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MESENCHYMAL STEM CELLS HAVE THE POTENTIAL TO MODULATE THE IMMUNE RESPONSE DURING INFECTIONS

Alvaro Avivar-Valderas*

Cell Therapy Sciences, Takeda, Madrid, Spain.

Correspondence to:
Dr. Alvaro Avivar-Valderas,
Cell Therapy Sciences, Takeda,
Tres Cantos, Marconi 1,
28760 Madrid, Spain.
e-mail: Alvaro.avivar@takeda.com

ABSTRACT

Mesenchymal stem cells (MSCs) can differentiate into various cell types and may play an important role in infections. Myeloid cells are a group of blood cells that derive from the myeloid lineage of hematopoietic stem cells, present in the bone marrow. These cells play a fundamental role in both the innate and adaptive immune systems. MSCs are a type of adult stem cell with immunomodulatory and regenerative properties. Their ability to influence the immune system makes them a potential therapeutic tool for many inflammatory diseases and their use in infections is still being developed. MSCs can induce macrophage polarization toward an M2 anti-inflammatory phenotype and can enhance macrophage phagocytic activity and modulate cytokine production by inhibiting pro-inflammatory cytokines such as TNF and IL-1β. Moreover, MSCs enhance antimicrobial activity, modulate the immune response against infections, and can secrete antimicrobial peptides that inhibit bacterial growth. MSCs are useful in sepsis processes where they modulate both inflammation and immune cell responses against infectious agents. They may provide new and promising applications for the treatment of various infectious diseases.

KEYWORDS: *Mesenchymal stem cell, immune response, infection, immunomodulation, inflammation*

INTRODUCTION

Mesenchymal stem cells (MSCs) can differentiate into various cell types and can be immunomodulatory (1). They interact with myeloid cells and may also play an important role in infections, a topic of considerable interest (2). Myeloid cells are important immune system elements which include dendritic cells (DCs), neutrophils, monocytes, and macrophages (3). MSCs influence myeloid cells through direct cell-to-cell contact and secretion of various soluble factors (4). MSCs can inhibit the maturation of DCs, resulting in a reduction in their ability to present antigens and stimulate T cells (5). These reactions are mediated by several important cytokines (5). MSCs can modulate DC secretion by inducing an anti-inflammatory state (5).

DISCUSSION

MSCs are multipotent cells useful in tissue regeneration and repair after a sepsis process (6). Their reparative effect in inflammatory processes is exerted partly by secreted exosomes which are extracellular vesicles with a diameter of about 50-150 nm (7). Exosomes can polarize macrophages to M1 (producing pro-inflammatory cytokines) or M2 (secreting anti-inflammatory molecules) (8). Therefore, MSCs can induce the polarization of macrophages towards an

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anti-inflammatory M2 phenotype which is involved in tissue repair and regeneration (9). These phenomena are mediated by cytokines such as IL-10 and TGF-β (10). In addition, MSCs can enhance the phagocytic activity of macrophages and modulate cytokine production, reducing pro-inflammatory cytokines such as TNF and IL-1β and increasing anti-inflammatory cytokines such as IL-10 and IL-37 (11). IL-37 is a new anti-inflammatory cytokine belonging to the IL-1 family that is known for its immunosuppressive and anti-inflammatory properties. IL-37 plays a crucial role in modulating immune responses during infections by suppressing pro-inflammatory cytokines such as IL-1β, IL-6, and TNF, and by reducing the severity of infection-induced inflammation. In addition, IL-37 inhibits the NF-κB and MAPK signaling pathways, thereby limiting immune hyperactivation. It also enhances regulatory T cell (Treg) function, inhibits excessive neutrophil infiltration, and is protective in sepsis by reducing tissue and organ damage. MSCs can enhance neutrophil survival by inhibiting apoptosis and modulating neutrophil functions, including chemotaxis and release of reactive oxygen species (ROS) (12).

MSCs enhance the antimicrobial activity of neutrophils against pathogenic microorganisms and monocytes can influence their differentiation into macrophages or DCs (13). In addition, MSCs are implicated in the migration of macrophages in inflammatory reactions (14). Therefore, MSCs can modulate the immune response during infections, regulating the immune reaction towards microorganisms and reducing tissue damage caused by an exaggerated inflammatory response (15).

In bacterial infections, MSCs can enhance infectious clearance by modulating macrophage activity and promoting phagocytosis (16). Recently, MSCs have been reported to secrete antimicrobial peptides, such as IL-37, which directly kill bacteria (17). In viral infections, MSCs act in a complex manner depending on the type of virus. In some cases, MSCs can enhance antiviral responses, while in others, they may promote inflammation that results in increased tissue damage (18). Moreover, MSCs can modulate the activity of various immune cells, including T cells and natural killer (NK) cells, which are critical for controlling viral infections.

In experimental models of sepsis, MSCs have shown promising results by showing a modulatory action in the inflammatory response, improving microbial clearance, and increasing survival in laboratory animals (19). The action of MSCs on infectious processes occurs in immune cells, which are reprogrammed to obtain a better response without worsening the inflammatory reaction.

The immunomodulation exerted by these cells occurs through different mechanisms: a) MSCs secrete various cytokines, chemokines, and growth factors such as IL-10, TGF-β, and PGE2, which influence the pathophysiology of immune cells; b) MSC-derived extracellular vesicles, including exosomes, carry bioactive molecules such as proteins, lipids, and miRNAs that can modulate the functions of immune cells; and c) they can act on cell-to-cell contact and therefore direct interactions between MSCs and immune cells through surface molecules including PD-L1 and ICAM-1, which are important for immunomodulatory effects (20).

ICAM-1 plays a significant role in the pathophysiology of sepsis. It is an adhesion molecule expressed on endothelial cells and immune cells which facilitates leukocyte adhesion and transmigration during inflammation. In sepsis, pro-inflammatory cytokines such as TNF and IL-1β increase ICAM-1 expression on endothelial cells, leading to excessive leukocyte recruitment and vascular inflammation. Increased ICAM-1 expression contributes to endothelial permeability, tissue edema, and organ dysfunction, all hallmarks of sepsis. Dysregulation of ICAM-1 has been linked to worsened outcomes in sepsis, including progression to septic shock and multiorgan failure.

MSCs can potentially be used in all infectious and inflammatory diseases, including autoimmune, bacterial, viral and fungal diseases that can affect various organs (21). In particular, in regard to infectious diseases, MSCs could be used when conventional treatments are insufficient or no longer effective. Another potential way of using MSCs is in tissue repair, promoting a regenerative environment through the modulation of immune cells and repairing tissues damaged by infectious and inflammatory processes (22).

CONCLUSIONS

MSCs are cells that may be useful in the processes of sepsis due to their capability of modulating both inflammation and immune cell responses against infectious agents. MSCs may play a crucial role in promoting the anti-inflammatory response and enhancing pathogen clearance. These cells can be considered new and promising applications for the treatment of various infectious and inflammatory diseases, especially in those cases where conventional therapies are not satisfactory.

Conflict of interest

The author declares that they have no conflict of interest.

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BACTERIAL EAR INFECTION MEDIATED BY NEUTROPHILIC GRANULOCYTES

Mario Felaco[1*], Paolo Felaco[2] and Lina Azzini[3]

[1] Department of Medicine and Science of Aging, University "G. D'Annunzio" of Chieti-Pescara, Pescara, Italy;
[2] Nephrology and Dialysis Department, Teramo Hospital, Teramo, Italy;
[3] Independent researcher, Via Grazioli n. 59, Trento, Italy.

**Correspondence to*:
Prof. Mario Felaco,
Department of Medicine and Science of Aging,
University "G. D'Annunzio",
66100 Chieti, Italy.
e-mail: mfelaco@unich.it

ABSTRACT

Microorganisms such as bacteria, viruses, and fungi can cause ear infections. Common bacterial ear infections trigger an immune response that begins with neutrophils arriving at the site of infection. Inflammation caused by microorganisms is mediated by immune cells. Neutrophils are recruited to the site of infection in response to signaling molecules such as cytokines and chemokines. They ingest bacteria, digest them, and release granules containing antimicrobial peptides that help eliminate the bacteria. Therefore, bacterial infections of the ear and, especially the middle ear, activate immune processes. Among the inflammatory mediators that are generated and released are cytokines and chemokines that are produced through protein synthesis. Reactive oxygen species (ROS) and products of arachidonic acid such as prostaglandins and leukotrienes also contribute to the inflammatory network. The immune system recognizes bacterial antigens through pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), located on immune cells in the inflamed ear. It can be concluded that middle ear infections cause inflammation through bacterial activation starting from neutrophils, followed by the involvement of other innate immune cells, and the activation of the adaptive immune system, including various types of T cells and B cells.

