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Role of Innate Immune Cells in the Control of Influenza A Virus Infection

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ABSTRACT: In human immune response against invading viruses, the innate immune system plays a critical role in the early defense towards variable viral infections before the adaptive immune response triggered, particularly against influenza viruses, like with influenza A virus type. Dendritic cells and macrophages are key players in this type of immunity, which is activated to kill infected cells and release antiviral cytokines like interferon-gamma that either reduce the infection or recruit other types of immune cells, like T cells, to the site of infection. The purpose of the study was to look at how innate immune cells contribute to the formation of viral reservoirs and long-term maintenance. Innate immune cells play a critical role in influenza spontaneous control. This study studied previous studies on the Influenza type A Viral infection and who Innate immune cell control this infection. Databases such as Google Scholar and PubMed were investigated. Neutrophils are examples of innate immune cells that can react to infection by phagocytosing virus-infected cells, creating neutrophil extracellular traps (NETs), which are crucial for immobilizing invasive viruses, and releasing inflammatory cytokines. Additionally, macrophages present antigens, phagocytose viruses, and produce cytokines to stimulate additional immune cells, including T cells. By stimulating T-cells, dendritic cells can operate as a mediator to activate the innate and adaptive immune systems. In order to develop treatment strategies aimed at improving basic immune responses and minimizing severe infection, it is crucial to comprehend the distinct roles of each innate immune cell in the defense against influenza.

Keywords: influenza type A virus, innate immunity, and influenza virus control

1. INTRODUCTION

Influenza A virus (IAV) is a major worldwide health threat, that causes seasonal epidemics and occasional pandemics. Rapid contamination with of IAV is strongly dependent on the initial immune system. Innate immune cells not lonely suppress initial viral replication but also can form the adaptive immune response through cytokine production and antigen presentation. The understanding of these early mechanisms is critical to develop new strategies and boost host defense [Iwasaki and Pillai,2014]. Innate immune cells such as macrophages, natural killer (NK) cells and dendritic cells (DCs) act in control early infection and preventing viral spread [Krammer et.al.,2018]. However, excessive activation can cause tissue damage and worsen conditions like pneumonia. A balanced immune response is so important to effectively control influenza without triggering detrimental inflammation.

2. DATA ACQUISITION

This study aimed to investigation the role of Innate Immune Cell against viral infection especially influenza type A. A comprehensive search was performed to identify relevant research studies in this area in the PubMed and Google Scholar databases. The following keywords were used during the search: “Influenza A Viral infection”, “Innate Immunity” and “Cellular Components of the Innate Response”.

3. RESULTS

3.1 THE ROLE OF INNATE IMMUNITY IN EARLY DEFENSE

The innate immune system represents the host's initial protective line of defense against IAV. Differing of adaptive immunity that takes days to be effective, the innate immune responses are in a fast manner can be activated within few hours after infection. The early response is crucial to contain the viral replication, to limit tissue damage, and to prime adaptive immune mechanisms. Pattern recognition receptors (PRRs), such as TLR7 and RIG-I, TLR3, sense viral RNA, activate downstream signaling pathways leading to the production of type I with type III interferons (IFNs), besides pro-inflammatory cytokines and chemokines [Iwasaki and Pillai,2014]. These molecules orchestrate antiviral conditions in neighboring cells and recruit immune cells to the site of infection. In most times, especially in healthy persons, the innate immune system can clear IAV and successfully without the need for pharmacologic therapies. This auto-control is considered as a result of a coordinated activity among many innate immune cell categories, each performing specialized activities, ranging from recognition of viruses towards immune modulation and direct cytotoxicity. Meanwhile adaptive immunity ensures long-term protection; it is often the effectiveness of the innate response which determines the early clinical outcome of infection (Krammer et.al.,2018).

3.2 CELLULAR COMPONENTS OF THE INNATE RESPONSE

The key cellular contributor of in innate immunity include macrophages, natural killer (NK) cells, dendritic cells (DCs), neutrophils, innate lymphoid cells (ILCs), and γδ T cells. Each of these cell types contributes uniquely to the defense against influenza. Macrophages and DCs are among the first to encounter the detected viruses in the respiratory tract, acting as cytokine producers and antigen-presenting cells. NK cells and Neutrophils provide rapid cytotoxic response that strongly eliminate the infected cells and form subsequent steps in immune reactions. γδ T cells and ILCs are less abundant just contribute to epithelial repair and inflammation control adding a layer of immunoregulation(Guo and Thomas ,2017).

