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"Review the IAV Influenza A virus"

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- **Abstract:**
During the 19th century, there were three major influenza pandemics that caused significant human suffering. These pandemics were caused by different strains of the influenza virus, namely H1N1 in 1918, H2N2 in 1957, and H3N2 in 1968. Throughout the century, a large number of people died and were infected, with an estimated 46 million fatalities and 50 million infections (Adam et al., 2017).
The respiratory tract has an inherent immune system. The virus may be eliminated by two mechanisms of the innate immune system. Firstly, by the action of dendritic cells (DCs), and secondly, through the involvement of non-immune macrophages (Manicassamy et al., 2010, Perrone et al., 2008). The innate immune response to the virus involves signaling via pattern recognition receptors (PRRs), which are ancient proteins located on the host cell membrane. PRRs transmit chemokines, eicosanoids, pro-inflammatory substances, and type-1 interferons (IFNs). Chemokines serve as chemo attractants for natural killer cells, monocytes, and neutrophils. These different types of immune system cells, together with phagocytic macrophages, work together to break down and eliminate infected or dead cells (Hogner et al., 2013, Jewell et al., 2007).

-Influenza virus:

Influenza is an RNA virus belonging to the Orthomyxoviridae family and has an enveloped structure. Shtyrya et al. (2009) is a well-established study in the field of human pathology, which is conducting known for causing both pandemics and seasonal epidemics (Neumann et al., 2009). The genome consists of eight RNA segments that encode eleven structural proteins. Viral replication begins rapidly during the first week after of infection. The fast multiplication of the virus results in severe respiratory complications, which subside only when the immune system suppresses the viral replication (Baum and Paulson, 1990; Imai et al., 2008). The influenza virus genera A and B have a distinct and considerable impact on human illness. On the other hand, the genera C and D are less noteworthy, with D not being associated with human disease at all (Neumann and Kawaoka, 2015; Iwasaki and Pillai, 2014). The influenza A virus (IAV) has two different kinds of surface glycoproteins, namely haemagglutinin (HA) and neuraminidase (NA). There are several variations of proteins, including 19 HA variants labelled as HA1 to HA19 and nine NA variants labelled as NA1 to NA9 (Tong et al., 2012; Tong et al., 2013). The unique mix of these two glycoproteins present in different viral subtypes determines their ability to infect certain species and transfer across other species. The entrance into cells is facilitated by the HA component. Table 1 indicates that the subtypes H1N1, H2N2, and H3N3 are capable of infecting humans, but H5N1 and H7N9 are classified as avian viruses. In order to enter the cell, HA specifically attaches to sialic acid molecules that are present on the cell membrane. Haemagglutinin, a cell-surface protein, was first discovered in 1942 as a protein associated with influenza that causes the clumping of red blood cells (Hirst, 1942). Neuraminidase, another cell-surface protein, was found to be an enzyme that breaks down glycoside bonds (Rogers et al., 1983). In the last century, many subtypes of influenza A have been the cause of human illnesses, as shown by Arzey et al. (2012), Ostrowsky et al. (2012), and Fouchieretal. (2004).

The cell surface hemagglutinin on IAV is the primary antigen that antibodies created during vaccination treatment target. IAV has the capability to often change the HA antigen epitopes, which effectively alters the structure of the antigen. This alteration allows the virus to evade the immune system and decrease its elimination by the innate immune response (Han and Marasco, 2011).

Neuraminidase, functioning as a receptor-disrupting enzyme, aids in the dissemination of the virus throughout the body by inducing the breakdown of target cells, therefore releasing replicated viral particles. Treatments for influenza Aim to hinder the activity of neuraminidase using medications such as oseltamivir, peramivir, and zanamivir (Spanakis et al., 2014). Neuraminidase functions by attaching to certain oligosaccharides on the surface of cells. Nevertheless, several scientists have uncovered disparities in the structure of neuraminidase between viruses that specifically affect humans and those that specifically affect birds. In humans, the activity of NA is linked to the Neu cα2,6Gal, but in birds, binding takes place via the NeuAcα2,3Gal (Rogers et al., 1983). In 1990, Baum and Paulson discovered the particular lectins that act as marker proteins and can distinguish between Neu cα2,6Gal and NeuAcα2,3Gal found in Sambucus nigra and Maackia amurensis, respectively. In addition, regarding the function of HA, there are specific ways in which different species are affected based on the connection between sialic acid and galactose.