KEYWORDS: *Neutrophil, granulocyte, ear infection, otitis media, bacteria*

INTRODUCTION

Ear infections are common and can be caused by bacteria, viruses, or even fungi (1) (Table I). They are classified into three types: otitis externa, also known as "swimmer's ear," which is an infection that affects the outer ear canal; otitis media, which is an infection of the middle ear that is commonly seen in children; and otitis interna, also known as labyrinthitis, which affects the inner ear.

Table I. *Common causes of ear infections.*

Bacteria	*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*.
Viruses	Respiratory syncytial virus (RSV), influenza, and rhinoviruses.
Fungi (less common)	*Aspergillus* and *Candida* (particularly in individuals with compromised immunity or chronic conditions).

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Various factors can affect the immune response and risk of developing an ear infection. Young children are more susceptible to infections due to an immature immune system and anatomical differences (e.g., shorter Eustachian tubes) and certain vaccines, such as the pneumococcal conjugate vaccine, can reduce the incidence of bacterial ear infections. Additionally, chronic conditions, including allergies or immune deficiencies, can increase susceptibility and environmental factors, such as exposure to smoke, pollution, and allergens, can compromise ear health and immunity.

Bacterial ear infection activates an immune response that begins with neutrophils, leading to inflammation and damage to the auditory system (2) (Table II). Understanding the role of the immune system in preventing and combating these infections is crucial. Otitis media caused by bacterial infection is common and involves complex immunological and biochemical responses.

Table II. *The immune response following ear infection.*

Innate immune response	a) The first line of defense includes physical barriers (e.g., earwax, skin).
	b) Antimicrobial peptides present in earwax and mucosal surfaces.
	c) Immune cells such as neutrophils and macrophages respond quickly to infection.
Adaptive immune response	a) Humoral response (B cells produce antibodies that target specific pathogens).
	b) Cell-mediated response (T cells help in recognizing and eliminating infected cells).

Bacterial or viral infections can appear during a flu illness and cause otitis media, which includes acute otitis media, otitis media with effusion, and chronic suppurative otitis media (3,4). The involvement of neutrophilic granulocytes, inflammation, and cytokines plays a significant role in the body's defense mechanisms (5). In this regard, it is necessary to take a closer look at the dynamics of bacterial ear infections.

Neutrophil granulocytes, or simply neutrophils, are a type of white blood cell that are most abundant in the bloodstream (about 70%) and are among the first to respond to bacterial infections (6). In the case of a bacterial ear infection, neutrophils are rapidly recruited to the site of infection in response to signaling molecules such as cytokines and chemokines (7). Neutrophils are one of the first responders to infections. They migrate from the bloodstream into the infected tissue via diapedesis and engulf and digest bacteria through the process of phagocytosis. They release inflammatory granules containing antimicrobial peptides and enzymes that help destroy the bacteria (6).

DISCUSSION

Inflammation is a defensive immune reaction against pathogens that occurs in bacterial ear infections to improve the pathological tissue state (8). Inflammation is mediated by the release of chemical mediators from immune cells, including neutrophils. The most common mediators that enhance the inflammatory response include cytokines (such as TNF, IL-1, and IL-6), chemokines, prostaglandins, histamine, and reactive oxygen species (ROS) (9). Neutrophils produce ROS that are important for killing bacteria, but because they are inflammatory cells, they can also cause tissue damage (10).

Bacterial ear infection leads to the activation of biochemical processes, including the generation of arachidonic acid compounds with the production of inflammatory products such as prostaglandins and leukotrienes, and the activation of the complement system which enhances the antibody effect and helps with phagocytosis to eliminate bacteria and decaying cells (11).

Ear infections are often caused by bacteria, the most common being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa* (12). Bacterial antigens are recognized by the immune system through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) located on immune cells in the ear (13).

PRRs, including TLRs, which recognize pathogen-associated molecular patterns (PAMPs) on bacteria, trigger the immune response (14) (Table III). Activation of PRRs triggers intracellular biochemical signaling, leading to activation of NF-kB and the secretion of inflammatory cytokines and chemokines (15). Endothelial cells are also involved in these processes, regulating the adhesion molecules ICAM-1 and VCAM-1, which are implicated in neutrophil migration to the site of infection (16). The cytokines TNF, IL-1β, and IL-6, with the chemokine IL-8, are key mediators in the immune response to bacterial infections and are produced by activated immune cells (17,18). They play a crucial role in recruiting neutrophils and other immune cells to the site of infection. However, there are also non-inflammatory cytokines such as IL-10 and TGF-β that help regulate and resolve inflammation, preventing serious tissue damage (19).

Table III. *Physiopathology of bacterial ear infections.*

i. Entry of pathogens	Bacteria enter the ear, often through the Eustachian tube, leading to colonization and infection.
ii. Immune activation	Recognition of bacteria by pattern recognition receptors (PRRs) on epithelial cells and resident immune cells triggers the release of cytokines and chemokines.
iii. Neutrophil recruitment	Certain cytokines and chemokines (such as IL-8) attract neutrophils to the infection site.
iv. Inflammatory response	Neutrophils and other immune cells release inflammatory mediators, leading to tissue edema, pain, and other symptoms of inflammation.
v. Bacterial clearance	Neutrophils phagocytose bacteria and release antimicrobial substances.
vi. Resolution	Anti-inflammatory cytokines and other regulatory mechanisms resolve the inflammation, and tissue repair processes begin.

There are various methods of treatment for bacterial ear infections. Obviously, if it is a bacterial infection, appropriate antibiotics are used, while if the infections are viral, they are often not treated as they resolve on their own (20). Fungal infections can be treated with anti-fungal medications and a diet rich in vitamins and minerals in order to help the immune system (21).

CONCLUSIONS

Bacterial ear infections are mediated by neutrophilic granulocytes that arrive at the infection site and induce an inflammatory response. The cascade of inflammatory molecules is fueled by the activation of immune cells that release cytokines, chemokines, arachidonic acid products, ROS, and chemical mediators, including histamine. Bacterial treatment involves antibiotics that help resolve the infection and thus, the inflammation.

Conflict of interest

The authors declare that they have no conflict of interest.

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IMMUNOLOGICAL RESPONSE IN LEISHMANIASIS INFECTION

Ilias Frydas[1*], Isaia Symeonidou[1] and Rhiannon Ross[2]

[1] Laboratory of Parasitology and Parasitic Diseases, School of Veterinary Medicine, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece;
[2] School of Veterinary Medicine, University of Pennsylvania, Philadelphia, USA.

**Correspondence to*:
Ilias Frydas,
Laboratory of Parasitology and Parasitic Diseases,
School of Veterinary Medicine, Faculty of Health Sciences,
Aristotle University of Thessaloniki,
54124 Thessaloniki, Greece.
e-mail: ilias.frydas@gmail.com

ABSTRACT

Leishmania is an intracellular parasite that causes the disease leishmaniasis in animals and humans. About 30 species of the genus *Leishmania* can generally infect canids, horses, sheep, cats, rodents, birds and reptiles. Canine leishmaniasis, which is potentially fatal, is present in Europe, Africa, Asia, and America. *Leishmania* parasites complete their life cycle in vertebrate and invertebrate hosts. After infection, the pro-flagellated forms are phagocytised by phagocytic cells and pass to the ovoid flagellated form. The immune response to *Leishmania* infection can be innate or acquired, which defends the host. *L. infantum* infection in humans is mediated by natural killer (NK) cells, monocytes, neutrophils, and cytokines that exert anti-parasitic activity. In leishmaniasis, both Th1 and Th2 lymphocytes are stimulated. Protective immunity against the parasite derives from the development of the Th1 cell response where macrophages play a central role in controlling the infection by linking innate immunity with acquired immunity. Activation of antigen-presenting cells allows activation of T cells against the parasite. Anti-*leishmania* activity can be carried out by tumor necrosis factor (TNF), IL-6, and by costimulatory cells B7-1 (CD80) and B7-2 (CD86).

KEYWORDS: *Leishmania, leishmaniasis, infection, immunity, parasite*

INTRODUCTION

Leishmania is a protozoa belonging to the Trypanosomatidae family (1). It is an intracellular parasite which causes the disease leishmaniasis in animals and humans. The approximately 30 species of the genus *Leishmania* can infect humans, dogs, wild species of the canidae family (e.g. foxes, jackals), horses, sheep, cats, various species of rodents, birds, and reptiles (2-4) and are found in almost country around the world (5). Canine leishmaniasis is caused by the species *Leishmania infantum* or the genetically identical species *L. chagasi* (6) and is a potentially fatal enzootic disease in regions of Europe, Africa, Asia, and America (7).

