

Cognitive Symptoms:	Memory loss (especially short-term memory)
	Difficulty with attention and concentration
	Problems with problem-solving and executive functioning
	Impaired judgment and planning abilities
Motor Symptoms:	Poor coordination and balance
	Slowness of movements (bradykinesia)
	Tremors
	Weakness in limbs
	Gait disturbances
Behavioral Symptoms:	Apathy and lack of motivation
	Social withdrawal
	Irritability
	Depression or mood swings
	Psychosis (in severe cases)

HAD begins with apathy, psychomotor slowing, memory problems, and loss of interest in usual activities (4). Sometimes, however, the onset can be characterized by psychomotor agitation. Later, HAD is characterized by disturbances in recent memory, the slowing down of mental processes, and personality changes (5). Headache, gait disturbances, aphasia, hemiparesis, ocular disorders such as nystagmus and gaze paralysis, and, more rarely, compulsive seizures, may be present. As the infection progresses, there is further slowing of mental processes which can lead to a state of confusion, disorientation, hallucinations, stupor, and coma (5). Microcephaly and progressive psychomotor disorders may also be present in children (6). In the absence of therapy, the decline is rapid, and an average survival period of less than 6 months is generally reported.

DISCUSSION

Neurological examination, laboratory testing, and imaging studies utilizing computed tomography (CT), or magnetic resonance imaging (MRI) are all applied to assess the severity of HAD (7) (Table II).

Table II. *Neurological and Laboratory Examinations performed to assess the severity of HIV-associated dementia (HAD).*

Neurological Examination:	Detailed medical history and symptom assessment Assesses motor function, reflexes, coordination, and sensory perception
Laboratory Tests:	HIV viral load test: Measures the amount of HIV RNA in the blood CD4 count: Assesses the immune system's health Blood tests: Rule out other infections or metabolic conditions that could contribute to neurological symptoms
Imaging Studies:	MRI or CT scan: Can reveal brain atrophy, white matter changes, or other abnormalities associated with HAD

In the initial stages, the neurological examination is often within normal limits, although some difficulty in rapid eye movement and profound hyperreflexia may be noted. Subsequently, anisocoria, hypertonia, myoclonia, and tremor may appear (8). A scale of severity of the patient with HAD has been developed which ranges from normal stage 0 to terminal stage 4 (9) (Table III).

Table III. *Clinical staging of HIV-associated dementia (HAD).*

Normal Stage zero:	Mental and motor functions are within normal capacity.
Subclinical Stage 0.5:	Absent, minimal, or equivocal symptoms, without affecting daily activities or working life. Rapid eye movements may be present.
Mild Stage 1:	The patient can carry out all aspects of work and daily life, but with unequivocal disturbances of intellectual or motor functions and the patient can walk without assistance.
Moderate Stage 2:	The patient can perform essential self-care activities but is unable to work or perform most activities of daily living. When walking, there may be ambulation.
Severe Stage 3:	Severe intellectual involvement occurs. The patient is unable to hold complex conversations. There is severe motor impairment and the inability to walk without assistance.
End Stage 4:	The patient's life is vegetative with rudimentary intellectual and social activity, mutism, paraparesis or peraplagia, and urinary and fecal incontinence.

Cerebrospinal fluid (CSF)

The cerebrospinal fluid (CSF) does not present specific abnormalities, and a normal standard examination cannot exclude a diagnosis of dementia. An increase in total proteins has been highlighted in approximately 65% of cases and IgG in 38% to 80% of cases, while the presence of oligoclonal bands on CSF electrophoresis was found in 24% to 35% of cases examined. The number of cells in the fluid per mm^3 is usually within normal limits, but sometimes there may be a modest pleocytosis with a ratio between CD4+ and CD8+ that is similar to that in blood (10).

Several biological parameters have been found to increase during HAD. Among other things, there is an increase in some cytokines such as tumor necrosis factor (TNF), IL-1, IL-6, and GM-CSF (11). In addition, there is an increase in ferritin, beta-2-microglobulin, the beta-2-microglobulin ratio, liquor/serum microglobulin, neopterin, and quinolinic acid (12). In particular, beta-2-microglobulin, which comes from the first class major histocompatibility complex (MHC 1), is present in high concentrations in activated T lymphocytes, and can therefore be considered an index, like neopterin, of immune system activation (13). Quinolinic acid, a metabolite of tryptophan, may reflect macrophage activation within the central nervous system (14). Occasionally, an increase in CD3 TCR gamma/delta lymphocytes has also been found in both CSF and peripheral blood of patients with HAD (15).

Electroencephalogram

A generalized slowdown in cerebral electrical activity has been reported, with the appearance of theta (τ) or delta (δ) rhythms (16). However, approximately a third of patients have normal traces of these rhythms. The appearance of certain electroencephalographic anomalies has been considered an early marker of the disease.