Viruses that infect humans require the α2,6 linkage (Saα2,6Gal), while viruses that infect birds require the Saα2,3Gal linkage (Matrosovich et al., 1997; Rogers and Paulson, 1983; Suzuki, 1994) (Matrosovich et al., 1997; Rogers et al., 1983; Suzuki, 1994). The virus's capacity to cross the species barrier is limited by its reliance on species-specific linkage. This linkage is directly linked to the amino acid profile of the receptor binding site, which is responsible for the preferred connection between HA and the host cell's SA-Gla. The Influenza A virus specifically attacks epithelial cells, including both ciliated and non-ciliated cells, as well as giant alveolar cells and macrophages (Shieh et al., 2010). Non-ciliated epithelium mostly expresses the α 2,6 linkage, while ciliated epithelial cells predominantly express the α 2,3 linkage. Ciliated cells, found in both the large and small airways, are susceptible to viral reproduction (Chan et al., 2010, Childs et al., 2009, Crystal et al., 2008, van den Brand et al.,2012).

- The respiratory tract:

The lungs, which are sponge-like organs, facilitate the process of breathing by oxygenating the blood and removing carbon dioxide from the human body (Livingstone, 2005). The respiratory tract encompasses not only the lungs but also the tissues that serve as a pathway for transporting gases to the lungs. The system is split into two main sections: the upper respiratory tract, which includes the nasal cavity, pharynx, and larynx, and the lower respiratory tract, which consists of the trachea, bronchia, bronchioles, lungs, and alveoli (Marib, 2001).

- **Cellular Organization of the Respiratory Epithelium:**

  The respiratory tract is lined by a pseudostratified epithelium, which consists of many distinct cell types, in order to facilitate the gas exchange function of the lung. The conducting airways, which include the trachea and bronchioles, include many key kinds of cells: club cells, goblet cells, basal cells, and ciliated cells. The alveolar area contains several cells, including alveolar epithelial cells responsible for gas exchange .
  Club cells are situated in the tracheal and bronchiolar airways. Formerly known as Clara cells, club cells are exocrine cells located intercalary to ciliated cells. Their secretory role is substantial, as they generate immunological proteins and pro-inflammatory cytokines that regulate the innate immune response and maintain homeostasis. In addition, they release glycosaminoglycans that also contribute to the protection of the bronchiolar lining (Whitsett and Alenghat, 2015).

Goblet cells possess a distinctive morphology and predominantly secrete lipids and gel-forming mucin glycoproteins (MUC5AC and MUC5B) from intracellular granules holding mucin onto the epithelial lining. These expelled substances form a substantial component of the mucus, which serves to capture and remove inhaled bacteria and debris from the airway. A respiratory tract injury or infection has an impact on the abundance of goblet cells and the volume of mucus production. Both of these circumstances may stimulate the proliferation of goblet cells, resulting in excessive mucus production, which can cause harm to the respiratory epithelium and lead to

metaplasia (Whitsett & Alenghat, 2015). Increased goblet cell counts are linked to several chronic respiratory conditions.

Basal cells serve as multipotent progenitor/stem cells for the epithelium. Their location is underneath the stratified and pseudo-stratified epithelium (Norden, 2017). Within the lungs, they maintain the lining of the airways after they have been harmed, and they possess the ability to transform into various types of cells (Whitsett and Alenghat, 2015).