Leishmania parasites are biphasic protozoa that alternate between proflagellate and α-flagellate forms and complete their life cycle in vertebrate and invertebrate hosts (8,9). Female midges of the genus *Phlebotomus sp.* are mentioned as intermediate hosts in Europe, Asia, and Africa and genus *Lutzomyia sp.* are intermediate hosts in America (5,8).

The ovoid flagellar forms (2-5 μm x 1.5-2 μm) are characterized by the presence of rodlike kinetoplasts, DNA-rich mitochondrion, and parasitize the macrophage cells of the skin, mucous membranes, and viscera of the definitive hosts (10). Flagellar forms are consumed by flies during blood sucking and are released into the posterior part of the mesentery where they are transformed into motile proflagellar forms and multiply rapidly by binary fission, attaching to several sites

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of the insect's mesentery wall via lipophosphoglycans (11). They then transform into infective metacyclic proflagellate forms, which migrate to the esophageal valve of the thoracic mesentery, pharynx, and mouthparts of the fly. The parasite is transmitted to vertebrate hosts during sandfly molt, primarily by reduction from the thoracic mesenchyme to the host's skin. After inoculation into the skin of the definitive host, the proflagellate forms are phagocytosed by antigen-presenting Langerhans cells (in the epidermis), dendritic cells (in the dermis) and macrophage cells, where they transition to the ovoid flagellate form (12-14). In turn, the female phlebotomes become infected when they consume female blood from infected dogs, and they acquire the astigmatism forms. In Greece, 12 species of sandflies have been described, showing intense activity from the beginning of May to the end of November (13).

DISCUSSION

In Greece, Portugal and the other Mediterranean countries, where the species *L. infantum*, *L. tropica* and *L. major* have been isolated, leishmaniasis has an enzootic character (15,16). In seroepizootic studies carried out in Italy, Spain, France, and Portugal, the number of infected dogs is estimated to be around 2.5 million (17,18).

Estimating the number of infected dogs presents problems due to the existence of asymptomatic carriers, the long incubation period of the disease (which can reach up to 7 years), and the inability of serological tests to detect infected but non-seropositive animals (18-20). Today, however, with the widespread use of molecular methods to detect the genetic material of the protozoan, it appears that the frequency of infection is much higher than the frequency of the symptomatic form of the disease (18).

The recent increase in the occurrence of cases in non-enzootic areas such as the Netherlands, Germany, and the United Kingdom is mainly attributed to the infection of dogs during their stay in enzootic areas as well as the importation of dogs from enzootic areas in Southern Europe, while the existence of autochthonous foci of L. infantum in Northern and Central Europe cannot be ruled out (21,22).

With regard to public health, it is now widely accepted that dogs are the main reservoir of *Leishmania* in nature and are directly involved in the epidemiology of some forms of human leishmaniasis in various regions of the world (5,7,20). The presence of infected dogs in populated areas is clearly related to the transmission of the disease to humans. However, ownership of an infected dog does not seem to significantly increase the probability of infection of owners in areas where the disease is endemic (20).

Immune responses

Clinical observations argue for the importance of the host immune response in control of leishmaniasis. The immune response is divided into innate and acquired immunity.

The innate immune response to *L. infantum* infection is mediated by natural killer (NK) cells and cytokines, and phagocytosis is mediated by monocytes and neutrophil polymorphonuclears. Blood phagocytes (monocytes and granulocytes) and tissue macrophages exert antiparasitic activity (26).

In addition to natural immunity, acquired immunity also participates in *L. infantum* infections in dogs. Cellular immunity plays a decisive role in the development of infection. The onset of leishmaniasis symptoms is associated with suppression of cellular immunity and humoral stimulation with the production of antibodies (27).

In protozoan diseases, the immune response depends on both the parasite itself and the host (23). Protozoan parasites develop survival mechanisms and ways to escape the host's immune response. The host, depending on the immune response it develops and its immune capacity, may be susceptible or resistant to infection (24,25).

Cellular immune response

Leishmania parasites stimulate both Th1 and Th2 lymphocytes in infection of dogs (7). Previous studies in experimental models have shown that symptoms, and their degree of intensity, depend on the type of immune response and, specifically, on the selective activation of the Th1 or Th2 responses (28). Today, it is widely accepted that protective immunity against the parasite results from the development of a strong Th1 cell response. Conversely, disease may occur if the Th2 cell response predominates (7).

Macrophages play a central role in controlling infection by linking innate and acquired immunity (29). In addition to their phagocytic capacity, macrophages can also process and present parasite antigens with simultaneous expression of costimulatory molecules, such as B7-1 (CD80) and B7-2 (CD86) (30). Their antigen-presenting abilities and concomitant secretion of cytokines, such as IL-1, tumor necrosis factor (TNF), IL-12, and IL-6, enable the activation of specific CD4+ and CD8+ T lymphocytes (29).

In addition to the activation of T lymphocytes, the above cytokines act protectively by stimulating the anti-*leishmania* activity of macrophages, primarily through the production of oxygen free radicals and nitric oxide (NO) (18).

NO is produced by activated macrophages and is mostly responsible for the intracellular death of flagellar forms of *Leishmania* through apoptosis (31). The production of NO and its anti-*leishmania* activity was confirmed after a series of *in vitro* studies, where macrophage cell lines from infected dogs were incubated with cytokines, including IL-2, TNF, and interferon-gamma (IFN-γ) (32). Similar findings were also found in a study where macrophage cell lines from healthy dogs were incubated with recombinant human IFN-γ after infection with proflagellate forms of the parasite (33).

The production of NO is catalyzed by the enzyme iNOS, whose activity is regulated at the level of transcription (34). Activation of appropriate transcription factors is regulated by the ERK1/2, p38, and JNK kinases message transduction pathways. Transcription factors, such as NF-κB, move to the cell nucleus after activation, where they bind to the promoters of various genes, regulating the expression of pro-inflammatory cytokines (e.g., TNF) and enzymes (e.g., iNOS) (35).

The T lymphocyte response to intracellular antigens consists of a series of sequential phases that begin with recognition of the antigen by naïve lymphocytes, activation and expansion of antigen-specific clones by proliferation, and differentiation of some of the progeny cells of these in reactive and memory cells (29). Differentiation of CD4+ T cells into Th1 or Th2 cells is a determinant of host resistance or susceptibility to parasite infection (Fig.1). However, to date, the exact molecular mechanisms that trigger the Th1 or Th2 immune responses have not been elucidated (36). Two hypotheses have emerged from *in vivo* human studies to interpret host resistance or susceptibility to *L. infantum* infection (26).

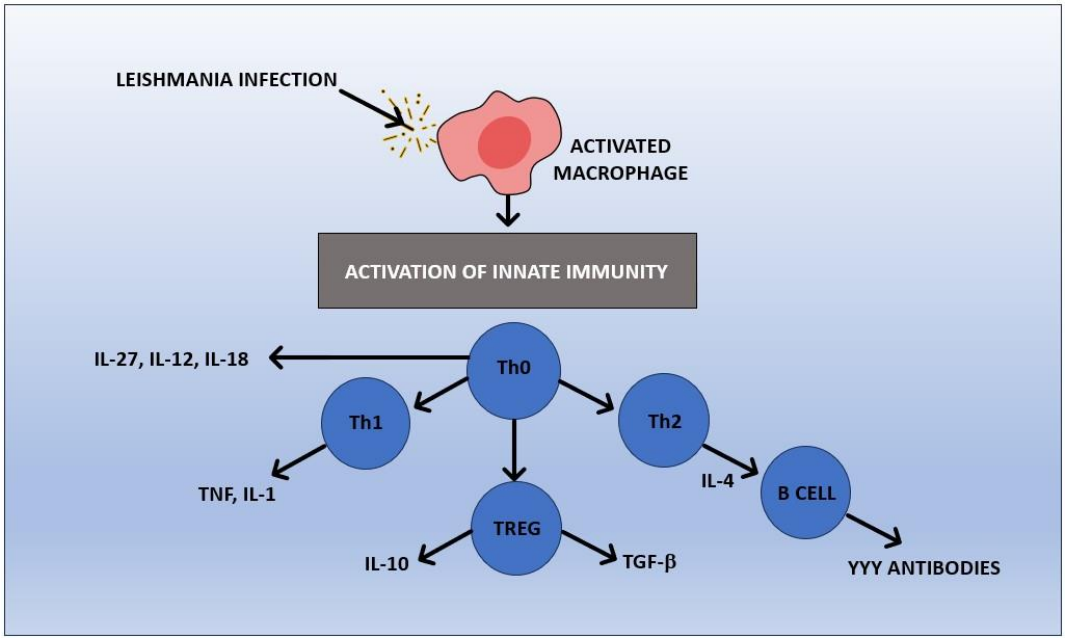

Fig. 1. *Schematic illustration of the cellular immune response in Leishmaniasis, showing the differentiation of Th0 to Th1 or Th2 cells and the corresponding cellular immune responses that are induced. Once Leishmania enters an organism, it induces the activation of macrophages. Th0 (T helper zero) cells are activated, followed by the release of the cytokines IL-27, IL-12, and IL-18. Th0 cells can mature into Th1 cells (with the production of inflammatory cytokines TNF and IL-1), Th2 cells (with the generation of IL-4 that helps B cells to produce antibodies), or Treg cells (with the production of anti-inflammatory cytokines IL-10 and TGF-beta).*