Imaging examinations

In approximately half of cases, widespread cerebral atrophy is evident, especially in the more advanced stages of the disease (17). More rarely, focal or hydrocephalic lesions are found. It is hypothesized that there is no parallelism between the evolution of cerebral atrophy and the clinical picture of HAD. However, a correlation was found between the presence of lesions and white matter damage. Several parameters have been proposed for the evaluation of atrophy (18). One of these is the extension of the ventricular area of the third ventricle (19). In one study, the presence of supratentorial atrophy was found in 14 out of 19 patients with HAD through examination with CT or MRI. However, no correlation was noted between the degree of atrophy and the severity of the cognitive deficit. Very often, the CT examination was sufficient to establish the degree of atrophy. In addition, a significant correlation was highlighted between the presence of brain atrophy and average survival (20). After examination with CT or MRI, there is a normal survival in normal patients, while in patients with cerebral atrophy, survival was reduced by 50%.

Psychological tests

Some studies have demonstrated a higher frequency of neuropsychological test abnormalities in asymptomatic HIV-1-positive individuals compared to HIV-1-negative controls (21). It has been noted that in the disease state, the first deficits are in memory and language (22). Memory and language disorders seem less important in the initial stages of HAD than in Alzheimer's disease (AD) (23). However, in a multicenter study on asymptomatic seropositive patients, no

cognitive alterations were highlighted. Often, the neuropsychological abnormalities found in HIV-1-positive patients are due to alcohol or drug use and not to the effects of the virus (24).

Neuropsychological testing is crucial for assessing the cognitive impact of HAD. These tests evaluate various aspects of cognitive functioning (25) (Table IV). Commonly used tests include the Mini-Mental State Examination (MMSE), the Montreal Cognitive Assessment (MoCA), the Digit Span Test, the Trail Making Test (Parts A and B), and the Wisconsin Card Sorting Test.

Table IV. *Neuropsychological tests that are utilized to assess the cognitive impact of HIV-associated dementia (HAD).*

Memory Tests:	Assess both short-term and long-term memory capabilities.
Attention and Concentration Tests:	Evaluate the ability to focus and sustain attention.
Executive Functioning Tests:	Measure planning, problem-solving and organizational skills.
Language Tests:	Assess verbal fluency, comprehension, and language production.
Motor Skill Tests:	Evaluate coordination, speed, and precision of movements.

Diagnosis

Patients with HAD are frequently tested for HIV-1 positivity by ELISA and confirmed with Western blot analysis (26). In children, there may be false positives in the first 12 to 15 months of life due to the presence of maternally derived anti-HIV IgG (27). The polymerase chain reaction (PCR) technique can be helpful in indicating the presence of infection in the child (28). HAD can be diagnosed clinically in HIV-1 seropositive patients with progressive dementia when other causes of dementia have been excluded. At autopsy, there may be leukoencephalitis with modest astrocytosis and the presence of giant multinucleated cells (29).

Treatment

The primary goal of HAD treatment is to manage HIV-1 infection and alleviate symptoms (30).

Nucleoside analogous antiviral agents are frequently used for therapy and include zidovudine, didanosine, and dideoxycytidine (31). These drugs are useful in inhibiting the activity of reverse transcriptase and have demonstrated a notable increase in survival times, even in subjects with advanced HAD. Furthermore, in patients with HAD, the treatment also causes an improvement in the neuropsychological state.

In addition, treatment with nimodipine, a calcium channel blocker, may also have a positive effect by inhibiting viral proteins that cause neurotoxicity (32). Patients often present agitation, and in these cases, could be treated with modest doses of neuroleptics (33) (Table V).

Table V. *Treatment options for managing HIV-associated dementia (HAD) .*

Antiretroviral Therapy (ART):	Highly active antiretroviral therapy (HAART) is the cornerstone of treatment. Effective ART can reduce HIV-1 viral load, improve immune function, and slow or prevent the progression of HAD.
Symptomatic Treatments:	Psychostimulants (e.g., methylphenidate) for apathy and cognitive slowing Antidepressants for mood disorders Antipsychotics for severe behavioral disturbances Medications for motor symptoms, such as antispasmodics
Supportive Therapy:	Cognitive rehabilitation and occupational therapy to improve cognitive and motor functions Psychological counseling and support groups for emotional and social support Physical therapy to enhance motor skills and coordination

CONCLUSIONS

HAD is a serious neurological condition that requires comprehensive management, including antiretroviral therapy, symptomatic treatments, and supportive care. Early diagnosis and intervention are crucial to improving outcomes and quality of life for individuals affected by this condition and regular monitoring and follow-up are essential to address the evolving needs of patients with HAD.