3.2.1 NATURAL KILLER (NK) CELLS

NK cells are an important component of the innate immune system that serve as the initial line of defense towards various viral infections like influenza virus. NK cells can recognize and eliminate the infected cells without needing prior sensitization, and make these cells as a key element in controlling initial-stage of viral infections (Gazit et.al.,2006). These cells also detect infected cells by recognition altered self-molecules, by including the stress- ligands with viral components expressed above the surface of those infected cells. The ability of NK cells in producing cytokines like interferon-gamma (IFN-γ) can also enhance the role of them viral replication and limited promoting in broader immune response (Orange and Ballas,2006). This first antiviral response made via NK cells is very important to control influenza virus replication prior to adaptive immunity to be activated.

The NK activation of cells during influenza infection happens when this recognition of infected done by stressed cells. NK cells then can display various receptors which help them to distinguish healthy from infected cells. The activating receptor NKp46 is included, which takes part recognizing the influenza virus-infected cells (Shibuya et.al.,2011). NKp46 then binds to viral hemagglutinin (HA) above infected cells surface, initiating activation of NK cell. Other receptors such as NKG2D can strongly recognize stress-induced ligands which upregulated on infected cells surface, further activating of NK cells can occur, too (Orange and Ballas,2006). Activated NK cells once initiate cytotoxic responses then secrete cytokines, obviously IFN-γ, which inhibit replication of viruses and coordinate immune response against them. This immediate recognition viral response is essential to control the viral spread before the adapting immune system becomes restricted strongly.

During activation process, NK cells can use the several cytotoxic mechanisms in eliminating influenza-infected cells. The early mechanism includes releasing cytotoxic granules which contain granzymes and perforin. Perforin can shape pores in infected cells membrane as their target, then granzymes enter and start apoptosis, effectively can kil infected target cell (Fehniger and Caligiuri ,2001). NK cells furthermore produce large quantities of IFN-γ, which are potent cytokines that not only a direct inhibitor of viral replication but can also act as enhancers of other immune cells functions against viruses, like dendritic cells and macrophages, which can support strongly overall immune response (Fehniger and Caligiuri ,2001). Upon these activities and mechanisms, the NK cells control viral replication and also limit tissue damage in early stages of infection, as shown in figure 1.

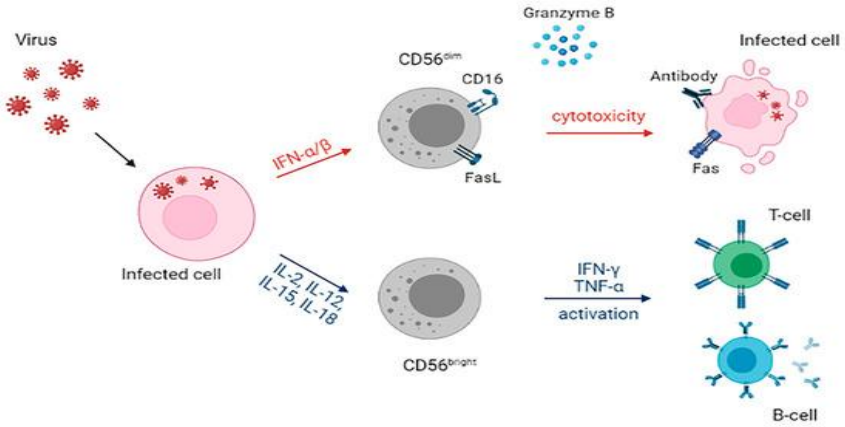

FIGURE 1. - NK cell activation during infection (Rizzo, et al. 2021)

In addition to the cytotoxic activity of NK cells, they can play a key role in modulating the extended immune response upon influenza infection. NK cells will produce IFN-γ, that can activate dendritic cells and macrophages, to enhance presenting antigens against viruses, stimulating adaptive immune response (Shibuya et.al.,2011). This cross-link between adaptive and innate immunity is so crucial for boarder immune protection. In addition to NK cell role, it can help in regulating the immune host entire environment to avoid extra inflammation, which could result in tissue damage by immunopathology (Shibuya et.al.,2011). Via balancing immune suppression and activation, NK cells mainly contribute to both of effective protection from immune-related damage and viral clearance, to ensure suitable immune response against influenza virus infection.

