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A Review of Strategic Immune Evasion by Influenza Virus and Antiviral Response of Interferon

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Abstract

Influenza virus is -ss RNA virus of family orthomyxovirida. The viral genome codes for 11 different types of proteins however Hemagglutinin (HA) and Neuraminidase (NA) proteins are important in virus classification. The insertion of a basic amino acid residue to the cleavage site of HA converts the low pathogenic avian influenza to highly pathogenic avian influenza. The infection of same cell by different influenza virus of human and animal origin may lead to viral re-assortment. Pigs may act as mixing vessels for the re-assortment that is responsible for viral establishment and spread of infections to human. Virus evade the immune system probably due to the immune stress, viral non-structural proteins are involved in innate immune evasion. The selective pressure of antibodies and positive genetic selection also helps in genetic drift and evasion of humoral immune evasion. Several mechanisms are adopted to evade cellular immune evasion however mutation in virus specific T cell receptors is important. Mutations are used as weapons to evade immune responses. Upon detection of viral components interferons are produced and secreted in antiviral response. Sinus and lungs are common and predominantly induces the expression of IFN-λ instead of IFN-α. IFN-λ may be a potential vaccine candidate for the influenza virus infections. The antigenic instability of influenza virus is probably the root cause of outbreaks. Despite the well-built immune system, influenza virus adopts various competent strategies to evade immune response. The present review is to highlight the important evasion mechanisms of influenza virus, furthermore, IFN-λ are discussed as vaccine candidates.

Keywords: Influenza Virus; Interferons; Evasion; Vaccine; virus infections; infections to human; orthomyxovirida; ssRNA; Recruitment Domains; Nuclear factor; Signaling protein; population; Pathogen Recognition

Abbreviations: HA: Hemagglutinin; NA: Neuraminidase; NP: Nucleocapsid Protein; HPAI: Highly Pathogenic Avian Influenza virus; CARD: Caspase Activation and Recruitment Domains; MAVS: Mitochondrial Antiviral Signaling protein; NK: Natural Killer; ER: Endoplasmic Reticulum; TCRs: T cell Receptors; HLA: Human Leucocyte Antigen; TIR: Toll-Interleukin-1 Receptor; NF: Nuclear Factor; MAVS: Mitochondrial Antiviral Signaling protein

Introduction

Influenza virus belongs to the family orthomyxovirida. It is a major pathogen that has wide host range including humans, horses, pigs, mink, marine mammals, felids and a diverse range of domestic birds but shorebirds and wildfowl are considered to be the reservoir host in nature [1]. The influenza virus has an enveloped, segmented genome comprised of eight segments of negative sense-single stranded RNA (-ssRNA). The –ssRNA has coding ability of 11 proteins as Matrix proteins (M1 and M2), Hemagglutinin (HA), Neuraminidase (NA), Nucleocapsid Protein (NP), Polymerase basic protein (PB1, PB2, and PA), PB1-F2 and non-structural proteins (NS1 and NS2) [2]. Based on the surface glycoproteins the Hemagglutinin (HA) and Neuraminidase (NA), influenza viruses are classified into three types A, B and C. Viral entry in the host cell is mediated by receptor binding and membrane fusion activity of HA while NA mediates the release of viral progeny by enzymatic cleavage.

The Influenza viruses that represent 16HA and 9NA antigenic subtypes have been identified in poultry and wild birds throughout the world. These antigenic subtypes can be found in different arrangements as H1N1, H16N3 [3]. Hemagglutinins are initially synthesized as a single polypeptide precursor (HA0), later these are cleaved into HA1 and HA2 subunits by proteases. The introduction of influenza virus subtypes H5 and H7 into the poultry is reported to be highly infectious and may cause outbursts of highly pathogenic avian influenza (HPAI, earlier known as B fowl plague) but this is not associated with other HA subtypes [4]. The introduction of basic amino acid residues into the cleavage site of HA0 converts the low pathogenic avian influenza virus to high pathogenic avian influenza virus, this HA0 helps in systemic replication of the virus [5]. The highly pathogenic influenza virus is responsible for the outbursts, as recurrent outbursts were recorded by influenza viruses of subtype H5N1 in Europe, the Middle East, Asia and Africa; H5N2 in Italy, Mexico and Texas; H7N1 in Italy; H7N3