Ciliated cells are present throughout the respiratory system, spanning from the trachea to the bronchioles. Their primary role is to facilitate the removal of mucus and debris. In terms of structure, the cells in the top region of the airway are generally thicker and become progressively thinner as the airway goes lower. The ciliated epithelium's microtubular membrane, which extends from the basal frame, consists of the cilia column known as the 9+2 axonemes (Satir and Christensen, 2007). The ciliated cells play a crucial role in facilitating the removal of mucus from the airways, a process known as mucociliary clearance (MCC). The airway surface layer (ASL) consists of two fluid layers: the upper mucus layer, which traps pathogens and particles, and the lower periciliary layer (PCL), which has a lower viscosity. The presence of this layer facilitates the rhythmic movement of cilia underneath the mucus, enabling the effective removal of mucus by a coordinated wave-like motion of the cilia (Bustamante-Marin and Ostrowski, 2017; Wanner et al., 1996). Ciliated cells possess several mitochondria on their apical surface, which are responsible for supplying the energy required for the movement of axonemal dynein (Knowles et al., 2013).

The cells in the alveolar area differ from those in the airways and primarily function in gas exchange. The alveolar type I (AT1) cells are thin epithelial cells that form the lining of the alveoli. The thin membrane of AT1 cells enables efficient gas exchange between the alveolus and pulmonary capillaries by passive diffusion. Moreover, these cells have a crucial function in maintaining homeostasis. They facilitate the movement of water and ions across the alveolus, which is a vital physiological function that removes pulmonary oedema from the air sacs in patients (Bhattacharya and Matthay, 2013; Westphalen et al., 2014).

Alveolar type II (AT2) cells have a crucial function in safeguarding the lung epithelium from damage and infection by producing and releasing surfactant lipids and proteins. The secreted constituents of AT2 cells have a crucial role in preserving the decreased surface tension that prevents the collapse of alveoli during exhalation (atelectasis). The proteins synthesised by AT2 cells initiate the inflammatory response via a cytokine-mediated mechanism, which is an essential immunological defence against infections. AT2 cells may also function as progenitors of alveolar epithelium (Westphalen et al., 2014; Bhattacharya and Matthay, 2013).

- **The primary defensive function of the non-specific or innate immune system:**

There are two distinct forms of immunity, namely innate immunity and adaptive immunity. Adaptive immunity requires the preceding sensitization of lymphocytes to trigger a response led by B-cells or T-cells, which results in the production of antibodies. Nevertheless, innate immunity

does not require previous exposure to the antigenic epitope (Iwasaki and Medzhitov, 2010). The innate immune system is characterised by a collection of receptors that detect pathogen products. Moreover, antimicrobial and antiviral enzymes have a crucial function in defending against bacterial membranes and viruses. They may disable and eliminate these pathogens, especially when inflammatory cells, mostly macrophages, are present. The antimicrobial enzymes and peptides may be regarded as the primary means of protection, whereas the second line of innate defence is distinguished by receptors that identify pathogen-associated molecular patterns (PAMPs). PAMPs are microbial compounds that are distinct from those found in host cells. Pathogen-associated molecular patterns (PAMPs) transmit signals via pattern recognition receptors (PRRs). The respiratory tract's epithelial cells serve as physical barriers that impede the entry of germs and aid in the body's defence mechanisms. Epithelial antimicrobial defence, achieved via the action of enzymes and peptides, plays a crucial role in enhancing the response of phagocytes to eradicate invading bacteria in the body (Kenneth Murphy, 2018). The adaptive response is composed of antigens guided by pathogen-specific lymphocytes, which serve as the third line of defense. These mechanisms provide durable and targeted immunity over an extended period of time.
Innate immunity is activated in response to various pathogens, such as viruses, bacteria, fungi, and parasites. Each of these pathogens has the ability to spread and reproduce, leading to the development of diseases. The innate immune response is crucial in fighting against all types of infections. These pathogens may be either intracellular, like viruses that are obligatory intracellular pathogens that induce apoptosis and cell damage by cell assaults and reproduction, or extracellular, like mycobacterium (Grayson et al., 2005; Hornef et al., 2002). Intracellular pathogens may be classified into many categories: those that undergo unrestricted replication inside cells (e.g., viruses), those that use intracellular vesicles (e.g., chlamydia), or those that reside in macrophages (e.g., NK cells or T cells). The references used are Grayson et al., 2005, and Hornef et al., 2002.