NK cell responses van be in a variable mode depending on influenza virus strains. For example, the NK cells considered to be more effective in infection control that cause highly pathogenic influenza strains like H5N1 in comparison to multiple seasonal strains. This difference in response may be as a result of variations in surface proteins of the virus, which can affect NK cell recognition (Martin et.al.,2007). Furthermore, NK cell effectively shares in responding against different strains influenced by host genetic factors which dictate receptor-ligand interactions of NK cells with infected cells. Understanding these variations is so important for developing strategies and enhancing NK cell in their response, especially towards highly influenza virulent strains.

NK cell is actively can regulate immune responses to avoid extra tissue damage in host. NK cells express both inhibitory and activating receptors. Inhibitory receptors like the killer immunoglobulin-like receptors (KIRs) with NKG2A specifically interact with self-MHC class I molecules on healthy cells, to prevent killing of normal uninfected cells (Shibuya et.al.,2011). upon influenza infection, sometimes infected cells often downregulate MHC class I molecules and express stress-induced ligands which reduce inhibitory signaling, then allowing NK cells and target the infected cells becoming activated. The balance between inhibitory and activating immune signals strongly ensures NK cells to efficiently eliminate infected cells and preserving host tissue integrity (Shibuya et.al.,2011).

In many studies involving NK cell-deficient in animal models, like NCR1 knockout mice, there is evidence that NK cell deficiency causes increased disease severity, higher viral loads, and delayed healing from influenza infections (Marquardt et.al.,2015). These animals also can exhibit much more susceptibility to secondary bacteria-mediated infections that usually follow viral infections. This suggests evidence regarding NK cells as crucial not only in controlling viral replication but also for in preventing complications like bacteria-mediated super infections. In human being, impaired NK cell functions can be linked in increasing risk of virus-mediated infections, including influenza, in aspect of the importance of these cells in antiviral immunity (Marquardt et.al.,2015).

On the other hand, NK cells play a vital role in the early control of IAV. They can recognize infected cells via activating receptors like NKp46, which can bind virus- mediated hemagglutinin. NK cells also eliminate infected cells using perforin and granzyme-mediated cytotoxicity to release IFN-γ that enhance antiviral responses (Rizzoet.al.,2021). Lacking of NK cells in mice leads to elevated viral titers besides enhancing delay clearance, which means they are strongly associated with spontaneous control (Gazit et.al.,2006).

3.2.2 NEUTROPHILS ROLES IN VIRAL INFECTION

Neutrophils, as the most present white blood cells in the human being body, play a crucial role in the early defense towards viral infections, like in influenza infections. They are considered as part of innate immune system and usually the initial immune cells that attract to infection sites. During influenza virus exposure, neutrophils strongly respond and migrate to the lungs, and they engage in phagocytosis of infected cells and pathogens rapidly, secreting cytokines to amplify immune response against invaders, and producing reactive oxygen species (ROS) that kill viruses and infected cells (Cameron et.al.,2013). While they are pivotal in controlling viral replication and imitating their spread in initial

inflectional stages, neutrophils must be carefully regulated in order to avoid extra inflammation which could cause tissue damage and immunopathology (Cameron et.al.,2013).

Neutrophil recruitment and activation are considered critical components of host immune response towards influenza infection. After virus recognition, the infected cells and macrophages release chemokines like granulocyte colony-stimulating factor (G-CSF) and IL-8, which make neutrophils migrate to the sites of the infection in the body (Kobayashi et.al.,2012). Furthermore, pattern recognition receptors (PRRs) on the neutrophils, surface, like Toll-like receptors (TLRs), can take part in detecting pathogen-associated molecular patterns (PAMPs) specific to influenza virus (Cameron et.al.,2013). This recognition can strongly trigger the neutrophils activation, leading to their migration within the infected tissue. During reaching infection sites, neutrophils shape as equipped to suit functions of phagocytosis and to release pro-inflammatory cytokines with antimicrobial peptides; all can help in limiting spread and replication of viruses (Cameron et.al.,2013).