The first hypothesis focuses on CD4+ T lymphocytes during the first days after infection. Analysis of cytokine production by CD4+ T lymphocytes showed a dramatic burst of IL-4 production, which on the fourth day after infection, gradually decreased in resistant patients, while remaining at high levels in susceptible patients. The above findings indicate that susceptible patients produce an excess of IL-4 and are highly sensitive to its action (26).

The second hypothesis focuses on the action of NK cells. In resistant patients, a strong NK cell response is observed after infection. Activated NK cells produce IFN-γ, which leads to a Th1 cell response resulting in host resistance. Infection with the parasite of BALB/c mice, which have a primary reduced number of NK cells, results in the manifestation of the disease with a clear predominance of the Th2 humoral immune response (26).

In 30-50% of dogs living in the enzootic areas of the disease, it has been established that their basic immune response is of the cellular type, which is also indicated by a positive intradermal reaction to an acquired protein of the parasite (37).

This delayed-type hypersensitivity (DTH) reaction is observed in disease-resistant dogs exposed to the parasite, while it is absent in those presenting with severe clinical presentation (20).

The ability to maintain an effective anti-*leishmania* acquired cellular immune response entails arresting parasitemia and parasite multiplication in target organs (38). The phenomenon is observed in resistant dogs, where infection with *L. infantum* remains asymptomatic or manifests with mild and self-limiting symptoms, while these responses decrease as the disease progresses in susceptible dogs (39). Blood parasite load and the acquired cellular immune response were shown to be inversely related during a long-term study of experimentally infected dogs (38).

The cellular basis and developmental mechanisms of T cell irresponsiveness in canine leishmaniasis are not fully understood. The non-response of cellular immunity in advanced stages of the disease may be due to:

(a) the reduced expression of co-stimulatory molecules by infected macrophages;

(b) the reduction of the number of peripheral CD4+ T lymphocytes (as recorded by flow cytometry studies); and

(c) the reduced production or clearance of IL-2 and IFN-γ by peripheral blood monocytes *in vitro* (27).

In vulnerable dogs, Th2 lymphocytes are activated and, through the release of interleukins IL-4, IL-5, IL-10 and IL-13, favor the uncontrolled proliferation of the parasite and the stimulation of humoral immunity (40) (Fig.1). IL-2, IL-4, IL-5, and IL-13 induce the proliferation of B lymphocytes and promote the production of IgG1, IgG4, IgE, and IgA (18).

Finally, the cytokines of the Th2 response act antagonistically with IFN-γ and suppress the activities of Th1 lymphocytes, NK cells, and monocytes/macrophages. It should be noted that the activation of the above mechanisms has been verified in mice and humans (41), while in symptomatic dogs, it is indirectly inferred from the reduced production of IFN-γ and TNF and the number of CD4+ and/or CD8+ lymphocytes (42).

CD8+ cytotoxic T lymphocytes have been shown to be involved in dog resistance to leishmaniasis, although studies regarding this cell population remain limited (43). Activated macrophages promote the activation of CD8+ T lymphocytes and IL-2 produced by Th1 cells, which act as autocrine growth factors and, together with IFN-γ, activate the proliferation and differentiation of cytotoxic CD8+ T lymphocytes (27).

CD8+ T lymphocytes have been detected in experimentally infected asymptomatic dogs (but not in symptomatic ones), suggesting that they represent an additional effective resistance mechanism (44). The participation of these lymphocytes in leishmaniosis is also indicated by the fact that in dogs naturally infected with *L. infantum*, a reduction of the specific cell population is observed as the infection progresses, while its restoration takes place after the administration of treatment (45).

Other studies attributed an additional role to CD8+ T lymphocytes, noting that they are able to stimulate an adequate Th1 response with production of IFN-γ and TNF and the ability to activate infected macrophages (27,46). Today, elevated levels of CD8+ T lymphocytes are the main phenotypic feature of the asymptomatic form of the disease (43,44).

In addition to the differences in the absolute numbers of lymphocytes, differences in their activation levels were also recorded. High levels of circulating activated leukocytes were observed in asymptomatic dogs, as evidenced by high expression of major histocompatibility complex (MHC) class II molecules, CD45RB and CD45RA. In contrast, symptomatic dogs showed reduced expression of MHC class II molecules, reduced antigen-presenting capacity, and reduced numbers of antigen-presenting B lymphocytes (43).

Subclinical infection is not necessarily permanent and, in cases of a compromised immune system due to immunosuppression or coinfections, it may progress to clinical infection (47). The humoral immune response is not protective and indicates failure to control the infection (7,27,38,41).

CONCLUSIONS

Leishmaniasis is a disease caused by the *Lieshmania* parasite that is transmitted by animals such as canids. *Leishmania* infection triggers an immune response that can be innate or acquired. *L. infantum* infection in humans is mediated primarily by innate immune cells such as NK cells, monocytes, and neutrophils. These cells react against the parasite to protect the body from *Leishmania* infection.

Conflict of interest

The authors declare that they have no conflict of interest.

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Letter to the Editor

THE COMPLEX RELATIONSHIP BETWEEN FGF2 AND SEPSIS

Irene Tsilioni*

Laboratory of Molecular Immunopharmacology and Drug Discovery, Department of Immunology, Tufts University School of Medicine, Boston, United States.

**Correspondence to*:
Irene Tsilioni,
Laboratory of Molecular Immunopharmacology and Drug Discovery,
Department of Immunology,
Tufts University School of Medicine,
Boston, United States.
e-mail: irene.tsilioni@tufts.edu

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INTRODUCTION

Sepsis is a life-threatening condition caused by the body's response to infection, which leads to systemic inflammation, tissue damage, and organ failure (1). Fibroblast Growth Factor 2 (FGF2), also known as basic fibroblast growth factor (bFGF) and FGF-β, is an essential growth factor cytokine involved in many biological activities such as angiogenesis, wound healing, cell growth, and differentiation. Additionally, it plays a key role in tissue regeneration and repair (2).

FGF-2 is important in the laboratory for differentiation of many hematopoietic stem cells *in vitro*. The protein degrades rapidly in culture with an effective half-life of less than 10 hours. FGF signals through multiple specific receptors and appears to show limited species specificity. This protein is so routinely used that concentration and source are usually not carefully considered. There are several FGF2s (about 16) that are used for the culture of human and mouse stem cells and for the nascent industry of cultured meat, fish, fats, and dairy products.

DISCUSSION

FGF2 plays a key role in the maintenance, proliferation, and differentiation of various stem cell types (3). The role of FGF2 in sepsis is complex but interesting and is still being studied by scientists around the world. It is not yet clear how FGF2 can influence some pathophysiological parameters in infections.

FGF2 could intervene in helping the formation of new vessels in sepsis, where there is vascular dysfunction with tissue hypoxia. In addition, FGF2 can potentially promote the formation of new blood vessels and thus play a role in cancer and metastasis. The action of FGF2 on angiogenesis could also affect the inflammatory response. In fact, this growth factor influences different cells of the immune system, including macrophages and neutrophils, by modulating the inflammatory response. This effect depends on various factors, including the concentration, timing of administration, and tissue reaction. In infectious states, including septic shock, FGF2 plays a protective role in organs, including the kidneys and heart, by inhibiting apoptosis and promoting cell survival.