in Pakistan, Canada, Australia and Chile; H7N4 in Australia; and H7N7 in the Netherlands. Potential pandemics of influenza virus makes it a public health concern [6]. During the 20th century, four pandemics were reported related to the novel subtype of influenza A virus. In 1918-1919 "Spanish Flu" swept the continents and affected almost 500 million people and caused over 40 million deaths. The pandemics in the recent past from swine-origin virus started infecting humans that needs serious attention to the contrary consequences might be devastating [7].

Human as the line of infection

The RNA of influenza viruses comprises eight distinct genes, when different strains of influenza A virus co-infect a single cell then re-assortment can occur. The re-assortments can occur between influenza virus of avian and human origins, probably the reason for antigenic shifts. The two viral strains H2N2 and H3N2 cause pandemics during the years 1957-1968 because of surface glycoproteins (HA) and PB1 gene switching. [8]. The infection of avian influenza in human beings remains for a short period of time that may be related to the one or more gene segments hindering the establishment of infection [9]. The pigs, however, are the common host for both avian and human influenza virus, they may be considered as mixing vessels where both of the human and avian viral strains re-assort their genes. The specific cellular receptors are present in pigs for both human and avian influenza virus that help in genetic re-assortment of viral strains for the release of novel genes. The genetic re-assortment results in providing necessary genes for the establishment and spread of influenza virus infection in the human population. The human may be considered as immunologically naive due to the presence of distinct hemagglutinin surface glycoproteins on the re-assorted viral genome [10].

The first report of Highly Pathogenic Avian Influenza virus (HPAI) to infect the human was recorded in 1959, the subtype H7N7 infected a patient with hepatitis. Later on, HPAI virus subtype H7N7 infected a laboratory worker with the development of conjunctivitis and LPAI subtype H7N7 to an animal handler from an infected seal [11]. The flow of influenza virus from birds to humans is also reported in many of the studies, the bird flu attack in Hong Kong China by H5N1 subtype of influenza virus swept three poultry farms. The decedents of this H5N1 subtype infected a child in the same regions leading to fatal viral pneumonia with violent complications. This was the first reported case of severing clinical respiratory disease in human due to avian influenza virus [12]. The LPAI subtype H7N7 infection cause mild conjunctivitis while HPAI subtypes H7N7 and H5N1 both cause intense respiratory diseases and mortality. The human is the line of infection for the influenza virus since its first report in 1956 until now many of the cases have been reported mainly due to H5N1 and H7N7 subtypes [13].

Immune evasion strategies adopted by influenza virus

The escape from the immune system is attributed to the immune stress. The binding of proteins with the component responsible for provoking the immune response is a key factor responsible for innate immune evasion. New influenza viral strains are established through combination of the immune pressure in human population and extraordinary mutation rate. This leads to evasion of the prevailing cellular and humoral immune responses by influenza A virus [13].

Innate immune evasion by influenza virus

The evasion of innate immune response is accomplished by viral transformation, the viral nonstructural proteins (NS1) particularly adopt several means to irritate the innate immunity against the virus. The retinoic acid-inducible gene I (RIG-I) receptors that work as sensors for viral recognition are inhibited by viral NS1 proteins, thus the RIG-I mediated recognition of 5'-phosphorylated ssRNA of the virus is hindered. Furthermore, the NS1 proteins interact with the coiled-coil domain and prevent the oligomerization of tripartite motif-containing protein 25 (TRIM25). Thus, it inhibits the ubiquitination of TRIM25-mediated RIG-I Caspase Activation and Recruitment Domains (CARD) required for the downstream signaling. The other RIG-I mediated factors responsible for viral recognition are also inhibited by viral NS1, as activation and translocation of activation and transcription factor (ATF-2/c-Jun), Interferon regulatory factor-3 (IRF-3) and Nuclear Factor (NF)-κB [14].