Conflict of interest
The author declares that they have no conflict of interest.

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Letter to the Editor

ATOPIC DERMATITIS AND ALOPECIA AREATA ARE TWO AUTOIMMUNE DISEASES THAT NEED ATTENTION

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INTRODUCTION

Atopic dermatitis (AD) and alopecia areata (AA) are both conditions that can be associated with autoimmune responses. AD is a chronic inflammatory skin condition characterized by itchy, red, swollen patches of skin. It is often part of the "atopic triad", which includes asthma and allergic rhinitis. AA is an autoimmune condition that causes hair loss, typically in round patches on the scalp, though it can affect other hair-bearing areas of the body. It is considered to be a tissue-specific autoimmune disorder that is cell-mediated, and it can complicate AD. AA is classified as a type 1 inflammatory disease, while AD is considered to be a type 2 inflammatory disease.

AA can complicate AD, and infections can sometimes trigger autoimmune responses or exacerbate existing autoimmune conditions. For example, certain viral or bacterial infections might precipitate or worsen AA or AD. People with AD often have a compromised skin barrier, making them more susceptible to skin infections, which can further complicate the condition.

DISCUSSION

AD, or atopic eczema, is a dermatological disorder that normally begins in childhood and is characterized by chronic inflammation of the skin. The disease presents with eczematous lesions and itching, and affected subjects have a greater risk of developing allergies, asthma, and other immune and inflammatory disorders (1,2). In AD, the immune system is altered with an increased response to Th2 cells and allergens, with exaggerated production of IgE antibodies (3). The dermis is altered and presents less protection and inflammatory patches. Corticosteroid therapy is still the most used treatment option and in severe cases, immunosuppressive drugs are also used, even if these are not specific. A better knowledge of the pathogenesis of AD, and of autoimmunity in general, could help in the development of new therapies.

AA is a disease where the immune system mistakenly attacks hair follicles, causing hair loss. Understanding the pathogenic mechanisms of this disease can certainly be useful in developing new therapeutic strategies. In this disease, the immune system targets hair follicles during the growth phase, an effect mediated by cytotoxic T lymphocytes (4). Hair follicle-associated antigens are presented by antigen-presenting cells (APCs) to CTLs that damage the follicles (4). There is a genetic predisposition to AA that involves multiple genes. Genes such as CTLA4, PTPN22 and IL2/IL21 have been associated with an increased risk of AA (5). Research studies have shown that Janus kinase (JAK)-signal transducer

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and activator of transcription (STAT) pathway are important in AA (6,7). These biochemical reactions are activated by the cytokines interferon-gamma (IFN-γ) and IL-15 which induce the transcription of genes that lead to inflammation and activate immune responses against hair follicles.

In immune-mediated diseases, such as erythema multiforme (Stevens-Johnson syndrome), toxic necrosis of the epidermis with vasculitis may occur. It has been observed that autoimmune phenomena in certain mammals, such as dogs, can predominantly affect certain parts of the body, including the muzzle and trunk of the animal, causing hair loss and inflammatory patches. Both the front and rear legs of the animal can also be affected. In animals with AA, therapy not only includes pharmacological treatment, but also mechanical stimulation utilizing a small roller with needles which, when slid over skin lacking hair, can reactivate the hair bulb and restore the presence of hair.

Immunological dysfunction can trigger pemphigus foliaceus with both histological and clinical pathological characteristics. Pemphigus foliaceus can present with pustules, erosions, crusts, ulcers and scars. At the level of the primary lesions, there may be flaccid vesicles that are easy to break, and the histological tissue may also present with soprobasal acantholysis with cleft formation, and basal cells remaining at the base (row of tombstones). In dogs, penphigus vulgaris can be treated with prednisolone or dexamethasone at a dose of 3-4 mg/kg of body weight.

AD can also affect other domestic animals such as cats with lesions that are predominantly located on the face and ears. The mechanism of the disease involves vascular cutaneous erythematosus, cutaneous mucus and inflammation, a phenomenon in which toll-like receptor 7 (TLR-7) participates. In fact, in autoimmune diseases, it has been seen that there is an aggravation of plaque in psoriasis when TLR-7 is blocked (8). The pathogenesis involves strong genetic predisposition and exposure to UV light and can appear a few years after birth.

CONCLUSIONS

AA is a complex disorder involving the interaction of genetic predisposition, immune system dysregulation, inflammation, and biochemical pathways like the JAK-STAT pathway. AD is a disorder characterized by chronic inflammation of the skin where the immune system shows an increased response to Th2 cells and allergens, with exaggerated production of IgE antibodies. Studies on these conditions are needed to develop targeted and effective therapies.

Conflict of interest

The author declares that they have no conflict of interest.

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