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Importance of Sialic Acid Receptor and RIG-I in Innate Immune Response of Poultry

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Abstract

Avian influenza is a viral infection found in domestic poultry and a wide range of other birds. Wild waterfowl and shorebirds are often asymptomatic carriers. RIG-I (retinoic acid-inducible gene I) and Toll like Receptors (TLRs) are well expressed in water fowls. In contract to this RIG-I gene were absent in chicken genome and makes the poultry more susceptible. Avian influenza outbreaks occur in poultry, depopulation (stamping out) of infected flocks is carried out with biosecurity measures.

Introduction

Waterfowl are the natural reservoir of Avian Influenza and Virulent Newcastle disease viruses and they play a role in the maintenance of HPAI (H5N1) viruses. Infected waterfowls are asymptomatic and excrete high concentrations of virus that are pathogenicto other poultry species. In poultry, low pathogenicity strains typically cause respiratory signs. High pathogenicity strains may cause widespread organ failure and sudden, high mortality. Avian influenza viruses are type Aorthomyxo viruses (Alphainfluenza virus or Influenza virus A). Influenza viruses are further divided into 16 hemagglutinin (H1-16) and 9 neuraminidase (N1-9) subtypes based on their hemagglutinin (HA) and neuraminidase (NA) surface glycoproteins. There is a difference in the innate immune response between the water fowls and poultry. RIG-I (retinoic acid-inducible gene I) and Toll like Receptors (TLRs) are well expressed in water fowls. In contract to this RIG-I gene were absent in chicken genome and makes the poultry more susceptible.

The avian immune system is the system of biological structures and cellular processes that protects birds from disease. The primary components of innate immunity of poultry are-

- Physical and chemical barriers, such as feathers and skin, epithelia and production of mucus.
- Phagocytic cells, including macrophages and natural killer cells.
- Complement proteins and mediators of inflammation.
- Cytokines.

Overall, the innate immune response to infection (bacterial or viral) is an immediate reaction designed to control and inhibit virus growth and spread and aid in developing pathogen-specific protection through the adaptive immune response.

Modifications in Avian Immune System

- Birds lack functional eosinophils, although avian heterophils functionally replace mammalian neutrophils.

• Birds lack lymph nodes, but have some avian specific primary lymphoid organs such as the bursa of Fabricius, which is the site of hematopoiesis and necessary for B cell development.

• Harderian glands in birds play an important role in adaptive immune responses.

• Birds and mammals use partly similar and partly distinct molecules for the same immunological antiviral mechanisms including TLR, defensins, cytokines, chemokines, antibodies and others.

Sialic Acid Receptor Distribution

Influenza virus gain entry into cells based on the availability of glycoprotein receptors with terminal sialic acid in appropriate linkages to which influenza hemagglutinin molecules bind. Human adapted influenza viruses prefers sialic acid α-2,6-galactose whereas, avian strains prefers sialic acid α-2,3-galactose. It was found that all the galliformes had both α-2,3-galactose and α-2,6-galactosesialic acid receptors in respiratory and intestinal tissues, whereas α-2,6-Gal SA receptors were absent from the intestine of water fowls. Kuchipudi *et al*. (2021) found that chicken trachea had dominant α-2,6-galactose receptor, while in ducks the α-2,3-galactose receptors were most abundant. These results suggest that chickens are more important hosts for the generation of influenza viruses with increased ability to infect humans (virus binds to sialic acid α-2,6-galactose).

Influenza Virus Pattern Recognition RIG-I like Receptors

RIG-I, MDA5 and LGP2 are three cytoplasmic RNA sensing proteins which included in RIG-I like receptors (RLRs) family and all three members share DExD/H box RNA helicase domain that recognizes dsRNA viruses whereas, C-terminal regulatory domain (RD) that undergoes a conformational change when the helicase domain binds to its target. MDA5 and RIG-I possess a tandem pair of N-terminal caspase activation and recruitment domains (CARD) that initiate a signalling pathway leading to type I interferon expression, but not LGP2.

RIG-I

RIG-I is the most important of the RLR family for recognizing influenza viruses and it is responsible for the early epithelial type I interferon responses in an influenza infection. RIG-I recognizes 50-triphosphorylated RNA “panhandle” structures formed by the complementary ends of each influenza genome segment. In ducks, RIG-I is ubiquitously expressed, especially in mucosal tissues, whereas chickens lack the RIG-I gene, hence, chickens are extremely susceptibility to influenza disease.