The RNA in influenza virus contains PB1 proteins in its second segment and a PB1-F2 protein that share the open reading frame with PB1 protein. The PB1-F2 has contained a serine at its position 66) while PB2 variants contain an aspartic acid at position 9. These proteins are thought to promote virally-induced cell death in all cell types. NS1 viral proteins utilize PB1-F2 and PB2 proteins to block the synthesis of IFN-β by Mitochondrial Antiviral Signaling protein (MAVS). The interferes with gene expressions especially the genes responsible for provoking an immune response at the cellular level is also thought to be mediated by PA-X, a new viral protein discovered [15].

Influenza A virus provokes the production of the interferon-dependent double standard Protein Kinases (PKR). The activation of PKR inhibits the viral replication and induce cellular apoptosis. Thus, for the influenza virus to replicate, the activity of PKR must be inhibited, and it is controlled by the recruitment of cellular p58IPK [16]. The p58IPK is the cellular protein that interferes with PKR activation, but it gets inactivated by a complex formation with heat shock protein 40 (hsp40). Here the Nucleoproteins (NP) of influenza virus plays part in the release of p58IPK from p58IPK-hsp40 thus NP indirectly inhibit the activity of PKR. Of the three proteins produced by influenza virus one is Matrix proteins (M1 & M2) and matrix proteins M2 are important in viral replications. This M2 protein also has the ability to binds the p58IPK-hsp40 complex, promotes the release of p58IPK leading to prevention of PKR phosphorylation and probably augment the release of viral particle [17].

The nonstructural proteins (NS1) of influenza A virus is involved in the inhibition of interferons that are primary antiviral

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agents in the body. The expression of SOCS (Suppressor of Cytokine Signaling) proteins is induced by influenza A infection which inhibits IFN α/β receptor signaling by the suppressing the Janus kinase (JAK)/ Signal transducer and activator of transcription protein 1 (STAT) [18]. Moreover, during the interference with innate signaling, influenza A virus imparts effects on cells of innate immunity. Monocytes are not capable to differentiate into mature dendritic cells in the course of influenza A virus infection [19].

The maturation of dendritic cells is inhibited by NS1, and thus responsible to inhibit the induction of virus-specific responses of the cluster of differentiation-8+ (CD8+) T cell [20]. The Natural Killer cells (NK) present in the innate immune system are also evaded by the Influenza A virus. Continuing mutation in glycosylation sites of influenza virus, the recognition of HA proteins is decreased by Natural Killer (NK) cell in virus-infected cells. Moreover, influenza A virus can themselves infect and kill NKC's [21].

Humoral immune evasion by influenza virus

The influenza A virus adopts several mechanisms to escape from the humoral immune response. The viral RNA becomes more error-prone at the transcriptional modification as they lack proofreading activity of viral RNA polymerases. All this results in mis-incorporation of nucleotides and genomic modification leading to the viral imitation [22]. The selective pressure of antibodies that exist in human population persuaded after influenza virus infection/ vaccination, but the re-assortment of the genes and positive selection of favorable genes leads to the genetic drift in influenza virus. This genetic drift permits the influenza virus to evade the immune system by providing novel haemagglutinin to increase viral replication [23]. The introduction of this antigenically distinct serotypes in human population is termed as a genetic shift in case of influenza virus. These novel haemagglutinin containing viruses become a source of pandemics in the human population as antibodies are absent against newly developed strains of influenza virus with novel HA at different positions of their genetic backgrounds [24]. The introduction of these antigenically distinct influenza virus subtypes in human may follow a zoonotic transmission. The influenza virus exchanges their genetic segments with those of swine influenza virus and causes pandemics in human [25]. The swine serve as mixing vessels as they have receptors for both of human and swine influenza A virus in their epithelial cell of respiratory tract but for the genetic exchange, the simultaneous infection of both viral stains is needed [26]. The similar re-assortment of influenza A/ H1N1 caused pandemics in 2009 [27]. The re-assortment of virus genome makes the conserved sequences unapproachable for the antibodies to recognize, as the surface proteins/ fusion peptides are buried inside following re-assortments [28].