Endotoxin is an extracellular component found on the outer membrane of bacteria that activates the innate immune system and leads to the release of cytokines. The studies conducted by Hornef et al. (2002) and Grayson et al. (2005) have shown that exotoxins generated by bacteria outside of cells may also lead to disease and negative health conditions. Both of these poisons elicit an immunological response and may potentially activate the adaptive immune system.

- **The first line of protection consists of physical and chemical barriers:**

The epithelium surface serves as the primary physical barrier of the innate immune system. The respiratory epithelium covers the whole respiratory tract, as previously mentioned. Physical barrier breaches may lead to the infiltration of pathogens into the epithelium, resulting in inflammation and illness. The mucosal epithelium of the respiratory system serves as a prominent physical barrier. The respiratory mucus that covers this epithelium collaborates with the ciliated epithelial cells to combat germs by means of mucociliary clearance. It is crucial to acknowledge that the healthy surface of the respiratory epithelium is defined by a normal microflora. This microflora consists of non-pathogenic bacteria, lactic acid, bacteriocins (as well as other peptides),

and antimicrobial enzymes (Aderem and Underhill, 1999). The innate immune defence mechanism also collaborates with other specialised immune cells. In 1905, Mechnikoff was the first to record the process of phagocytosis, which is used by mononuclear phagocytes and neutrophils to break down microorganisms. This process entails the internalisation of macroscopic particles, including infectious agents like bacteria and viruses, as well as senescent cells and cellular waste. Several types of mammalian phagocytes have been discovered, such as macrophages, dendritic cells (DCs), and neutrophil granulocytes (Gordon et al., 1986). The majority of macrophages possess surfaces that are linked to CX3CR1hi, CCR2, and Gr1 (Geissmann et al., 2003). Macrophages are characterised by the presence of macrophage mannose receptors (MMR), which are phagocytic receptors (Ezekowitz et al., 1990; Taylor et al., 1990). Importantly, this molecule is part of a group of C-type lectins that form a calcium connection with the carbohydrate domain. C-type lectins include transmembrane proteins, including DC-SIGN, Endo-180, and Dectin-1 (Cambi et al., 2005). A distinguishing characteristic of these transmembrane proteins is their incorporation of a carbohydrate ligand.

Antimicrobial proteins, known as chemical substances that hinder the development of bacteria, are released by both epithelial cells and innate immune cells. Antimicrobial enzymes, including lysozyme and phospholipase A2, specifically attack bacterial cell membranes and the phospholipids inside them (Cash et al., 2006). Various antimicrobial peptides, such as defensins and cathelicidins, have been discovered. Defensins are cationic proteins consisting of short sequences of 30–40 amino acids, which are distinguished by the presence of three disulfide linkages. They promote death in bacteria, fungi, and certain viruses by creating lesions in the cell membrane. Defensins may be classified into α, β, and У forms, each of which is linked to a certain amino acid sequence that provides defence against particular types of grammeme-positive bacteria, grammeme-negative bacteria, and fungi. Antimicrobial peptides are generated from inactive propeptides by proteolytic cleavage. Neutrophils generate α-defensins by enzymatically converting a propeptide of around 90 amino acids using cellular proteases, therefore removing the anionic propiece. The outcome of this procedure is a fully developed cationic defensin protein, which is then stored in the main granules. It is important to mention that the main granules of neutrophils include unique vesicles surrounded by a membrane, which are different from similar lysosomes. These vesicles contain various antimicrobial substances. Epithelial cells in the respiratory tract produce β-defensins and specific α-defensins. In regards to the У variations of defensins, they are present in several primate species, but in humans, these genes have become non-functional due to mutations (Ganz, 2003). Neutrophils and macrophages create the cathelicidin group of proteins. Cathelicidins exist as dormant propeptides before they are secreted. Cathelicidins are stored in secondary granules inside neutrophils. Activation of these granules happens through proteolytic cleavage after fusion with phagosomes and the action of neutrophil elastase, which is released by primary granules. There are other host defence peptides that play a role in the innate immunological defence of the respiratory tract>