Once recruited to the site of infection, neutrophils contribute to the clearance of the influenza virus through various methods, with phagocytosis being one of the initial mechanisms Neutrophils engulf and digest infected cells or pathogens, so reducing the viral load with preventing further viral replication will occur (Cameron et.al.,2013). Furthermore, neutrophils secrete antimicrobial peptides called cathelicidins and defensins have direct antiviral activities. These peptides disrupt envelops of viruses and inhibit virus from entering the host cells (Cameron et.al.,2013). In addition, neutrophils heavily produce reactive oxygen species (ROS) in time of respiratory bursts that can directly damage infected cells and viral particles to limit viral spread. However, the excessive ROS production can lead to tissue damage in host, which maintains balanced neutrophil response in time of infection occurrence (Cameron et.al.,2013).

Neutrophils are also related in shaping Neutrophil Extracellular Traps (NETs), which are consisted of histones, and antimicrobial proteins with composed DNA. NETs are released from neutrophils are important in trapping and neutralize invasive pathogens, such as viruses, so preventing their spread is important to keep host health (Musharrafieh et.al.,2017). In the aspect of influenza infection, However, the formation of NETs is a double-edged issue as they help to eliminate viral particles, but excessive NET formation can result in host tissue damage, especially in the lungs, making respiratory symptoms to be worse. Therefore, secreted NETs can contribute to clearance of viral clearance, but the overproduction of them can result in lung injury then extra disease severity (Tate et.al.,2011). NETs can specifically capture viral particles and prevent the viral further replication in host tissues (Musharrafieh et.al.,2017).

The neutrophils are considered to be essential in influenza infection control, but their excessive activation cause immunopathology, mainly in host lungs. Neutrophils release proteases enzymes called elastases and matrix metalloproteinases (MMPs), which are effectively involved in remodeling tissues and cause tissue damage when overproduced (Tate et.al.,2011). These enzymes can degrade the extracellular matrix, causing impaired respiratory function after lung injury. In addition, excessive activation of neutrophils can cause a hyper-inflammatory condition, resulting in widespread damage of lung tissues and worsen disease symptoms (Kobayashi et.al.,2012). While neutrophils are responsible of pathogen and viral clearance, their overproduction of cytokines is very harmful to host tissues if not be controlled (Kobayashi et.al.,2012).

Neutrophils also take an important part in modulating process of immune response via pro-inflammatory cytokines secretion process. In influenza infection, the activated neutrophils release IL-1β, TNF-α and IL-6 cytokines, that specifically connected other additional immune cells, like T cells and macrophages and causing their migration towards the site of infection (Tate et.al.,2011). This controlled release of cytokines helps in amplifying the immune response besides facilitating the viral clearance process. In all infections, the excessive production of such cytokines can result in a phenomenon called cytokine storm, which is a pathological overproduction of the initial inflammatory cytokines, strongly associated to poor outcomes in influenza infection and makes it worse. So, regulating the duration and intensity of cytokines produced by neutrophils release is very essential in viral load and controlling without causing excessive symptoms (Kobayashi et.al.,2012)

Neutrophils are migrating early to the lungs during IAV infection to kill virus-infected cells by many immune mechanisms like oxidative burst, phagocytosis and the release of neutrophil extracellular traps (NETs). Their role is considered to be protective in early stages but more or prolonged released cytokines with neutrophilic infiltration can cause immunopathology and, emphasizing to understand regulated responses in viral infections in an immunological aspect (Tate et.al.,2009).

3.2.3 MACROPHAGES ROLES IN VIRAL INFECTION

Macrophages play a pivotal role in the innate immune response towards influenza virus infection. As considered to be main players in early stages of defense mechanism, the macrophages contributed in various infected tissues and are crucial for recognizing invasive pathogens, resulting in activating inflammatory responses, and the additional immune cells are well abundant to the site of infection (Taylor et.al.,2013). During influenza infection, macrophages guide the adaptive immune response. Even thou, macrophage activation should be highly controlled to create balanced effective virus control to prevent damage resulting from excessive inflammation by secreted cytokines and enzymes. Their dual role is promoting host defense besides causing immunopathology to make them central to influenza pathogenesis (Wong and Webby,2013).

Macrophages recognize influenza virus particles using pattern recognition receptors (PRRs), TLRs, which can detect PAMPs as in RNA viruses. The activation of TLRs on macrophages surface can lead to the activation of downregulating signaling pathways, including the NF-κB as well as MAPK pathways, which trigger the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β (Takeuchi and Akira,2010). These cytokines take an important part in promoting inflammation process, recruiting other immune cells to migrate to sites of the infected tissues, resulting in enhancing antiviral immune responses. Furthermore, macrophages in the lung tissues can tightly interact with the influenza virus, then enhancing phagocytosis against viruses in order to limit viral replication during initial stages of lung infection. On the other hand, the prolonged activating of tissue macrophages in influenza infection durations can contribute acute lung injury and severe pathology in host infected tissues (Taylor et.al.,2013).