Cellular immune evasion by influenza virus

Influenza virus adopts several tactics to avoid detection by virus-specific T cells. The extensive mutation and increased pressure of virus-specific T lymphocytes are means to evade the cellular immune response to the influenza virus. In case of influenza virus, more non-synonymous mutations happen in the Cytotoxic T Lymphocyte (CTL) region of Nucleoprotein (NP) that is indicative of increased mutational pressure on CTLs. The liberation of antigenic peptides from proteins and antigen processing in the Endoplasmic Reticulum (ER) by the Transporters Associated with antigen processing (TAP) are also involved in the mutation of CTL epitopes [29]. The substitution of amino acids interferes with CTL presentation, there may be a substitution at the anchor site leading to complete loss of epitope making it unable to bind to the class one major histocompatibility complex (MHC-1) molecule [30]. There may be a mutation in T cell Receptors (TCRs) rendering it incapable to recognize the antigenic epitopes [31]. Such mutations are used as weapons to escape the cellular immune system by the influenza virus and other viral pathogens that give a chronic infection to the host. One such example is a substitutional mutation in Human Leucocyte Antigen (HLA) restricted NP epitope at an anchor residue proceeding to lose to cytotoxic activity by the CTLs in influenza virus infection [32]. The higher degree of mutation in CTLs or maybe the loss of complete epitope where existing CTLs are unable to recognize the epitopes are the reasons for the influenza virus to escape from humoral as well as the cellular immune response [33].

The signs of antigenic drift are also evident from the distinction in epitopes that edicts the specific response to the CTL against the contemporary viruses with historic strains, it also accounts for the cross-reactivity in cytotoxic T cells [34]. The accumulation of these substitutional mutations in the arginine to glycine at the position 384 of the nucleoproteins renders the CTLs ineffective to perform their functions as the CTLs are unable to recognize the mutated epitopes of the virus [35].

Virus replication by hijack immune system

The invasion of influenza virus involves multiple steps, the receptor-mediated viral endocytosis occurs following the attachment of viral Haemagglutinin (HA) to the sialic acid-containing receptors. The initial attachment of the virus to the receptors is followed by pH-dependent fusion and release of ribonucleoprotein complex form the viral genome [36]. The sailyted glycoproteins exhibit two main types of relations between sialyl-oligosaccharides (SAs) and galactose (Gal) are SA-α2, 6-Gal, and SA-α2, 3-Gal. In case of avian influenza virus, the Haemagglutinin (HA) proteins attach to the SA-α2, 3-Gal while the HA proteins of human influenza virus bind to the SA-α2, 6-Gal and adopt the endocytic pathway to enter into the host cell. The fusion of sialyl-oligosaccharides (SAs) and galactose (Gal) linkages and a decrease in pH of endosome lead to the conformational changes in the haemagglutinin proteins exposing the hydrophobic fusion peptides. The virus internalizes into the cytoplasm following the synthesis of vesicles with the endosome and forms viral Ribonucleoproteins (RNP) complexes with nucleoproteins, RNA dependent polymerase II, PB1, PB2, PBA subunits these complexes are transported into the nucleus where they cut-

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apart [37]. In the nucleus, the heterotrimer (PA-PB1-PB2) of viral ribonucleoproteins ingrained in the matrix of the nucleus. The virus adopts cap filching protocol to synthesize viral RNA and use RNA processing machinery of the host as poly A tail together with 5′-capped RNA primer sequences. Here viral non-structural proteins 2 (NS2) referred to as viral NEPs are essentially involved in hijacking the host transcriptional machinery by inhibiting the host's mRNA processing and import of viral RNPs.