Recombinant human FGF2 is a 17 KDa protein comprised of 145 amino acids. It is recommended primarily for the proliferation, maintenance, and differentiation of induced pluripotent stem cells, embryonic stem cells, and mesenchymal stem cells (4). Recombinant FGF2 is highly bioactive and is used to support the maintenance of human embryonic stem cells and proliferation and differentiation of induced pluripotent and mesenchymal stem cells. It is highly pure, with a core structured region and N-terminal extension, and is free of carrier proteins.

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The effects of FGF2 on inflammation, tissue repair, and angiogenesis nominate it as a potential therapeutic molecule in sepsis. However, besides being beneficial, FGF2 is also a pro-inflammatory factor, and therefore, its use should be considered with caution (5). Treatment of sepsis with FGF2 in animal models has shown that this protein acts on tissue protection and repair, reducing organ damage and increasing survival of the rodent. In contrast, other evidence indicates that FGF2 can worsen the state of sepsis and lung fibrosis by fueling inflammation.

CONCLUSIONS

FGF2 is a growth factor implicated in angiogenesis, tissue repair, and cellular protection. These effects suggest that this molecule has therapeutic potential in sepsis. However, since FGF2 is also pro-inflammatory, its therapeutic use requires careful consideration of timing, dosage, and the specific context of its use to avoid potential adverse effects on the organism. However, further studies are needed to fully elucidate the role of FGF2 in sepsis and in other physiopathological states.

Conflict of interest

The author declares that they have no conflict of interest.

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RESPIRATORY SYNCYTIAL VIRUS

Shadrokh Nabili[1] and Livio Giuliani[2*]

[1] Department of Ophthalmology, University Hospitals Of Morecambe Bay NHS Foundation Trust, United Kingdom;
[2] European Cancer and Environmental Institute (ECERI), Bruxelles, Belgium.

Correspondence to:
Livio Giuliani, PhD,
European Cancer and Environmental Institute (ECERI),
Bruxelles, Belgium.
e-mail: giuliani.livio@gmail.com

ABSTRACT

Respiratory syncytial virus (RSV) is a common and highly contagious virus that primarily affects the respiratory system, particularly in young children, older adults, and individuals with weakened immune systems. RSV causes lung and airway damage, resulting in the common respiratory disease. The virus enters the airways and creates epithelial inflammation with edema of the submucosa and adventitia. The infection involves the pulmonary alveoli and can cause epithelial necrosis and inflammation due to the accumulation of immune cells. RSV is known to induce alterations in the innate and adaptive immune system response. It activates the NF-κB pathway which leads to the transcription of pro-inflammatory cytokines. Infection triggers the innate immune response to the virus, involving pattern recognition receptors (PRRs) and Toll-like receptors (TLRs), particularly TLR3 and 4 that recognize RSV RNA. These receptors trigger signaling pathways that lead to the production of inflammatory cytokines, such as type I interferons (IFNs), IL-6, TNF, and IL-1β. Prophylaxis for RSV is performed either with monoclonal antibodies or with the recently developed vaccine.

KEYWORDS: *Respiratory syncytial virus, respiratory disease, inflammation, immune response, virus, infection*

INTRODUCTION

Respiratory syncytial virus (RSV) is a virus that primarily causes respiratory tract infections, especially in infants, young children, the elderly, and immunocompromised individuals (1). It is a major cause of hospitalization in infants. It usually causes mild cold-like symptoms but can also cause serious respiratory illnesses such as bronchiolitis and/or pneumonia (2). RSV is an RNA virus belonging to the Paramyxoviridae family that is divided into types A and B based on the antigenic differences of the membrane glycoproteins F and G, which are responsible for the adhesion and penetration of the microorganism into the membrane of the host cell (3).

Once it has penetrated the subject's airways, the virus localizes at the level of the smaller branches. Edema of the submucosa and adventitia appears simultaneously with epithelial inflammation (4). This results in obstruction of the small airways, with the appearance of areas of atelectasis, hyperinflation, and often, small areas of consolidation. RSV is a contagious virus and a common cause of respiratory disease worldwide (5). The virus can affect the lungs and airways of an infected individual, potentially causing severe disease or death (6).

The infection can cause necrosis of the epithelium followed by a process of regeneration of cells that accumulate inside the small lumen with inflammatory cells (7). This situation causes a substantial alteration of the normal gas exchange at the pulmonary level with consequent hypoxemia, associated with hypercapnia in the most severe forms (8). Alveoli are generally normal, except those immediately adjacent to the bronchioles. Extensive involvement of the alveoli may occur, with increased cellularity and formation of alveolar sweat.

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Specific anti-RSV antibodies play an important role in the pathogenesis of the disease (9). In this regard, it has been shown that the presence of specific IgE for RSV in nasopharyngeal secretions of individuals affected by bronchiolitis correlates with the severity of the disease and with possible development of respiratory sequelae.

Numerous studies demonstrate that there is an association between RSV bronchiolitis, recurrent wheezing, and asthma (10). Several analyses show that the highest frequency of asthma occurs when both a family history of atopy and RSV bronchiolitis are present as risk factors, although some cases have been described without a history of atopy (11). One of the most accredited hypotheses to describe this relationship considers the possibility that RSV can induce alterations in the response modalities of the innate immune system (12).

DISCUSSION

RSV infection activates both innate and adaptive immune responses (13). In the innate immune response to the virus, pattern recognition receptors (PRRs) are activated. Infection by RSV involves PRRs and Toll-like receptors (TLRs), particularly TLR3 and 4 that recognize RSV RNA (14). This recognition triggers signaling pathways that lead to the production of type I interferons (IFNs) and pro-inflammatory cytokines such as IL-6, TNF, and IL-1β (15).

Once RSV has penetrated the lung, the virus can directly or indirectly damage the bronchial epithelium by downregulating the p53 gene responsible for cellular apoptosis (16). The resulting viral replication stimulates the expression of genes that regulate the cascade of pro-inflammatory chemokines such as CCL5, CCL2, CCL3, CXCL8, CXCL6, and CXCL10, and cytokines IL-1, 6, 11, GM-CSF, and TNF (17). In this way, the virus predisposes both children and adults to the onset of chronic respiratory disease.

Macrophages, dendritic cells (DCs), natural killer (NK) cells, and neutrophils also play a key role (18). Macrophages are activated when the RSV F protein binds to their wall through TLR-3 and -4 (18). Once recruited into the lungs, they activate the transcription factor NF-kB with the consequent production of pro-inflammatory cytokines, such as TNF, and the chemokines CXCL6 and CXCL12 (19).

Plasmacytoid DCs, a subset of DCs found in the blood and peripheral lymphatic tissue, produce IFN-α and β which are pro-inflammatory cytokines that inhibit viral replication (20). By way of its NS1 and NS2 proteins, RSV is able to inhibit the production of IFN-α and β persisting within the bronchial tree in its active form (21).

NK cells contain a serine protease called granzyme B that triggers the classic pathway of programmed cell death. In subjects affected by RSV bronchiolitis, NK cells cause a reduced expression of this enzyme, which triggers constant viral replication (22).

During RSV infection, 75% of recruited cells are neutrophils (23). Their role in the pathogenesis of the disease is clear; these cells produce large amounts of cytokines and have a long survival rate due to delayed apoptosis and are also the main cells involved in long-term exacerbations. The surfactant proteins SP-A, -B, and -D produced by the alveoli and airway epithelial cells also play a pathogenetic role (24). They bind the F and G proteins of the virus and help prevent RSV infection by promoting its clearance. Affected subjects show low levels of SP-A, -B, and -D, which results in prolonged persistence of the virus in the airways and poor viral clearance.

DCs and macrophages are also important in engulfing and processing the virus. These innate immune reactions induce the production of cytokines and present viral antigens to activate adaptive immune cells. NK cells recognize virus-infected cells, causing cell lysis and secreting antiviral cytokines such as IFN-γ to limit viral replication (25). Humoral or adaptive immunity involves B cells and plasma cells which produce neutralizing antibodies to the RSV fusion protein (F) and glycoprotein (G). Antibody neutralization prevents the virus from entering host cells, although this immune effect tends to wear off and lead to reinfection of the host. CD8+ cytotoxic T lymphocytes (CTLs) kill infected cells; while CD4+ helper T cells support both CTLs and B cell functions (26). However, T cell dysfunction can lead to increased inflammation.