Macrophages are considered the first immune cells to encounter influenza virus particles and infected cells, playing an essential role in their removal via phagocytosis. This process is particularly critical in controlling viral replication in the early stages of infection. Macrophages engulf then digest cells infected with viruses and perform apoptosis; thereby limiting the spread of the virus with apoptotic particles presence will occur (Wong and Webby,2013). These effective cells will also achieve clearance of infected epithelial cells of lungs, preventing further viral load and replication; besides phagocytosis, macrophages will secrete antiviral cytokines especially IFN-α/β, that effectively interfere with viral replication via activating antiviral state within surrounding cells (Cameron et.al.,2013). This coordinated response will help in reducing the viral load and make its replication limited in the next stages of the infection, mainly in the initial phase (Cameron et.al.,2013).

Macrophages can also exhibit plasticity via duration of activation and polarized in influenza virus infection locations, macrophages can basically apply either a pro-inflammatory M1 phenotype or an anti-inflammatory M2 phenotype. The M1 macrophages are said to be involved in fighting infections and inflammation, releasing cytokines such as IL-1β, TNF-α, and IL-6, which are crucial for antiviral defense and displaying additional immune cells (Wong and Webby,2013). Contrarily, M2 macrophages are associated specifically with tissue damage repairing process inflammation resolution. Upon influenza infection, the predominant M1 polarization will be observed, included to acute inflammatory response in infected organs, but a shift to an M2 phenotype is very important in prognosis of inflammation and promoting healing of tissue as the infection process will be controlled (Perry et.al.,2020). The balance between M1 with M2 polarization is vital in determining the outcome of influenza infection, because excessive amounts of M1 can cause tissue damage and acute lung injury subsequently (Perry et.al.,2020).

Macrophages secrete a variety range of cytokines with chemokines which are essential for local and systemic immune response in influenza virus infections. Cytokines like TNF-α, IL-6, and IL-1β can play critical role in mediating inflammation besides activation of immune cells to control viral replication (Taylor et.al.,2013). These cytokines mainly promote the cascade of other immune cells secretions, including T cells, neutrophils, and other macrophages, towards infection location. Chemokines like CCL10, CCL5, and CXCL2 are released to attract the immune cells towards infected tissue as a guide of them to reduce viral replication. Macrophages can also produce type I interferon (IFN-α/β), that helps in establishing the antiviral state in next cells and inhibit viral replication (Cameron et.al.,2013). However, the cytokine resulting in overactive immune response, then resulted phenomenon of cytokine storms will cause tissue damage, especially in the lung tissues (Cameron et.al.,2013).

While macrophages are very essential for controlling the replication of viruses, the excessive activation upon influenza stages can lead to organ immunopathology like acute lung injury and then respiratory failure (Taylor et.al.,2013). Besides, the activation of large sets of immune cells at infection sites in host tissues will damage them and the impaired gas exchange in the lungs will be disrupted; step by step a hallmark of severe influenza infection will occur (Wong and Webby,2013). Macrophages can extensively release matrix metalloproteinases (MMPs) and other proteases enzymes which degrade extracellular matrix components then disrupt tissue integrity and more exacerbating lung damage (Perry et.al.,2020). Understanding the high-level balance among protective and pathological activities of macrophages in influenza infections is very crucial to develop therapeutic strategies in minimizing tissue damage and enhancing antiviral immunity (Perry et.al.,2020).

Alveolar and tissue macrophages act as viral sentinels, to detect IAV by pattern recognition receptors such as TLR7 and RIG-I; so in activation they will produce pro-inflammatory cytokines, type I interferons and TNF-α, IL-6. Furthermore, they will help in controlling viral replication and activating other immune cells. Depletion of macrophages can cause higher viral loads and then impaired adaptive responses (Aldridge et.al.,2009).