The binding of viral RNA to the cap bearing oligonucleotide of host released from cleavage of host mRNA is necessary to initiate the elongation of cap bearing oligonucleotides. This initiation is supported by the signaling of RNA and Cap binding subunits PB1 and PB2 respectively. Pol II offers many of the necessary tools and raw materials required for appropriate construction and exportation of mRNA to translate into proteins [38]. The viral messenger RNA and complementary RNA (cRNA) are synthesized from the viral RNP templates in the nucleus. The mRNA is exported to the cytoplasm for the synthesis of viral proteins that are re-exported to the nucleus for final assembly. The cRNA is involved in synthesizing negative sense mRNA and amplification of mRNA to form progeny viruses [39]. The viral nucleocapsid assembled in the nucleus and transported into the cytoplasm from where they form buds followed by the release of the new viral particles [40].

Antiviral immune response to influenza virus

The significance of interferon (IFN) in the activation of innate immune and adaptive immune activations cannot be neglected responses. As the excessive response of cytokine is often associated with highly pathogenic viruses [41]. When viral components are detected within the infected cells, the IFNs are expressed and secreted, and subsequently IFNs bind to its specific surface receptor proceeding to the establishment of the 'antiviral state' by upregulating various Interferon-Stimulated Genes (ISGs), thus efficiently prevent promotion of viral replication and spread [42]. Of these interferon-stimulated genes, various genes have been recognized to possess the direct anti-influenza virus activity. The ISGs stimulated Mx family of GTPases are considered to form oligomeric rings around the nucleocapsid to prevent viral replication and/or nuclear import [43]. The viral entry is limited through the IFN-induced transmembrane (IFITM) family members (especially IFITM3) by interfering with the fusion between the endosomal and viral membrane and further viperin, that hinders the budding of the virus also limits the released viral particles from invaded cells [44].

On the basis of amino acids sequence and signaling receptors, the interferon is grouped into three. The viral infections especially influenza virus undergo direct up-regulation of type I and the type III IFNs that Includes IFN-α, IFN-β and IFN- λ subtypes respectively [45]. Whereas, type II IFNs have IFN-γ is secreted by activated NK cells and T lymphocytes. In the course of influenza virus infection, Macrophages, epithelial cells of airways and plasmacytoid dendritic cells (pDCs) are the key activators of IFN [46]. Primarily airway epithelial cells are documented for the production of type III IFN whereas alveolar macrophages and dendritic cells are potential activators of type I interferons [47].

The viral ligands and signaling receptors involved in the activation of type I and III interferons are considered to be the same in virus-infected epithelial cells. Moreover, there is complete overlap of the upregulated ISGs in airway epithelia in response to type I and III interferons upon influenza virus infection [48]. The surface of all the cells express receptors of type I IFN whereas only the epithelial cells of gastrointestinal and respiratory tract express receptors of type III [49]. The activation of the immune response to influenza virus is attributed to this differential expression of type III IFN receptor in the epithelium of lungs [50].