RSV causes infection and activates inflammatory mechanisms that help control the infection, but excessive inflammation can lead to tissue damage and exacerbation of respiratory symptoms (10.1007/s12016-013-8368-9). The excess production of inflammatory cytokines, including IL-1, IL-6, IL-8, and TNF, can cause a 'cytokine storm' characterized by the excessive release of immune mediators (27). TNF and IL-1β contribute to vascular permeability, which leads to fluid accumulation in the lungs and worsens inflammation. The IL-1 and TLR families share similar functions and are associated with innate immunity.

It has been reported that over 95% of organisms use the innate immune system for survival (28). IL-1 triggers inflammation through IL-1 receptors, while TLRs induce inflammation through microorganisms. IL-6 is involved in fever induction and acute phase responses, while IL-8 is an attractive chemokine that primarily recruits neutrophils to the site of inflammation. Reactive oxygen species (ROS) are produced by infected immune cells and are a defense mechanism

due to their capability to kill RSV, but they also cause oxidative stress and tissue damage (29). ROS can damage the lung epithelium causing leaks and altered permeability, which are serious symptoms.

The RSV F protein is involved in the entry of the virus into the host cell. The role of the F protein is to fuse the virus to the target cell, and it is the main target for neutralizing antibodies. In addition to mediating the attachment of the virus to the cell, the G protein modulates immune responses (30). This protein acts similarly to chemokines and can bind to host immune receptors, such as CX3CR1, inhibiting immune responses and promoting immune evasion (31). This allows the virus to carry out its pathogenic action and cause persistent inflammation.

RSV encodes the NS1 and NS2 proteins, which antagonize the response to IFN. They block the signaling pathways that induce the production of antiviral IFN, weakening the host's ability to control viral replication. RSV infection recruits large numbers of granulocytes to the lungs. These immune cells release proteolytic enzymes, ROS, and inflammatory mediators, which can cause tissue injury and worsen airway inflammation, a hallmark of severe RSV disease (32).

RSV activates the NF-κB pathway, which leads to the transcription of pro-inflammatory cytokines. NF-κB activation is a major contributor to lung inflammation and exacerbation of respiratory symptoms in RSV infections (33). The JAK-STAT pathway is involved in mediating IFN signaling. RSV uses its NS proteins to interfere with JAK-STAT signaling, reducing host antiviral defenses and contributing to immune dysregulation (34).

When RSV infection is severe, a pathological immune response occurs that is harmful to the body. If the severe immune reaction involves adaptive immunity with Th2 lymphocytes, there may be excess production of some cytokines such as IL-4, IL-5, and IL-13, with airway inflammation and mucus production. In addition, excessive infiltration of immune cells, such as granulocytes, can cause bronchial blockage and alter respiratory function (10.1128/JVI.73.10.8485-8495.1999).

Prophylaxis

Prophylaxis is necessary to avoid or prevent the spread of RSV. It is the passive protection of the lower respiratory tract (36). Currently, the main form of prophylaxis, which aims to prevent or reduce RSV infection, is with the use of monoclonal antibodies such as palivizumab (synagis) and nirsevimab (beyfortus) (37). The monoclonal antibody palivizumab is given to high-risk infants, such as premature infants, and those with chronic lung disease or congenital heart disease (38). Nirsevimab is a newer generation monoclonal antibody approved by the FDA in July 2023, that provides broader and longer-lasting protection than palivizumab and is aimed at preventing severe RSV disease in infants and children (37). Active immunization with a recombinant bivalent vaccine is now available in Europe and the United States to protect infants and the elderly, but also adults at risk.

CONCLUSIONS

RSV infection triggers an immune response that can lead to a pathological state mediated by inflammation. RSV infection causes a complex immune response involving both protective and pathological mechanisms. While innate and adaptive immune responses are critical for viral clearance, they can also drive inflammation, causing lung damage and worsening respiratory conditions. Understanding the biochemical mechanisms of immunity and inflammation at play in RSV infection can guide vaccine development and targeted therapies that won’t trigger excessive inflammation.

Conflict of interest

The authors declare that they have no conflict of interest.

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THE CLINICAL AND IMAGING ASPECTS OF LUNG INFECTIONS CAUSED BY PATHOGENIC MICROORGANISMS

Giuseppe Pio Anastasi[1*] and Klara Trawny[2]

[1] Department of Biomedical, Dental Sciences and Morphological and Functional Imaging, University of Messina, Messina, Italy;
[2] Ruhr-Universitat, Bochum, Germany.

**Correspondence to*:
Prof. Giuseppe Pio Anastasi,
Department of Biomedical, Dental Sciences and Morphological and Functional Imaging,
University of Messina,
Messina, Italy.
e-mail: anapuc@unime.it

ABSTRACT

Pathogenic microorganisms can enter the respiratory tract and cause infection in the lungs. Microorganisms can be divided into viruses, bacteria, and mycoplasmas, which can all cause pneumonia. Mycoplasma, a bacterium that does not have a cell wall, can also cause an atypical pneumonia that may present with mild symptoms. Viral lung infections affect the lung alveoli and are very common in childhood. Diverse viruses are involved in this pathology and the most common are adenoviruses, enteroviruses, influenza viruses, parainfluenza viruses, syncytial viruses, cytomegaloviruses, and herpes viruses. Bacterial lung infection is usually caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, and some Gram-negative bacteria. The severity of lung infection depends on the virulence and the type of pathogen. Viruses can induce pneumonia and cause serious breathing difficulties. In addition, pneumonia in children is often caused by mycoplasma. *Mycoplasma pneumoniae* can cause an atypical pneumonia that is milder than other forms and can be treated with specific medications. X-ray imaging is utilized for the diagnosis and during therapy of pneumonia.

KEYWORDS: *Lung infection, microorganism, pneumonia, imaging, clinical, bacteria, virus*

INTRODUCTION

Viruses, bacteria, and *Mycoplasma pneumoniae* are pathogens that can cause lower respiratory tract infections. Each type of infection affects the lungs differently, with varying symptoms, severity, and treatment options (1). *M. pneumoniae* causes approximately 30% of pneumonia in infancy and school age, while it is rare under 3 years of age (2).

Viruses are the most common cause of upper and lower respiratory tract infections in infancy and childhood, accounting for 65% of childhood pneumonia and 90% of pneumonia in children under 2 years of age (3). Viral lung infections are among the most common causes of respiratory tract diseases. They typically affect both the upper and lower respiratory tracts and can range from mild to severe (Table I). Bacterial infections of the lungs often result in pneumonia, which can be more severe than viral infections (4). These infections usually affect the alveoli in the lungs, leading to the accumulation of fluid or pus.

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Table I. *Viruses that typically cause respiratory tract infections.*

Upper respiratory tract infections	
Adenovirus	Causes pharyngitis, conjunctivitis, and sometimes pneumonia.
Respiratory syncytial virus (RSV)	Can also progress to lower respiratory infections.
Parainfluenza virus	Causes croup (laryngotracheobronchitis).
Influenza virus	Causes seasonal flu, which can lead to complications.
Coronavirus (SARS-CoV-2)	Can cause mild to severe respiratory illnesses.
Rhinovirus	The most common cause of the common cold.
Lower respiratory tract infections	
Adenovirus	Can cause severe pneumonia, particularly in immunocompromised children.
Respiratory syncytial virus (RSV)	The leading cause of bronchiolitis and pneumonia in infants.
Parainfluenza virus	Causes croup and sometimes bronchitis or pneumonia.
Influenza virus	Can cause viral pneumonia or predispose to bacterial superinfection.
Coronavirus (SARS-CoV-2)	Can cause respiratory distress in some infants and children.
Human metapneumovirus (hMPV)	Affects young children and can lead to bronchiolitis.

M. pneumoniae is a type of bacteria that lacks a cell wall, making it unique compared to other bacteria (5). It causes atypical pneumonia, often referred to as walking pneumonia because the symptoms are milder, and patients can often remain ambulatory (6).

DISCUSSION

The most common viruses which cause pneumonia are adenoviruses, enteroviruses, influenza viruses, parainfluenza viruses, syncytial viruses, cytomegalovirus, and herpes virus (7). The most common bacteria that cause lung infections are *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, Gram-negative bacteria, *Escherichia coli*, *Klebsiella*, and *Proteus*. Inhalation-aspiration of microorganisms or aspiration of infected gastric secretions are the most frequent mechanisms of spreading airway and lung infections (8).

The evolution and severity of lung infection is strictly connected to the virulence and the inoculated quantity of pathogenic antigens, and the immune response of the subject. The clinical picture is related to the severity of acute infection, with fever, pharyngitis, headache, chest and abdominal pain, and increased heart rate and respiratory rate (9). Subsequently, respiratory symptoms appear such as cough and respiratory noises.