3.2.4 DENDRITIC CELLS (DCS)

DCs are an important immune key of human cells, acting as the primary sentinel's link between the innate immunity with adaptive immunity. DCs response is critical for detecting and capturing the invading pathogens, including the influenza virus, then initiating immune responses and trigger T cell to be activation to form immune memory (Steinman,2007). In influenza virus infection, DCs are recognize the viral components by pattern recognition receptors (PRRs), like RIG-I-like receptors (RLRs) and Toll-like receptors (TLRs), which activate other cells to produce initiate immune activation and cytokines (Kawai and Akira,2010). The role of DCs is not only restricted to pathogen recognition, but also act as antigen-presenting cells (APCs)that promote activation of virus-specific T cells for infection clearance and long-term immunity (Yoneyama M, Fujita,2007). The complete balance of DC function

upon influenza infection directs the infection prognosis and prevents excessive inflammation (Yoneyama M, Fujita,2007).

The DCs ability in influenza virus recognition is largely mediated by detected PRRs on viral RNA and proteins. For example, TLR8, TLR7, and TLR3 which are displayed on DCs endosomal compartments can recognize the viral parts like RNA, make the signaling pathways to start pro-inflammatory cytokines and type I interferons (IFNs) production (Kawai and Akira,2010). The RLRs, like RIG-I and MDA5, can also play a vital role in influenza RNA virus detection in DCs cytoplasm leading to activating transcription factor IRF3 then producing of IFN-β (Yoneyama and Fujita,2007). These immune responses can specifically help in viral replication limitation and providing the initial antiviral defense. Additionally, DCs can express the surface receptors like C-type lectin receptors (CLRs), which assist capturing of influenza viral particles as a response to the virus (Li el.al.,2011). Through these subsequent immune mechanisms, DCs contribute to initiation immune recognition against influenza virus in early stages (Li el.al.,2011).

In addition to their role in viral infection response, DCs serve as the main antigen-presenting cells in both innate and adaptive immunity. After influenza virus recognition, DCs make a bridge of viral antigens to present them on the major histocompatibility complex (MHC) molecules, and then activate naïve T cells (Steinman,2007). In a specific manner, the influenza virus uptake by DCs results in tight internalization of viral particles, which degrade into sort peptides and then loaded on MHC class I and II molecules' surfaces. The MHC class I molecules will present viral antigens to CD8+ cytotoxic T lymphocytes (CTLs), meanwhile MHC class II molecules will present them to CD4+ T helper cells (Palucka and Banchereau,2012). This antigen presentation is vital in virus-specific T cell response that is too necessary for clearing infected cells in providing long-lasting immunity. DCs can help in T cell differentiation within memory and effector cells, regarding to host's ability to provide protection against future infections (Palucka and Banchereau,2012).

There are multiple subtypes of DCs which have certain roles of immune response against influenza virus infection. The two major categories of DCs within lung tissues are conventional DCs (cDCs) besides plasmacytoid DCs (pDCs). The cDCs are related mainly in antigen presentation and adaptive immunity induction (). They can capture viral antigens, migrate to lymph nodes, and present viral antigens to T cells; but initiation of immune response to viruses can be contrarily monitored by pDCs to produce large amounts of type I interferons (IFN-α/β) during stage of viral recognition. This production of interferons will assist in establishing reduces viral replication in surrounding cells (Liu et.al.,2008). Both groups of DCs are essential during influenza infection. However, the interaction between these DC subtypes with other immune cells, like T cells and NK cells, will determine the prognosis of viral infection, influencing the risk of immune-induced tissue damage and viral clearance process (McGill et.al.,2013).

DCs not only regulate the magnitude but also initiate antiviral immunity in inflammation process. During influenza virus infection, DCs influence inflammatory response by secreting chemokines and cytokines. The activation of DCs can lead to pro-inflammatory cytokines release like IL-6, TNF-α, and IL-12, to promote the activation of rest immune cells, like NK and T cells, and to enhance antiviral responses (Palucka and Banchereau,2012). However, the inflammatory response is regulated to avoid excessive inflammation that damage tissue of the host in time of severe influenza infections. DCs can also produce IL-10 and other immunoregulatory cytokines for dampening harsh pathogenesis and promoting the resolution of infection (Palucka and Banchereau,2012). The ability of DCs in pro-inflammatory with anti-inflammatory signals balance is too important in determining the outcome of influenza infections to ensure effective viral immune response while minimizing host tissue damage (Palucka and Banchereau,2012), as shown in figure 2.

