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Unmasking The Immune Response: A Deep Drive into Defense Against Viral Respiratory Infections.

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ABSTRACT

The immune response to respiratory viral infections includes both innate and adaptive immunity, with neutrophils, CD8+ T cells, and antibodies playing important roles. However, it can also result in detrimental inflammation and viral immune evasion. Antigen-specific T and B cells are part of the adaptive immune response in respiratory viral infections, which eliminates the virus and creates immunological memory. However, overreactions can cause tissue damage and make a person more vulnerable to subsequent infections. Although the innate immune response is essential for identifying and combating respiratory viral infections, viral evasion tactics can reduce its efficacy, resulting in insufficient protection and possible tissue damage. Innate immune cells' antiviral response is triggered when pattern-recognition receptors identify viral components. This triggers signalling pathways that generate cytokines and interferons, which limit viral replication and trigger adaptive immunity. In order to regulate and eradicate viral infections while preserving immunological memory, the adaptive immune response to viral infections includes T and B cells, memory cell formation, and interactions with innate immune components such as interferons and NK cells.

KEYWORDS

Innate immunity, adaptive immunity, influenza, respiratory viral infection , immunological response, respiratory syncytial virus, alveolar macrophages (AM) , antigen-presenting cells(APC) , natural killer cells(NK) , dendritic cells (DC), invariant natural killer T cells (iNKT) , interferons (IFNs).

I. INTRODUCTION

The immune system is a multifaceted, intricately controlled system of tissues and cellular (immune cells, lymph nodes, and mucosal tissues) and humoral (antibody, antimicrobial, and complement proteins) components as shown in Fig.1 that have developed to work together to defend people against infectious diseases. The immune system is further divided into innate immunity and adaptive immunity as shown in Fig.2 [1,2]. The innate immune system, which is composed of physical barriers, various phagocytic cells, a variety of cytokines, interferons (IFNs), and IFN-stimulated genes, provides the initial line of defence against infection. The innate immune response, which is rapid to react but nonspecific, is the first line of defence against viral infection [3,4,5]. Innate immune cells with pattern recognition receptors (PRRs) are able to identify pathogen-associated molecular patterns (PAMPs). Similar to innate immunity cells, other host cells use PRRs to detect viral PAMPs, which then set off the innate immune response signal pathway, generate pro-inflammatory cytokines, chemokines , and interferons (IFNs), and start the cell's antiviral response[2,6]. The three main categories of PRRs are intracellular DNA receptors, RIG-I-like receptors (RLRs), and toll-like receptors (TLRs). TLR3 (also present in the cell membrane) recognizes double-stranded RNA (ds RNA), whereas TLR7 and TLR8 recognize single-stranded

RNA (ssRNA). The endosome contains TLRs [3]. Through the capture and destruction of the pathogen, B cells and T cells—which possess antigen-specific memory cells—mediate adaptive immunity. T cells and B cells are crucial for adaptive protection against viral infections. CD4+ T cells and CD8+ T cells are the two main subtypes of T cells. CD8+ T cells mature into cytotoxic T lymphocytes (CTLs), which produce cytokines and effector chemicals to halt viral replication and eradicate virus-infected cells. Thus, T cells play a crucial role in reducing viral infection [7]. Before discussing the primary components of the immune system, we will look at the initial challenges that viruses must overcome in order to infect a host. The main entry points for infections into the body are the skin and mucosal surfaces[1].Viral infections are one of the leading causes of disease and mortality worldwide[1,4]. Known as infectious diseases of the respiratory tract, respiratory tract infections are the most common illness in the world. These diseases are the most common cause of morbidity and mortality, particularly in underdeveloped nations, and are categorized as upper and lower respiratory tract infections [6,8].

One of the prevalent illnesses that affect people of all ages is upper respiratory tract infections. The most common upper respiratory tract infections include sinusitis, tonsillitis, otitis media, pharyngitis, and nasopharyngitis [9]. These issues are typically brought on by viruses. RTIs are more prevalent in underdeveloped nations, where they are the second leading cause of pneumonia-related deaths in children, after diarrhoea [8].Viruses are also the cause of common respiratory diseases like influenza, croup, pneumonia, bronchiolitis, and the common cold. The viruses that cause these respiratory diseases include respiratory syncytial virus (RSV), SARS-COV2, influenza, adenovirus, para-influenza virus, and human meta-pneumovirus [6,8,10]. Viruses are essentially required intracellular parasites. They require a host in order to replicate their genetic material, spread to other cells, and eventually to additional hosts. Most viral infections in humans are not considered to be lethal, despite the fact that the virus can kill individual cells at the cellular level. Higher host mortality causes immunosuppression or immunological compromise because of ongoing genetic changes that can alter the antigenic content of viruses such as coronaviruses or influenza [1]. This review paper's objective is to compile a broad variety of research and offer a thorough and understandable evaluation of the body of information regarding immune response in respiratory illnesses. It enables readers to rapidly understand the main findings and knowledge gaps in the field. The innate and adaptive immune systems, as well as the antiviral reactions of their various cell types, are the main topics of this review. PRRs, TLRs, IFNs, natural killer cells, neutrophils, dendritic cells, and macrophages are examples of innate immune cells. B cells, antibodies, T cells (CD4 and CD8), and natural killer T cells are examples of adaptive immune cells.