- The innate immune defense system in influenza:

The influenza virus gains entry into the body via the nasal or oral pathways and proceeds to infect the mucociliary layer of the respiratory tract. The virus is disseminated by the immune system via two mechanisms: dendritic cells (DCs) and macrophages (Manicassamy et al., 2010; Perrone et al., 2008). The virus triggers an innate immune response by activating pattern recognition receptors (PRRs), which are ancient proteins located on the host cell membrane. PRRs transmit chemical signals such as chemokines, eicosanoids, pro-inflammatory substances, and type-1 interferons (IFNs). Chemokines exert chemotactic effects on natural killer cells, monocytes, and neutrophils. These diverse components of the immune system, together with phagocytic macrophages, collaborate to breakdown and eliminate infected and deceased cells. Eicosanoids and pro-inflammatory cytokines induce anorexia and fever in individuals with influenza. Interferons are secreted by several types of cells, such as dendritic cells (DCs), plasmacytoid DCs (pDCs), pneumocytes, and macrophages. Activated macrophages, dendritic cells (DCs), and plasmacytoid dendritic cells (pDCs) induce adjacent cells to downregulate protein synthesis, therefore safeguarding them from viral infection (Högner et al., 2013; Jewell et al., 2007). Interferon-stimulated genes (ISGs) play a crucial role in the host's response to viruses. A considerable number of these genes have been discovered; however, the exact function of many of them remains unclear (Högner et al., 2013; Jewell etal.,2007).

- Host defence proteins involved in influenza infection:

The host defence proteins play a crucial role in recognizing influenza and are considered a prominent category of innate immune mediators. Mucins are a diverse group of glycoproteins that are produced by goblet cells or surface epithelial cells. In the bronchia and trachea, MUC5AC and MUC5B, which are big proteins with a high amount of sugar molecules attached to them, play a significant role as innate defence proteins. Certain mucins, such as MUC1 and MUC4, are receptors located on ciliated cells at the top surface of the epithelia (Voynow and Rubin, 2009; Williams et al., 2006; Wheeler et al., 2011). The α2–3 sialylated O-glycan is a significant constituent of mucin (Lo-Guidice et al., 1997). The branching structure effectively captures influenza virus particles that adhere to α2–3 (Couceiro et al., 1993). Nevertheless, the virus's capability to infect the respiratory epithelium is likely due to the NA enzyme breaking α2–3 connections. C-type lectins also have a role in the body's defence against influenza. Surfactant proteins A and D (SP-A and SP-D) have a role in influenza infections via two mechanisms. SP-A has a sialylated component that specifically binds to the viral HA protein, therefore blocking the virus from connecting with cell receptors. However, it does not induce any reactions from the receptors. SP-D functions by inhibiting the entrance of the influenza virus into cells through its interaction with the viral HA or NA proteins (Kingma et al., 2006). Increased glycosylation of HA by SP-D reduces the pathogenicity of the virus (Reading et al., 1998).

conclusion:

suffering, with an estimated 46 million fatalities and 50 million infections. The respiratory tract has an inherent immune system that can eliminate the virus through two mechanisms: dendritic cells (DCs) and non-immune macrophages. The innate immune response to the virus involves signaling via pattern recognition receptors (PRRs), which transmit chemokines, eicosanoids, pro-inflammatory substances, and type-1 interferons (IFNs).

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