Dendritic cells can also contribute to resolution of influenza viral response. After the virus is cleared, DCs help to call tissue homeostasis again by promoting anti-inflammatory process and healing impaired tissue. Moreover, DCs act as generator of the memory T cells to provide long-term immunity against coming infections (McGill et.al.,2013). Memory T cells concluding of both CD8+ and CD4+ T cells are both essential in responding and recognizing rapidly to further infections by the same virus into organ of the host. By facilitating the memory formation and immune resolution, DCs will ensure that host immunity can respond to secondary influenza infections effectively and minimize long-term damage of host tissues as shown in figure 2.

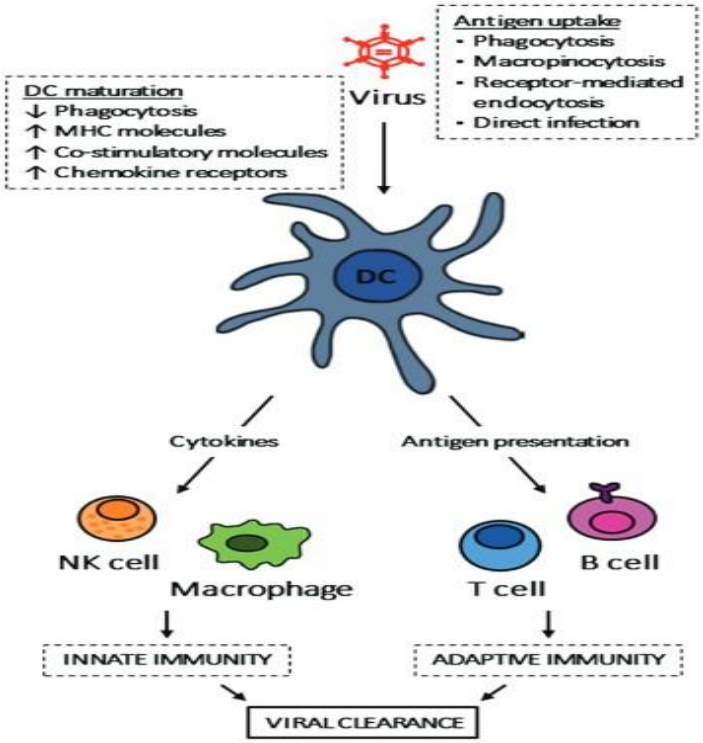

FIGURE 2. - function of dendritic cells in the generation of anti-viral (Kumar *et.al*.,2021)

DCs link which connects adaptive and innate immune systems can strongly respond to IAV, migrate to lymph nodes and can also upregulate co-stimulatory molecules. Additionally, they can present viral antigens to naive T cells and produce type I IFN that has direct antiviral effects promoting Th1-skewed adaptive response (Fernandez-Sesma,2007).

3.2.5 INNATE LYMPHOID CELLS (ILCS)

ILC1s produce IFN-γ upon initial viral infection, related to viral suppression, whereas ILC2s secrete IL-5 and amphiregulin which promote recovery of damaged lung tissue with eosinophil recruitment. The dynamic balance among ILC categories results in viral clearance and inflammation control (Kim et.al.,2019).

3.2.6 ΓΔ T CELLS

Are considered as unconventional T cells that behave like innate cells. They respond fast to infection and produce IFN-γ with cytotoxic molecules such as granzyme B. These cells are activated in independent way on classical MHC mechanisms and can clear viruses in early stages of lung infection (Kim et.al.,2019).

4. INTERACTIONS AND REGULATION

The high coordination among innate immune system cells is vital for effective control of viruses in order to avoid excessive inflammation upshots. For example, type I IFNs macrophages with DCs extra producing can enhance NK cell cytotoxicity; meanwhile neutrophil besides ILC activity can be regulated by immune system in order to organ and tissue damage. Imbalances in these immune interactions and responses can cause severe immunopathology, as seen in pandemic strains of IAV in viral lung infections (Kim et.al.,2019). Previous study in Iraq to measure the levels of some cytokines type that secreted by immune cells in patients infected with a viral infection showed a noticeable increase in their levels (Ahmed ,2024; Khalaf,2024).

5. CONCLUSION

Innate immune cells are very important in spontaneous control and viral infection clearance. Their fast activation and interplay express the integrity of human immune response against viral infection affecting the downstream of adaptive responses and to maintain tissue viability during viral infections. Understanding these pathways and immune

mechanisms highlights effective and early therapies in enhancing and regulate innate immunity components during severe influenza stages.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest

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