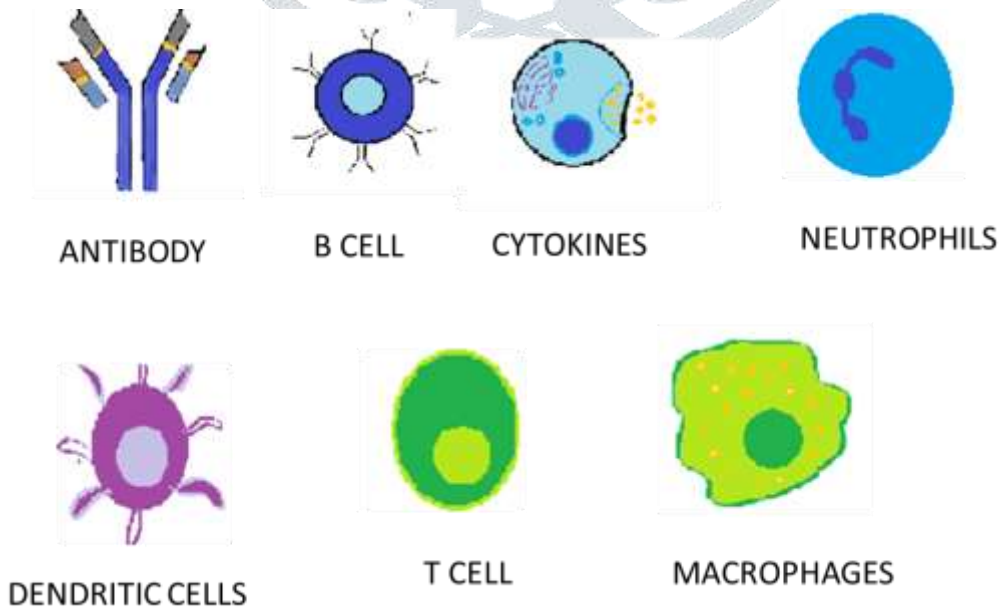

Fig.1. Humoral and cellular components which regulate our immune system.

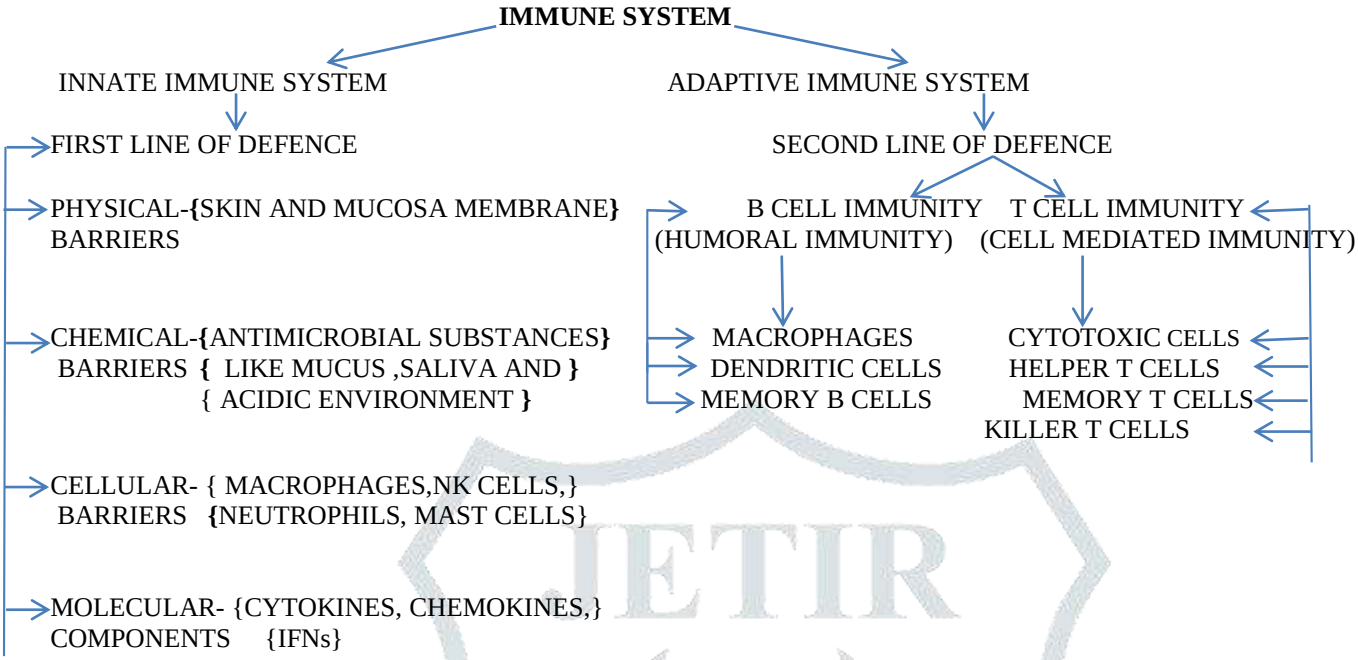

Fig.2. Types of immune system.

II. IMMUNE RESPONSES IN RESPIRATORY VIRAL INFECTIONS

When a virus infects the cells of the respiratory mucosa, as might happen when virus particles are inhaled or come into direct touch with the mucosal surface of the nose or eyes, viral respiratory infections follow. When an infected person coughs, sneezes, or simply breathes quietly, they release the virus into the air [4,6]. Large droplets of virus are frequently released from the air within a short space when coughing or sneezing. A person can spread the virus by touching the infected surface and then touching their mouth, nose, or eyes if the virus lands on a surface and survives [11]. Both touch and airborne transmission can spread influenza viruses, while aerosols and respiratory droplets are the primary means of transmission for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [12]. While coronaviruses are far more durable in the environment, some viruses are more brittle than others. For instance, respiratory syncytial virus (RSV), the most significant respiratory virus in early childhood, does not persist long on inanimate surfaces [13].