Receptor-based Induction of Interferon

The cascade IFNs are stimulated in response to the recognition of pathogen-associated molecular patterns (PAMPs) on the infected cells. The Pathogen Recognition Receptors (PRRs) essentially involved discrimination of the self and non-self-molecules are also involved in the stimulation of IFNs by influenza viruses. PRRs as Toll-Like Receptor (TLR) family of transmembrane proteins identifies different kind of microbial ligands and stimulate IFN expression signal downstream either through TTRIF [Toll-Interleukin-1 Receptor (TIR)-domain-containing adaptor inducing interferon (IFN)- β] adaptor proteins or MyD88 [myeloid differentiation primary response 88], depending on the particular TLR [51]. TLR-7 receptors recognize ssRNA of attacking the influenza virus to plasmacytoid dendritic cells (pDCs) for the release of IFNs [52]. TLR-7 is unessential for the induction of IFNs by other RNA viruses including influenza virus that infects the cells other than pDCs probably due to its localization [53]. TLR-3 recognizes dsRNA and infection of influenza virus can also activate TLR3. It plays role in the activation of pro-inflammatory signaling pathways in the context of influenza virus infections [54].

Specificity of type III interferon

Recently, discovered interferons are type III IFNs categorized as IFN-λ1, IFN-λ2, and IFN-λ3, also designated as interleukin 29 (IL-29), IL-28A, and IL-28B, respectively [55]. The signaling of type III IFNs is mediated by IFN-λ receptor complex, the core components of IFN-λ receptor complex are IFN-λR1 chain and a common IL-10R2 chain that also serves as the second subunit of the IL-22, IL-10, and IL-26 receptor complexes [56]. Regardless of their alterations, phosphorylation of the receptor-associated tyrosine kinases, Tyk2 and Jak1 occurs by the activation of either the type I or type III IFN receptor, that further phosphorylate STAT1 and STAT2 [57]. The phosphorylated STATs with the DNA-binding proteins the interferon regulatory factor 9 (IRF9) forms a complex termed as interferon-stimulated gene factor 3 (ISGF3). The translocation of the ISGF3 complex into the nucleus and its attachment to the Interferon-Stimulated Response Element (ISRE), that act on the promoters of Type-I and Type- III responsive genes as the activation of ISGF3 by either type of IFN leads to the transcriptional up-regulation of the same set of ~300

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genes that arbitrate similar activities [58]. The mechanism of III IFN receptor is depicted.

Type III Interferon the sterling vaccine candidates

As the type III interferon use IFN-λR1for the activation of JAK-STAT signaling from pathways [59]. The IFN-λR1 have the specialty in their expression as they are not unanimously expressed for type I and type II interferon except for the type III IFN. This unique expression of IFN-λR1 receptors for IFN-III may be helpful in the eradication of viral infection by eliciting the immune response against the invading viral pathogen [60,61].

Similarly, the viral infection of the respiratory tract especially the sinus, and lungs are common and predominantly induces the expression of IFN-λ instead of IFN-α. No doubt the inflammation following the respiratory infection by avian influenza virus is well controlled by the IFN-α but the over elicitation of the immune response by IFN-α leads to the immune pathology [62,63] Perhaps this immune pathology is due to the frail action of IFN-α on the endothelial cells of the respiratory tract.

Thus IFN-λ may be considered as a potential candidate for the vaccine development against the influenza virus infection [64]. The IFN-λ have the ability to suppress the immune response in indoleamine 2, 3 dioxygenase upregulation. The therapeutic properties of IFN-III can be used in controlling and eradication of influenza virus infection [65-67].

Conclusion and future perspective

Global health is greatly influenced by influenza A virus. The plethora of strains of this zoonotic virus comprises different pathogenic profiles. The consequences of the pathogenesis of influenza A virus are dependent on the interaction between host cellular protein and virus. By these interactions influenza A virus hijacks the molecular machinery of host and accomplish the life cycle. These interactions may provoke host immune defense to eliminate the virus. Humoral and cellular immunity play a significant role in protection from influenza A virus infection. But due to the high mutation in influenza proteins (HA and NA), it is becoming obvious that vaccine strategies are required for protection from influenza A virus infection, which can induce strong and persistent immunity.

In the future novel vaccines candidate can be developed through manipulation of viral genetics and interferon. The targeted deletions in viral genome that codes for IFN antagonists is favorable candidates for the development of interferon based therapeutic strategies.

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