In pneumonia forms caused by *Staphylococcus aureus*, a superinfection may occur in particularly debilitated patients, often during hospitalization (10). Pneumonia may be particularly virulent with rapidly evolving pulmonary edema and haemorrhage. After a few days, the evolution may lead to pneumatocele due to necrosis of the bronchiole walls and air infiltration into the interstitium. In a high percentage of these patients, pneumothorax occurs due to rupture of the pneumatocele (11).

Most pneumonia infection in school-age children are caused by mycoplasma, which is rarely the cause in children under three years of age. The disease presents with general malaise, headache, fever, and mild cough. Radiographic signs are often more serious than the patient's clinical conditions (12).

Viral pneumonia mainly affects infants and very young children, causing severe respiratory distress, respiratory noises, tachypnea, cyanosis, dyspnea, and rib indentations (13). Radiographically, signs indicate the presence of viral infection, but specific details are not evident. Chest X-ray examination in pulmonary infections is the investigation that requires the greatest commitment and professionalism of the radiologist (14). In fact, it is necessary to identify the pneumonic focus, its extension, the probable cause, and any other complications that are involved. For this reason, it is essential to know the patient's age, his/her clinical history, the duration and intensity of the symptoms, and the result of laboratory tests, since the clinical conditions can often mimic a pneumonic process in a large number of patients (15). It

is also essential to acquire radiograms in the inspiratory phase in high definition with very short exposure times and minimal respiratory movements in the two posteroanterior (P-A) and lateral (L-L) projections (16). The airways in children are more susceptible to obstruction by secretions in inflammatory processes causing hyper-insufflation with areas of irregular aeration, atelectasis and thickening of the bronchial walls (17).

It's not always possible to differentiate between pneumonia, bronchopneumonia, lobular pneumonia, and interstitial pneumonia through clinical-radiographic correlation. In fact, the forms with initial involvement of the interstitium can progress towards areas of parenchymal consolidation and the forms with initial parenchymal opacities can evolve by subsequently involving the interstitium (18). In bacterial pneumonia, the penetration of the germs into the alveolar lumen causes an exudative edema that rapidly extends to an entire alveolar group, segment, or lobe, creating an area of massive and homogeneous opacity (hepatization) on the radiogram with segmental or lobar extension on which the air bronchogram stands out.

In bronchopneumonia, multiple, patchy nodular opacities are seen on the radiogram, with involvement of the peribronchial interstitium with a predominantly segmental distribution. In the forms caused by *Staphylococcus aureus*, the nodular opacities evolve towards cavitation with a cystic appearance (pneumatocele). In the acute form, the radiographic picture of interstitial pneumonia of viral origin is characterized by areas of faint parenchymal consolidations with a reticulonodular appearance, disseminated throughout the lung fields with thin streaks of opacity that branch radially from the hilar regions to the upper and basal lung regions (19). Therefore, for example, when performing a chest X-ray of an individual with pneumatocele in *Staphylococcus aureus* pneumonia, characteristic air bubbles may be noted in the context of parenchymal opacity. In addition, in bacterial pneumonia, a large area of homogeneous opacity (hepatization) affecting the lung may be highlighted on X-ray imaging. Again, in interstitial pneumonia, the X-ray may show parenchymal consolidations, even small ones, of reticulonodular appearance, with areas of hyperdiaphany in the lung lobes (12). The streaks of opacity intersect each other, delimiting areas of irregular hyperdiaphany, which is often the predominant radiographic sign in children (20)

Bronchiectasis is a chronic respiratory disorder characterized by permanent dilation and damage of the bronchi with accumulation of mucus, recurrent infections, and progressive lung disease. Bronchiectasis is an almost always reversible dilation of a portion of the bronchial tree which is frequently the result of prolonged respiratory tract infections (21). Cough is always present, often accompanied by hemoptysis and dyspnea. Chest X-ray may show dilation and thickening of the bronchial walls surrounding an area empty of parenchyma, while high-resolution chest CT/CT scan allows for a more in-depth evaluation of the involved areas (22). Multidisciplinary therapy includes respiratory physiotherapy with postural drainage, the possible use of mechanical ventilators, and proper use of antibiotics (23). The role of inhaled corticosteroids in the individual is controversial, although aerosolized antibiotics have been shown to be useful in treating certain conditions, such as cystic fibrosis (24).

CONCLUSIONS

Lung infections are caused by diverse bacterial and viral pathogens. Viral lung infections are often mild but can cause serious illnesses such as viral pneumonia, as has happened with COVID-19. Bacterial lung infections tend to be more serious and require antibiotics, especially if they lead to pneumonia. *M. pneumoniae* causes a milder, atypical pneumonia that can be treated with specific medications. Early diagnosis and proper treatment are key to managing respiratory tract infections caused by these pathogens. Vaccinations and preventative measures can also help reduce the risk of infection.

Conflict of interest

The authors declare that they have no conflict of interest.

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PULMONARY INFLAMMATION IS MEDIATED BY CYTOKINES IN COVID-19

Pierdomenico D'Andrea[1*], Lucio Tauro[2] and Soufun Qin[3]

[1] Macular Degeneration and Photobiomodulation, University of Chieti, Chieti, Italy;
[2] Unit of Clinical Pathology and Microbiology, Miulli General Hospital, Acquaviva delle Fonti, Bari, Italy;
[3] Drug Discovery, Center for Research and Development, Kexing Biopharm Co., Ltd., Shenzhen, China.

**Correspondence to*:
Dr. Pierdomenico D'Andrea
Macular Degeneration and Photobiomodulation,
University of Chieti,
Chieti, Italy.
e-mail: Dandreapierdomenico3@gmail.com

ABSTRACT

The immune system is activated in response to pathogens (bacteria, viruses, or fungi), toxins, or physical trauma. Alveolar macrophages and epithelial cells recognize foreign antigens through pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs). Immune cells activated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) release pro-inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6), causing a strong inflammatory response. In serious cases, a cytokine storm may occur in which excessive cytokine production causes uncontrollable systemic inflammation. Additionally, elevated levels of interferon-γ (IFN-γ) and inflammatory chemokines attract neutrophils and other immune cells to the lungs, contributing to tissue damage. Immune activation in COVID-19 leads to the recruitment of inflammatory cells and the release of harmful mediators that lead to fibrosis and respiratory failure. Impaired tissue damage and lung function causes respiratory failure that, if untreated, can result in death.

KEYWORDS: *Pulmonary inflammation, cytokine, COVID-19, SARS-CoV-2, virus, coronavirus, infection*

INTRODUCTION

Viral lung infections can be caused by pathogenic viruses such as respiratory syncytial virus (RSV) or coronaviruses such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that can induce a cascade of inflammatory cytokines that damage the lungs (1). The immune system fights viral infection and triggers inflammatory pathways to contain and eliminate the virus (2). However, in some cases, excessive or dysregulated inflammation can cause diseases such as viral pneumonia or acute respiratory distress syndrome (ARDS), which can result in fluid accumulation in the lungs with poor oxygenation and multiorgan failure from systemic inflammation (3).

Coronaviruses are a group of similar RNA viruses that cause diseases in mammals and birds (4). They cause diarrhea in cows and pigs and hepatitis and inflammation in mice (5). In human beings, the virus can cause mild respiratory diseases but also causes severe diseases such as severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and COVID-19 (6,7).

COVID-19 disease is an infectious pathology caused by the Sars-Cov-2 virus. It first appeared as cases of acute pneumonia of viral origin in December of 2019 in China (8). Most individuals affected by COVID-19 show mild to moderate symptoms that heal with special care.

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Sars-Cov-2 is mainly transmitted through salivary droplets from infected individuals by sneezing or exhalation (9). Others can become infected by inhalation if they are in close proximity to someone who has COVID-19, or by touching their eyes, nose, or mouth after having touched a contaminated surface (10).

During SARS-CoV-2 infection, the activated immune system produces several mediators such as cytokines, that cause inflammation if secreted in excessive quantities (11).

DISCUSSION

Lung inflammation can be induced by the immune response to SARS-CoV-2 infection. This can lead to tissue damage, lung irritation, and edema, which are potentially serious complications that may be fatal (12). The virus activates immune cells such as macrophages, neutrophils, lymphocytes, and mast cells (MCs), which release signaling molecules, including cytokines, that increase lung inflammation. COVID-19, caused by SARS-CoV-2, primarily affects the respiratory system, especially the lungs. In severe cases, the virus can cause acute lung injury and lead to ARDS (13).