The greatest surface of the human body that comes into contact with the outside world is the lung epithelium. Massive volumes of air and aerosols travel past these cells every day, exposing the lung tissue and the rest of the respiratory system to germs and viruses found in the air we breathe. Common lung-invading viruses with RNA genomes include influenza, respiratory syncytial virus (RSV), rhinoviruses, and coronaviruses (CoVs) [1]. The main location for viral infection and replication is the airway epithelium. The mucus layer serves as a first line of defence against invasive diseases, and viruses must first pass through it [5]. The innate immune system is triggered when this mechanism malfunctions. A number of germ-line encoded receptors that are expressed on innate immune cells and epithelial cells form the foundation of innate immunity [6]. Club cells, which generate proteases; goblet cells, which produce mucus that serves as the first barrier for an entering virus; and ciliated and non-ciliated epithelial cells are among the diverse cell types that make up the respiratory epithelium. Pneumocytes lining the lungs' alveoli and alveolar macrophages are two examples of the ciliated or non-ciliated epithelial cells of the airways that many respiratory viruses selectively bind and infect [4]. Human influenza viruses, for instance, infect non-ciliated epithelial cells, while avian influenza A viruses infect ciliated epithelial cells [11]. The innate immune system serves as the initial line of protection along the whole tract, from the nasopharynx to the alveolar membrane [14]. This first line of defence involves several different cell types, such as alveolar macrophages, innate lymphoid cells, dendritic cells (DCs), and airway epithelial cells. Sensing and several subsequent unique molecular intra- and intercellular communication cascades in these and other respiratory tract cells ensure the creation of the antiviral state in the lungs [4]. Before adaptive immunity takes over to eradicate these viruses from the lungs entirely, this state can avoid or at least lessen sickness by

preventing the establishment of a productive infection with each of these invasive viruses. Crucially, invading respiratory viruses develop strategies to either evade or inhibit the innate immune responses as a countermeasure against these complex defence mechanisms. This allows the virus to replicate efficiently and frequently results in illness. The outcome of the disease is ultimately determined by the balance between the virulence and ability of the virus to elude the host's immune responses on the virus's side, and the effectiveness of the host's combined innate and adaptive responses [15,16,17]. Early in life, when adaptive processes are still developing, the innate immune system is more significant. However, the innate immune system is crucial for protecting young infants against respiratory infections because they are likely to be exposed to the same number of incoming pathogens as adults and older children. The innate immune system is crucial in the fight against respiratory viruses, and in the lungs, alveolar and interstitial macrophages, DCs, airway epithelial cells, innate lymphocytes, and neutrophils are mostly responsible for these initial defences against invading viruses [4,16]. Pattern recognition receptors (PRRs) identify pathogen-associated molecular patterns, which initiates the signalling cascade of the innate immune response. The Toll-like receptors (TLRs) 3, 7, and 8, which are expressed on a number of the cell types listed, are crucial PRRs for RNA viruses in the lungs. Additionally, intracellular cytosolic PRRs like MDA5 and RIG-I are found in almost all cell types, including lung cells [18]. All of the aforementioned receptors, also known as sensors, are able to identify types of RNA (such as 5′ triphosphate RNA and double-stranded RNA [ds RNA]) that are differentiated from the RNA species that are typically found in cells (like capped mRNA in the cytosol) and that are produced by (respiratory) RNA viruses during their infection process. Thus, when the innate immune system detects potentially harmful foreign material, it sets off a chain of events that eventually results in the induction of transcription factors in the nucleus, which in turn promotes the production of pro-inflammatory cytokines such as types I and III interferons (IFNs) [8]. The expression of numerous interferon-stimulated genes (ISGs) that create a so-called antiviral state is then guaranteed by a second wave of autocrine and paracrine signalling in both infected cells and the nearby uninfected cells. This condition effectively prevents the infection from spreading further while also inducing additional adaptive reactions that, in the majority of situations, will ultimately remove the virus from the sick person [19]. Phosphorylation events and ubiquitination of various linkage types (K48, K63, K27, etc.) on a variety of pathway factors strictly regulate the activation and inhibition of signal transduction in the cascades during all of these signal transduction pathways [18]. These processes play a crucial role in controlling downstream signalling to guarantee that innate immune responses are triggered powerfully but not explosively, and that these responses are promptly down regulated to shield the person from harmful immunopathology [2,20]. Recent research has demonstrated the importance of particular type III IFNs (IL-28/29), also referred to as IFN lambdas, in preserving epithelial surfaces such as the lung. They appear to stimulate downstream signalling that is triggered by the same PRRs that trigger type I IFNs, despite binding to a distinct hetero-dimeric receptor composed of IFNLR1 and IL10RB (as opposed to type I IFN, which binds to IFNAR1/2) [2,20,21,22]. However, IFN lambdas are mostly expressed by epithelial cells and DCs, while type I IFNs are produced by a wide variety of cell types like macrophages, dendritic cells [23]. Despite the obvious similarities between the types I and III IFN signalling pathways, recent research indicates that the type III IFN machinery appears particularly well-suited to defend epithelial surfaces against pathogenic assaults and serves as the main local defence when low concentrations of bacteria and viruses invade. The more systemic type I IFN machinery serves as the second line of defence throughout larger regions of the tissue when the initial activation of the type III IFN machinery is insufficient because of higher dosages of pathogens entering the body [24,25]. Furthermore, type III IFN does not appear to cause inflammation as much as type I IFN, which likely suggests a significant and distinct feature of type III IFN induction that could help shield, for instance, lung epithelial tissue from immunopathology. Epithelial cells, patrolling immune cells, or antibodies recognize pathogens and trigger an immune response to help eliminate them [2,20,26,27].

Adaptive immunity, also known as acquired immunity, develops in response to infection with particular pathogens over the course of an organism's life. The adaptive immune response is sometimes called particular immunity since it is very antigen specific, a bit slow, and effective at getting rid of antigens [28]. Adaptive immunity is essential for eliminating viral infections and developing a lasting immunological memory against a specific pathogen that reacts faster to repeated attacks. Three primary cell types are involved in the adaptive immune response: T CD4 cells, which include various subtypes (Th1, Th2, Th17, T-regulatory cells (Treg),

and T follicular helper cells (Tfh); T CD8 cells, which are in charge of directly eliminating infected cells in the airways; and B cells, which are in charge of producing antibodies [4] as shown in Fig.3.

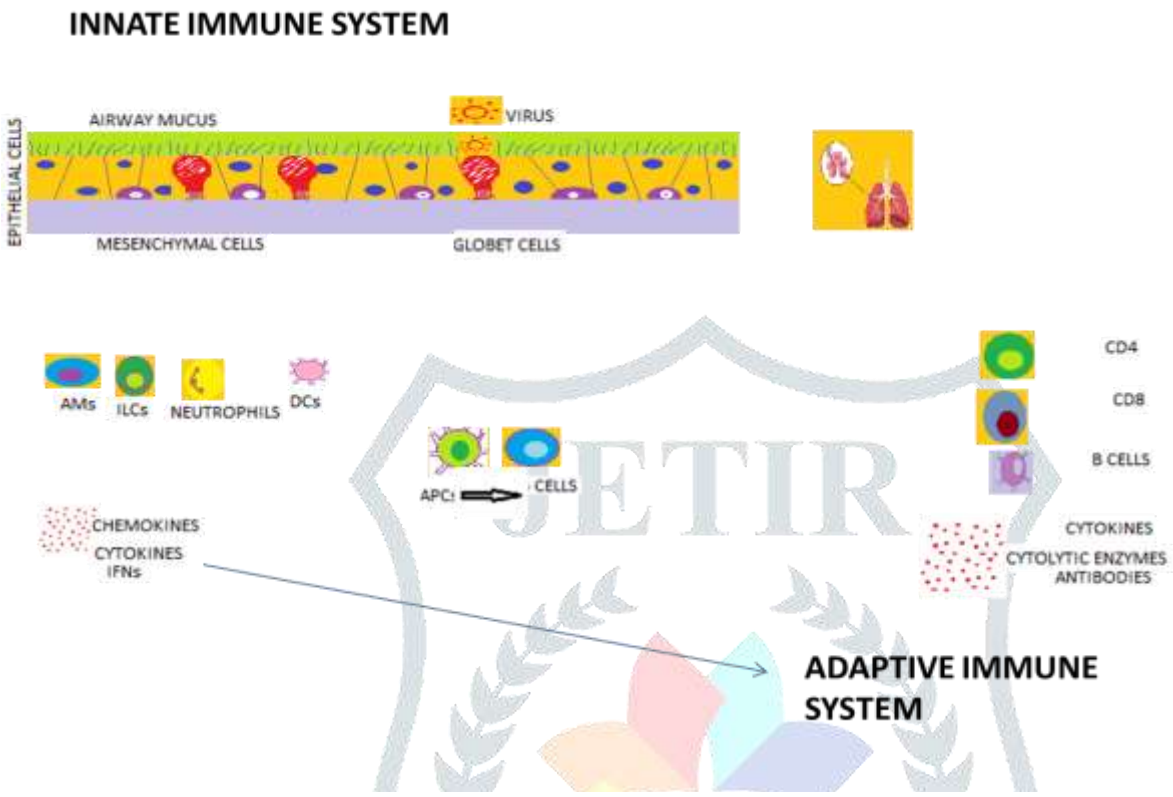

Fig.3. Illustration of the immune system's reaction to viral respiratory infections. A number of immune cells, including alveolar macrophages (AMs), innate lymphoid cells (ILCs), dendritic cells (DCs) and neutrophils, as well as structural cells like epithelial and mesenchymal cells and chemical barriers like mucus made by goblet cells, are involved in the virus's initial activation of an innate immune response. Additionally, cytokines, chemokines, and interferons (IFNs) aid in the removal of viruses. The draining lymph nodes are where the adaptive immune response begins following interactions with particular cells (such as T CD4 and T CD8 cells, B cells), as well as the antigen-presenting cells (APCs).

III. THE CONSEQUENCES OF RESPIRATORY VIRAL INFECTION IN THE HOST

The onset of clinical signs and symptoms of a respiratory virus infection is preceded by an incubation phase. The virus adheres to cells, replicates its DNA, and spreads to infect other cells during the incubation phase. While influenza normally has a brief incubation time of 1-2 days, SARS-CoV-2 has a longer incubation period of 4.5-5.8 days [29]. Clinical symptoms and indicators of a productive viral infection of respiratory epithelial cells vary depending on the area of the respiratory tract that is infected. A runny nose, coughing, sneezing, and sore throat are symptoms of infection of the nasal, nasopharyngeal, and oropharyngeal mucosa, [30,31] while trachea-bronchitis or croup manifests as a distinctive barking seal-like cough. While bronchiolitis, which affects the smaller distal airways and is indicative of RSV infection in young infants, manifests as wheezing, bronchitis, which is an inflammation of the bronchi, manifests as a cough [32,33]. Coughing and shortness of breath are symptoms of pneumonia, which is caused by infection and inflammation of the lung parenchyma and alveoli. Infections with human coronavirus, adenovirus, and rhinovirus often only affect the upper respiratory system. Croup is caused by para influenza viruses, while bronchiolitis is caused by RSV, influenza and pneumonia can be caused by SARS, MERS, and SARS-CoV-2. Secondary bacterial infections, especially in the lungs (pneumonia), can occasionally exacerbate respiratory virus infections. After an influenza virus infection, the finest illustration of this is a secondary bacterial illness brought on by Streptococcus pneumoniae or Staphylococcus aureus [11].

IV. KEY COMPONENTS OF INNATE IMMUNE SYSTEM AND THEIR ANTIVIRAL RESPONSE

[A] PATTERN RECOGNITION RECEPTORS (PRRs)