SARS-CoV-2 enters cells by binding the ACE2 receptor which is found in large quantities in lung tissue (14). The infection can trigger excessive immune responses, particularly in the lower airways, leading to lung inflammation and difficulty in exchanging oxygen (15).

Cytokines are protein signaling molecules that help regulate the immune system's response to infection. They play a critical role in the severity of COVID-19 and, in some cases, can contribute to fatal outcomes (16). This occurs due to a phenomenon called the 'cytokine storm', which is a severe reaction by the immune system where there is an excessive release of inflammatory molecules, including pro-inflammatory cytokines, which provokes severe inflammation and tissue damage (17). This overproduction of cytokines causes increased vascular permeability which leads to fluid accumulation in the lungs that results in low oxygen levels (hypoxia) and further lung injury (18).

In COVID-19, the cytokine storm has been described as one of the critical mechanisms that leads to disease progression and death. In fact, when severe disease affects vulnerable individuals, such as immunocompromised patients and the elderly, COVID-19 can also lead to death (19). Therefore, when SARS-CoV-2 infects the body, it triggers an immune response that can successfully contain and eliminate the virus in mild cases but can overreact in some severe cases and release large amounts of pro-inflammatory cytokines, including tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) (20). In the latter case, inflammation is not limited to the site of infection but becomes systemic, affecting multiple organs and tissues.

In severe, virus-induced lung inflammation, coagulation is dysregulated and thrombin is activated, which disturbs the balance between coagulation and fibrinolysis (21). Excess fibrin deposition in the alveoli impairs gas exchange and contributes to alveolar damage (22). In these cases, microvascular thrombosis may occur, leading to hypoxia (23). Inflammatory cytokines such as TNF and IL-1 damage the endothelium of pulmonary blood vessels, increasing vascular permeability (24) (Fig.1). This phenomenon allows plasma proteins and immune cells to leak into the interstitial and alveolar spaces. In addition, endothelial damage also impairs the production of nitric oxide (NO), causing vasoconstriction and pulmonary hypertension (25). Infiltration of immune cells contributes to the formation of edema, with accumulation of fluid in the alveoli, impairing oxygen exchange.

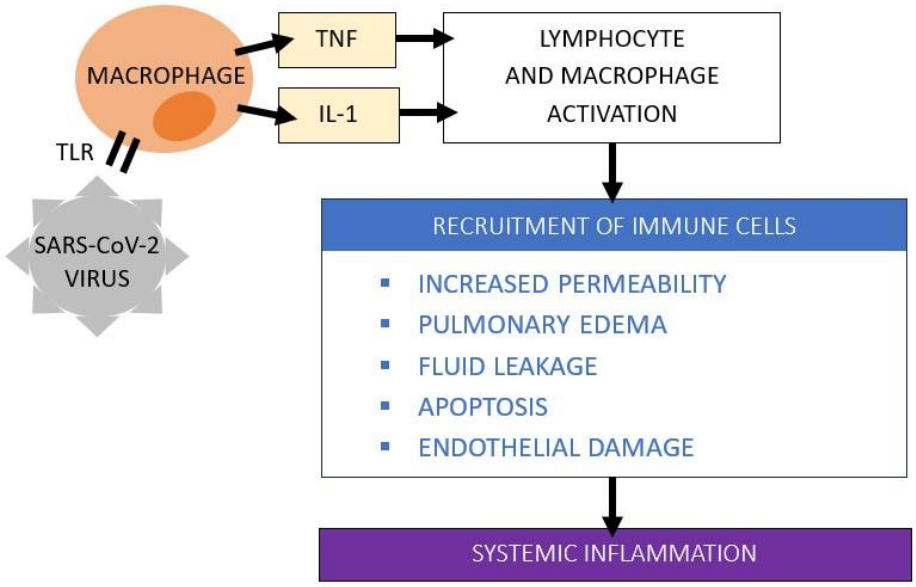

Fig. 1. *SARS-CoV-2 binds the Toll-like receptor (TLR) on macrophages. Macrophages secrete tumor necrosis factor (TNF) and IL-1, inflammatory cytokines that activate immune cells, producing increased permeability, pulmonary edema, fluid leakage, apoptosis and endothelial damage. These effects cause systemic inflammation.*

IL-1 is one of the first cytokines released after pulmonary viral infection as part of the body's innate immune response. This cytokine produces fever, promotes the production of other pro-inflammatory cytokines, and recruits immune cells (e.g., neutrophils and macrophages) to the lungs to fight the infection (26). Excessive IL-1 production has the potential to cause harmful levels of inflammation which damages lung tissue and worsens respiratory symptoms.

IL-6 is a major pro-inflammatory cytokine that has a wide range of effects, including promoting immune cell differentiation and stimulating the acute phase response such as C-reactive protein production in the liver (27). It acts both locally in the lungs and systemically and contributes to fever and systemic inflammation. High levels of IL-6 are associated with severe lung inflammation and tissue damage and are often implicated in a hyperinflammatory state seen in severe viral infections such as SARS-CoV-2 (28).

TNF is a critical cytokine released during viral infections, and it can also be induced by IL-1, which fuels the inflammatory situation (29). TNF helps activate immune cells and increases the permeability of blood vessels in the lungs, allowing immune cells induced by chemokines to migrate to the site of infection (30). This cytokine is also involved in the regulation of apoptosis and the control of viral replication. Excess TNF can cause hyperactivation of immune responses, increasing vascular permeability to the point of edema and contributing to acute lung injury or ARDS in severe cases of viral infection (31).

Cytokine storms can lead to coagulopathies with complications such as pulmonary embolism, stroke, or, in severe cases of COVID-19, heart attack (32). Systemic inflammation can cause damage to organs such as the heart, liver, and kidneys (33). Studies show that corticosteroids (for example, dexamethasone) reduce mortality in severe cases by moderating the immune response (34). IL-6 inhibitors, such as tocilizumab, are used to block the action of IL-6, one of the key cytokines implicated in the cytokine storm (35). In addition, janus kinase (JAK) inhibitors, which block cytokine signaling pathways, have been explored to control excessive inflammation (36). Although they do not directly target the cytokine storm, antiviral drugs can help reduce the viral load, which could potentially prevent excessive levels of cytokines (37).

Supportive care for COVID-19 includes oxygen therapy, ventilation, and organ support for those with severe symptoms. Some individuals will experience mild symptoms from a cytokine storm, while others rapidly worsen to severe conditions. The immune dysregulation triggered by this overreaction highlights the importance of finding the correct balance in immunomodulation during treatment (38).

SARS-CoV-2-induced lung inflammation is a severe and often life-threatening condition, in which inflammation in the lungs leads to respiratory failure, multi-organ damage, and ultimately death. Lung inflammation involves a complex interplay of immune responses, cellular damage, and dysregulation of multiple molecular pathways.

Vaccine

The purpose of the COVID-19 vaccine is to prevent infection or reduce the severity of the disease by providing immunity against SARS-CoV-2 (39). Work to develop a vaccine for coronavirus diseases was already underway before the COVID-19 pandemic, with efforts aimed at preventing SARS and MERS. Research in this field provided a better understanding of the structure and function of coronaviruses and enabled the accelerated development of various vaccines (40).

Many countries have implemented phased distribution plans for the COVID-19 vaccine that prioritize those who are at highest risk of complications, such as the elderly, the immune-compromised, and those who are at high risk of exposure and transmission, such as healthcare workers.

mRNA vaccines use messenger RNA which instructs cells to produce a piece of the virus's spike protein, which triggers an immune response (41). Viral vector vaccines use a modified adenovirus to provide instructions for making the spike protein; while protein subunit vaccines contain harmless pieces of the virus to stimulate an immune response (42). COVID-19 vaccines have been highly effective at reducing severe disease and preventing hospitalizations and deaths, although their effectiveness may be reduced by new variants. Because immunity can wane over time and due to the emergence of variants such as Delta and Omicron, booster doses are recommended to maintain strong protection (43). Vaccines have played a crucial role in controlling the spread of COVID-19, reducing the burden on healthcare systems and saving lives (44).

CONCLUSIONS

The production of pro-inflammatory cytokines is a crucial factor in severe COVID-19 disease. When the immune system becomes overactive and produces a cytokine storm, there can be significant damage to the lungs that results in respiratory failure. The excessive inflammatory response in COVID-19 is a critical and highly complex component, and treatments that target this phenomenon can help improve the clinical condition of this disease that has caused millions of deaths globally.

Conflict of interest

The authors declare that they have no conflict of interest.

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