Pattern recognition receptors are an essential part of the innate immune system (PRRs). These are also referred to as PAMPs, or pathogen-associated molecular patterns. PRRs are found in several places within the cell; some are found on the plasma membrane, which is the cell surface, and they are able to identify extracellular pathogens. These are mostly seen on epithelial and immunological cells [34]. Other PRRs are found inside cells and are able to identify intracellular pathogens like viruses (cytoplasm/endosome membrane). Additionally, intracellular PRRs can exist free in the cytoplasm or membrane-bound within the endosome membrane. All cell types frequently have them [1,6,35]. They distinguish self from non-self by identifying elements shared by numerous pathogens that are absent from the host and are found on the cell surface of a variety of cell types, including immune cells, epithelial cells, endothelial cells, etc.[4,6]. PAMPs include substances found on the surface of several bacterial pathogens, such as peptidoglycan, flagellin and lipopolysaccharide (LPS). Additionally, they are able to identify the genetic material of certain viruses (ds RNA/ssRNA) as well as other common elements that are shared by parasites, fungus, and other microbes [35,36]. PRRs cells have determine the ability to recognize various infections, which in turn determines the subsequent immune response. Toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I) like receptors (RLRs), C-type lectin receptors (CLRs), interferon gene stimulators (STING), nucleotide oligomerization domain (NOD)-like receptors (NLRs), [37] inflammasomes and DNA sensors are among the various classes of viral sensing PRRs based on protein domain homology [4]. Despite the fact that a wide variety of microorganisms, microbial metabolites, and host-derived damage-associated molecular patterns (DAMPs) can be detected by these receptors [38].Multiple PRRs are frequently activated by pathogens, facilitating receptor-to-receptor communication and a stronger immune response [1,6].

[B] TOLL LIKE RECEPTORS (TLRs)

Toll C-type lectin receptors (CLRs), retinoic acid inducible gene-I (RIG-1) like receptors (RLRs), and nucleotide-binding oligomerization domain (NOD) like receptors (NLRs) are the most extensively researched form of TLR [4,37]. There are ten functioning TLRs in humans. These can be found in the endosome or plasma membranes as homodimers or heterodimers [1,39]. The plasma membrane contains TLR1, 2, 4, 5, 6, 10, while the endosome membrane contains TLR 3, 7, 8, and 9 (which are used to identify intracellular pathogens).These TLRs are endosomal. The primary TLRs that identify the presence of viral genetic material are TLR 3, 7, and 8. While TLR9 identifies hypomethylated CpG DNA, TLR3 recognizes ds RNA and TLR7/8 ssRNA, which may be the viral genome's composition or an intermediate created during viral replication [6,38]. Viral proteins have also been demonstrated to activate several of the cell surface-exposed TLRs in addition to recognizing viral genetic material. The respiratory syncytial virus (RSV) F protein, which is visible on the cell surface and has the ability to directly activate TLR4, is one example [1,40].

[C] CYTOSOLIC DNA SENSORS

The innate immune system includes DNA-binding proteins called DNA sensors. They might detect alterations in the DNA homeostasis of the cell and initiate intracellular signalling cascades of the innate immune system in reaction [41]. Numerous immune and tumor cell types carry cytosolic DNA sensors (CDSs), which are able to detect double-stranded DNA (ds DNA) in the cytoplasm. These molecules become active after dsDNA recognition, initiating a sequence of events that ultimately lead to the activation of both acquired and innate immunity [42]. Type 1 INFs can be induced by DNA sensors, which is crucial during viral infection. As an innate immune response to the infection, DNA sensors cause programmed cell death in addition to type I IFNs [42,43]. Cytosolic DNA sensors like interferon-g (IFNg)-inducible protein 16 (IFI16) and cyclic GMP–AMP synthase (cGAS), which cooperate with the adaptor protein STING . For instance, IFI16 and AIM2 can cause pyroptosis, but cGAS-STING and TLR9 can cause apoptosis [1,42].

[D] INTERFERONS (IFNs)

Important members of the cytokine family, interferons (IFNs) are essential elements of the innate immune response to viruses [44,45]. In humans, IFN comes in three different forms: type I, type II, and type III [6,20]. 17 cytokines make up type I IFNs, one cytokine makes up type II IFNs, and four cytokines make up type III IFNs [1,46]. The interferon alpha and beta receptor subunit (IFNAR) is the signalling pathway for type I, which includes several IFN-α subtypes as well as single IFN-ß, IFN-ε, IFN-κ, and IFN-ω. Airway epithelial cells, alveolar macrophages (AMs), monocytes, and plasmacytoid dendritic cells (pDCs) are among the cells that produce type I IFNs, which have more inflammatory effects. The two main cytokine families that are crucial to the antiviral immune response are type II interferon (IFN-γ), which stimulates Th1 differentiation and macrophage activation [47]. IFN-λ1 (IL-29), IFN-λ2 (IL-28A), IFN-λ3 (IL-28 B), and IFN-λ4 are type III IFNs that all signal via the IFN lambda receptor (IFNLR) [48,49]. Type III IFNs regulate the infection locally rather than systemically and are the first line of defence against viral replication in mucosal barrier epithelial cells [4,6,20]. By influencing cell survival, replication, and protein translation, IFN production and activation can limit viral replication and spread. They can also encourage tissue healing and the establishment of adaptive immunity. Because of their extensive impact on the host, their expression is strictly regulated, ultimately aiding in viral clearance. Type I interferons (IFNs) and pro-inflammatory cytokines are released, [50] cellular translation is inhibited, and an antiviral state is generated when viruses invade host cells. Nonetheless, a number of respiratory viruses have the ability to prevent apoptosis and impede IFN activation and/or signalling. In addition to preventing the host from efficiently eliminating virally infected cells, this also causes an antiviral state in nearby cells, which encourages viral reproduction in infected tissues and could be a factor in the pathology that is seen [11]. Following their expression and secretion, IFNs attach to host cell surface IFN receptors, which phosphorylate the Janus tyrosine kinase (JAK) proteins JAK1 and tyrosine kinase TYK2, thereby initiating a downstream signalling cascade [19] .This facilitates the recruitment of additional signalling proteins, including the signal transducer and transcription activator proteins (STAT1 and STAT2), which are phosphorylated once more. This route is called the JAK/STAT pathway [1,2]. IFN-stimulated gene factor (ISGF) is a hetero-trimeric transcription factor complex that is formed when these STAT proteins join forces with Interferon regulatory protein (IRF). After trans-locating into the nucleus of the host cell, this complex attaches itself to the promoter of interferon-stimulated response elements (ISREs) and triggers the production of several interferon-stimulated genes (ISGs). These genes affect every stage of the viral life cycle and have a profound impact on the host [1,4].

[E] DENDRITIC CELLS (DC) AND MACROPHAGES

The innate immune system in the lungs depends on macrophages and dendritic cells (DCs) [51]. They assist in bridging the gap between the innate and adaptive immune responses by serving as sentinel cells that identify viral infections. DCs and macrophages are usually found inside the walls of alveoli and on the mucosal surface of the airways close to the airway epithelial cells. The respiratory tract contains a variety of macrophage types, such as monocyte-derived macrophages, interstitial macrophages, and alveolar macrophages (AMs). By secreting inflammatory cytokines and chemokines and activating transcription factors in the pathophysiology of inflammatory lung disorders, macrophages aid in the initiation and advancement of acute or chronic inflammatory reactions [51,52]. Through PPRs, pro-inflammatory cytokines, and chemokines generated by airway epithelial cells and other local immune cells, viruses can activate DCs. During respiratory viral infections, pDCs are essential IFN-α producers and help initiate the innate immune response. By exposing CD4 and CD8 naive and memory T cells to viral antigens, conventional DCs—which are mostly linked to the mucosal epithelium of the conducting airways- play a significant part in promoting the adaptive immune response [2].

[F] NATURAL KILLER (NK) CELLS

Innate lymphocytes known as natural killer (NK) cells serve as the body's initial line of defence against infection [53]. Natural killer (NK) cells have the ability to release cytokines and carry out cytotoxic functions when they are activated [1]. In addition to their cytotoxic capabilities, natural killer (NK) cells can stimulate T cells to trigger the adaptive immune response and release cytokines such as interferon gamma (IFN-γ). NKs use cytotoxic mechanisms to stop the spread and replication of viruses [2,4]. NK cells target

either infected or healthy host cells. They can also target infected cells more effectively by using antibody-dependent cell-mediated cytotoxicity. Natural killer (NK) cells, which recognize weaker cells by activating NK cell surface receptors, may attack host cells after viral infection. NK cells have two different types of cell surface receptors: activating and inhibitory receptors [54]. Normal, healthy host cells carry MHC class I molecules on their surface, which are recognized by NK cell inhibitory receptors and promote self-tolerance [55]. NK cell activating receptors attach to host cell surface patterns concurrently. NK cells are activated when virus-infected cells lose surface MHC class I expression, which inhibits the NK cell inhibitory signal [1, 56] as shown in Fig.4. The immune response to a number of respiratory viruses, such as influenza, respiratory syncytial virus (RSV), and SARS-CoV-2, is mediated by NK cells. These viruses have the ability to impact NK cell function, which can occasionally result in immune suppression or changed NK cell activity [57,58].

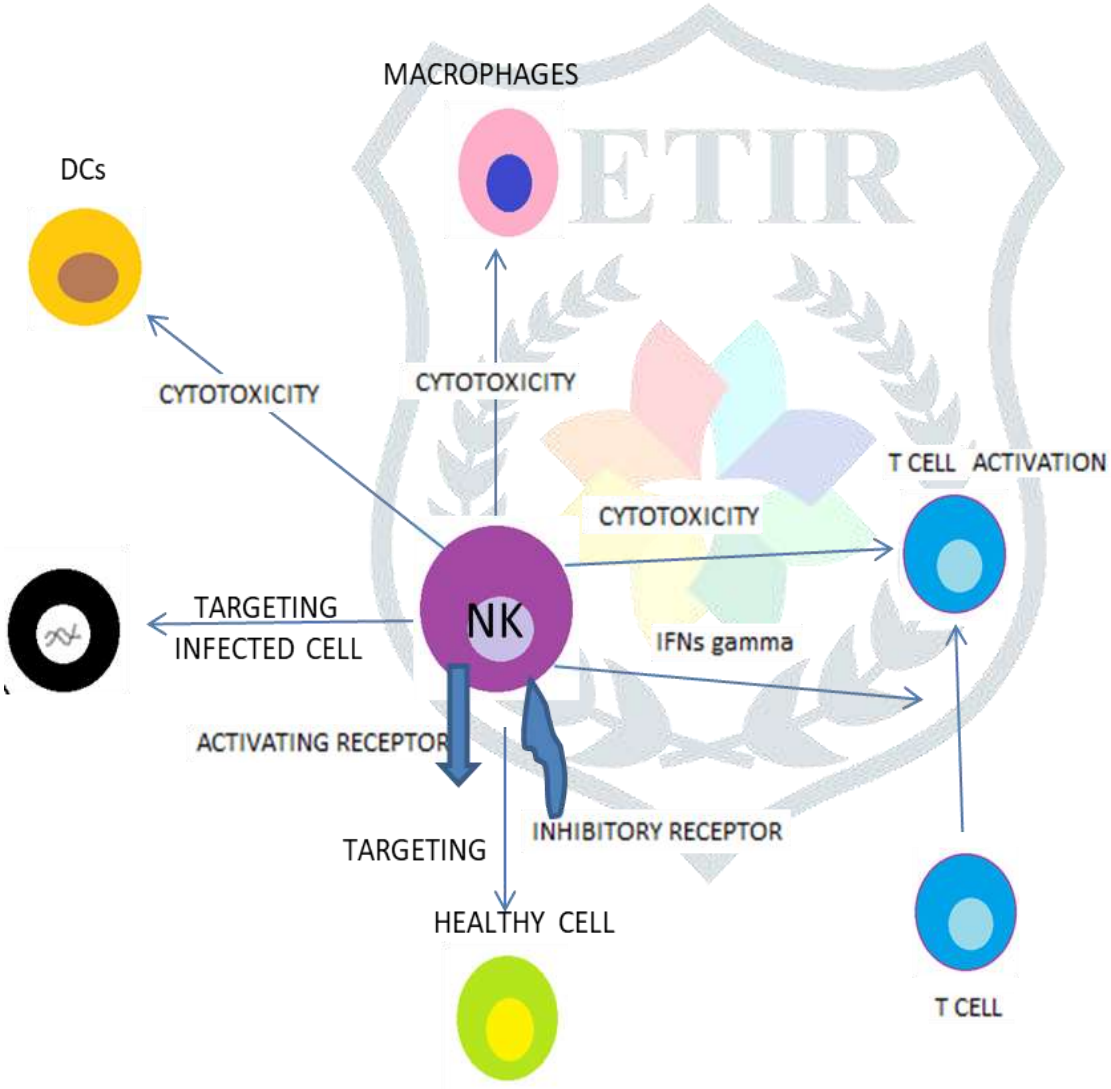

Fig.4. By stimulating T cells and generating cytotoxic cytokines, natural killer cells contribute to respiratory viral infections. NK cells target both healthy and sick cells by activating and inhibiting receptors.

[G] NEUTROPHILS

The first immune cells to reach the infection site are neutrophils, the most common circulating white blood cell in the body [59]. Neutrophils are crucial for maintaining immunological balance and combating microbial infections. Neutrophils can secrete inflammatory mediators that significantly increase pathogenicity and host defence during viral infections, among other things [60]. Neutrophils enhance antiviral defences by interacting with other immune cells, internalizing and destroying viruses, and producing cytokines, chemokines, and antimicrobial components [61]. The three main processes of pathogen removal include degranulation, phagocytosis, and the most recently discovered technique of producing Neutrophil Extracellular Trap (NET) [62].

V. KEY COMPONENTS OF ADAPTIVE IMMUNE SYSTEM AND THEIR ANTIVIRAL RESPONSE

Three primary cell types are involved in the adaptive immune response: T CD4 cells, which include various subtypes (Th1, Th2, Th17, T-regulatory cells (Treg), and T follicular helper cells (Tfh); B cells, which produce antibodies; and T CD8 cells, which kill infected cells directly in the airways [62,63].

[A] B CELLS AND ANTIBODIES

Antigen presenting cells (APCs), particularly DCs, in the lymphoid tissues like nasal -associated lymphoid tissue and bronchus-associated lymphoid tissue (NALT and BALT) activate B cells during initial respiratory viral infection [64]. The immune response to viruses is characterized by the function of B cells, particularly those that make antibodies (plasma B cells). All vaccinations are based on the production of neutralizing antibodies, which are effective against a variety of viral infections, including influenza, SARS-CoV-2, and others. These frequently also generate long-lived memory B cells, which quickly create antibodies and recognize the same pathogen in subsequent encounters. However, in many cases, such as those involving SARS-CoV-2 and RSV, the development of antibodies to viral infections are transient, allowing reinfection to take place [65]. B cells in the lungs have the ability to establish local germinal centres, which are crucial for selecting B cell repertoires that target conserved viral epitopes. Through this process, antibody repertoires are modified to combat viral alterations, resulting in a more potent defence against reinfections. During viral infection, B cells can also act independently of antibodies [66, 67]. This mainly involves the synthesis of pro- and anti-inflammatory cytokines, which interact with other cells and alter their immune responses. Additionally, they deliver antigen to T cells via MHC class II molecules, which aids in determining how T cells react to viral antigens [1,66].

[B] T CELLS

CYTOTOXIC T LYMPHOCYTES (CD8+)

A vital part of the adaptive immune system, cytotoxic T lymphocytes (CTLs) are essential for eliminating virally infected cells [68]. Through their T cell receptor, which is displayed in MHC class I molecules, these T cells are able to recognize antigen. All of the body's nucleated cells have MHC class I molecules on their surface. Endogenous (intracellular) peptides are the source of the peptides produced in these cells and loaded onto MHC class I molecules. This comprises peptides produced by intracellular pathogens like viruses as well as host cell proteins. CTLs use two primary host cell killing strategies to eliminate contaminated cells. The process involves the synthesis and release of cytotoxic granules, which are mostly made up of granzyme and perforin and resemble those made by NK cells [69]. The peptides generated in these cells and loaded onto MHC class I molecules are endogenous (intracellular) peptides. This includes both host cell proteins and peptides made by intracellular invaders like viruses [1,4]. The pro-inflammatory cytokines that CTL release, including TNF-a, IFN-g, and IL-2, interact with other immune cells to stimulate a T helper cell response and further CTL development.

CYTOTOXIC T LYMPHOCYTES (CD4+)

The immune response against respiratory viruses like influenza can be directly influenced by CD4+ T cells. Strong effector CD4+ T cell responses, which are best recognized for supporting B cell and CD8+ T cell responses, are frequently induced by viral infections [70]. The development of memory subsets that offer long-term immunity is another function of these cells. The majority of CD4+ T cells are linked to T helper (Th) cell subsets, [71] and use their TCR to identify antigens displayed in MHC class II molecules on immune cells [72]. The type of immunological response and the type of T cell that is produced are ultimately determined by the specific cytokines that are present in the microenvironment. The cytokines IL-12 and IL-4, respectively, cause differentiation of the T helper (Th1) and T helper (Th2) subsets [73]. Other subgroups of T helper include regulatory T cells (Treg), Th22, Th9, follicle helper T cells (Tfh), and Th17 cells. The cytokines that these cells primarily produce interact with other immune system cells and determine the subsequent immunological response [1,73,74]. Like CD8+ T cells, CD4+ CTLs can release cytotoxic granules that contain perforin and granzyme B, which can destroy the target cell when they come into direct contact with it. Additionally, they use the Fas/Fas L connection to destroy target cells. They have proven to be catalytically active against virus-

infected cells [75]. As CD8+ CTLs lose their ability to operate during persistent infections, CD4 CTLs can take their place, demonstrating the significance of CD4 CTLs [4]. By reducing over reactive immune responses and averting autoimmune disorders, regulatory T cells (Tregs) preserve immunological homeostasis. These cells primarily function by producing cytokines, which interact with other immune system cells and determine the subsequent immunological response [2,76].

NATURAL KILLER T CELLS (NKT)

The Natural Killer T cell is another cell type that may be significant during viral infections. These are innate-like cells that have the ability to react quickly to novel antigens. This varied population of innate T cells has gained interest due to the capacity of natural killer T (NKT) cells to regulate immunological responses to a variety of illnesses [77]. The diverse population of T cells known as natural killer T cells (NKTs) combines the characteristics of T and NK cells. Depending on the kind of TCR expressed, NKTs can be categorized as type I also known as invariant NKT cells (iNKT) or type II NKT cells. In the setting of viral infections, invariant NKT (iNKT) cells—which express a semivariant TCR that may detect lipid molecules—are the best-characterized subset of NKTs. Lipid antigens presented in an MHC class I similar molecule (CD1d) are recognized by the invariant TCR found in these cells [2,78,79]. When these cells are active, they can release a variety of cytokines and chemokines that affect other immune system cells (such T helper cells), including T cell polarization, B cell antibody production, and dendritic cells (DC) maturation. Like CTLs, these cells can also use cytolytic proteins (granzyme/perforin) to directly lyse infected cells [80]. The cell establishes an immunological synapse a highly organized structure between the target cell and the T cell by engaging with receptors and ligands on their surfaces.

Once released, perforin causes a pore that allows the granzyme protein to enter the cell, damaging the host cell membrane. When this protease enters the cell, it breaks down proteins and DNA, preventing the production of viral proteins and ultimately killing the infected host cell [1,69] as shown in Fig.5.

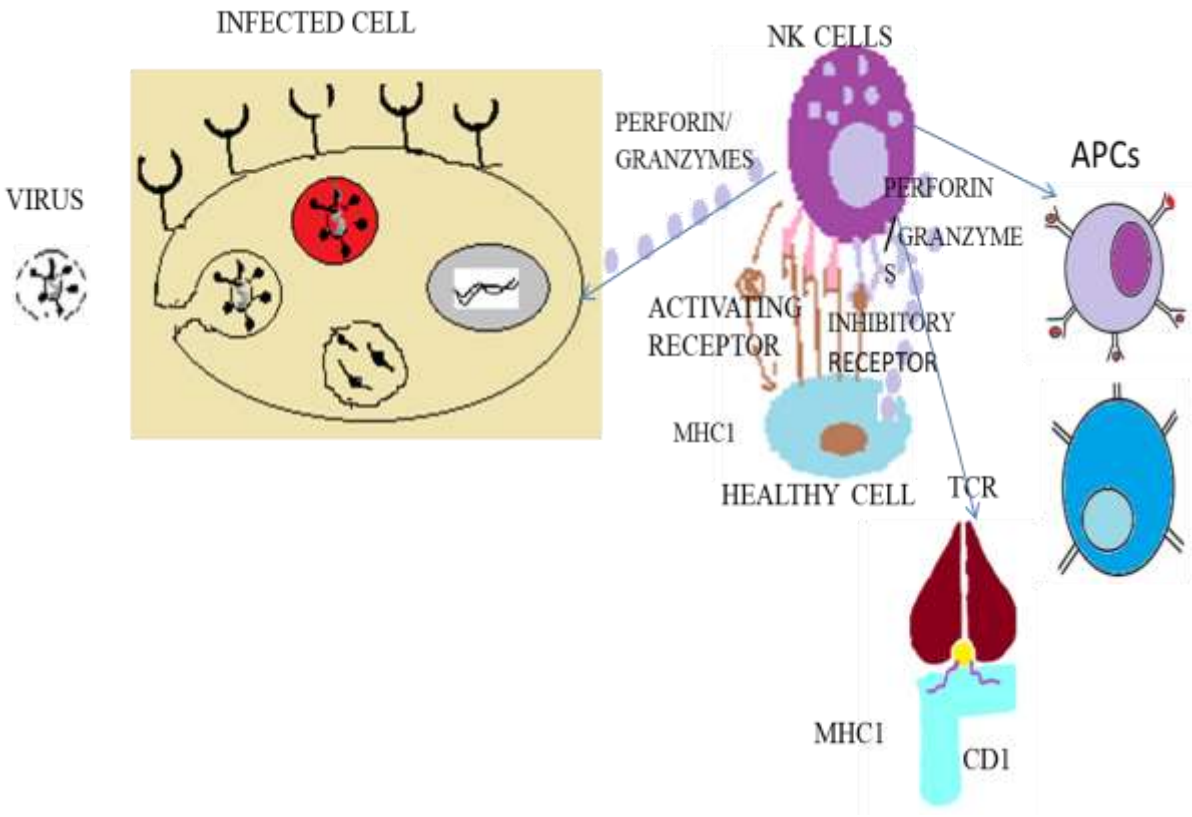

Fig.5. Natural killer T cells play a part in respiratory viral infections by recognizing cytokines, chemokines, granzymes, and perforin.

VI. CONCLUSION

Preventing respiratory viral infections is mostly dependent on innate and adaptive immune responses in the airways, especially in pregnant women and babies. In respiratory viral infections, the immune response is essential for eliminating viral pathogens, building long-term immunity, and avoiding severe inflammation. In order to overcome obstacles and create efficient antiviral therapies, it is essential to understand how the virus interacts with the host during respiratory infections. The creation of vaccines is aided by the innate and adaptive immune responses to respiratory virus infection, which may also lessen the prevalence of respiratory viral illness. The production of monoclonal antibodies and antivirals depends on the immunological response. T cells, cytokines, and antibodies play important roles in the immune response to respiratory viral infections, which includes both protective and potentially harmful roles of innate and adaptive immunity. However, the response can differ greatly depending on the disease-causing virus and host factors like age and disease severity.

VII. CONFLICT OF INTEREST

There was no conflict of Interest.

VIII. AUTHOR'S CONTRIBUTION

Literature Survey was done by Monika. Manuscript preparation was done by Monika and Gurinder. Proof reading and guidance was done by Dr. Puneet and Harpreet Kaur.

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