•RIG-I and Toll-like receptor 7 (TLR7) are the main detectors for influenza viruses. RIG-I involves in the cytosolic detection of initially infected cells by influenza, whereas TLR7 is responsible for IFN-α production by leukocytes.

• Respiratory tract epithelial cells are initially infected with H5N1 strains. Since, ducks have an intact and functional RIG-I, while chickens appear to lack the gene for the receptor. However, chickens have MDA5 receptor, which uses the same signalling pathway as RIG-I.

• RIG-I is a cytoplasmic RNA sensor (10), and triggering by influenza virus leads to production of IFN-β and expression of downstream IFN stimulated antiviral genes.

• RIG-I lacks from the chicken genome sequence which is derived from the ancestral chicken Red Jungle Fowl. Many authors reported that that chickens may have lost RIG-I before their domestication process.

Action of RIG-I on Viral Replication

RNA virus, can be detected by the pattern recognition receptors (PRRs)

↓

That recognizes evolutionarily conserved structures known as pathogen-associated molecular patterns (PAMPs)

↓

Leads to cytokines storm and actives adaptive immune response

Recognition of PAMPs by PRRs, either alone or in heterodimerization with other PRRs

↓

Like toll-like receptors (TLR); nucleotide-binding oligomerization domain proteins (NOD); RNA helicases, such as retinoic acid-inducible gene 1 (RIG-I) or MDA5; C-type lectins)

↓

Induces intracellular signals responsible for the activation of genes that encode for pro-inflammatory cytokines, anti-apoptotic factors, and antimicrobial peptides

↓

The virus is first recognized by host sentinel proteins, including TLR and NOD proteins

↓

Producing rapid signalling and transcription factor activation

↓

Lead to production of soluble factors, including interferon and cytokines

↓

Limit viral replication

MDA5

MDA5, the second member of the RLR family, detects uncapped mRNA and long dsRNA (>1 kbin length) in the cytoplasm. MDA5 is a detector of long double-stranded RNA, polyinosinic–polycytidylic acid [poly (I:C)], and picornaviruses. RIG-I and MDA5 may share similar signaling features and structural homology. MDA5 is uniquely triggered during virus infections or in the presence of a synthetic RNA polymer consisting of annealing strands of inosine and cytosine, poly (I:C).

LGP2

The third member of the RLR family, LGP2, may act as a positive or negative regulator of RIG-I. It lacks its own CARD domains but can oppose RIG-I signaling either by competing for RNA ligands or by directly repressing its CARD domains with its own regulatory domain.

Inhibition of Host MDA5 by Virus

Upon viral infection, the cytosolic receptor MDA5 recognizes long viral dsRNAs and initiates an antiviral signaling cascade by interacting with the downstream partner MAVS, located to the mitochondria. This signaling pathway leads to the establishment of an antiviral state characterized by expression of antiviral cytokines and interferons. The MDA5 protein belongs to the RNA helicase family.Several viruses encode proteins that directly interfere with MDA5 to decrease interferon production by infected cells. For example, all viruses from paramyxovirinae subfamily encode a protein V able to interact with MDA5 and block MDA5 interaction with MAVS, its downstream partner in the cascade (Brisse Morgan and Hinh Ly, 2019).

Toll-like Receptors (TLRs)

The Toll-like receptors (TLRs) play a fundamental role in the activation of innate immunity by recognizing pathogen-associated molecular patterns, including the genome of single-stranded RNA viruses such as NDV, through TLR7, in mammals as well as in the chicken.

• TLR3 is a membrane-bound protein that resides in an endosomal membrane where it recognizes dsRNA and polyinosinic-polycytidylic acid (poly I:C), a synthetic analogue of dsRNA (Alexopoulou *et al.,* 2001). TLR3 plays an important role in defending against viral invasion by up regulating the expression of antiviral type I IFN. TLR3 recognizes dsRNA formed during viral genome replication or transcription.

• TLR7/8 sense viral derived ssRNA, while TLR9 senses the unmethylated cytosine phosphate guanine (CpG) motifs of viral DNA.

• TLR7 has been identified in birds.

•TLR8 is a pseudogene in chickens, which is disrupted by several introns, while it has been proposed that TLR9 has been deleted from avian genomes over evolutionary time.

Conclusion

Prevention is accomplished by biosecurity. When H5 or H7 avian influenza outbreaks occur in poultry, depopulation (stamping out) of infected flocks is usually carried out. In addition surveillance of nearby flocks with culling if disease is detected.

References

Alexopoulou, L., Holt, A.C., Medzhitov, R., Flavell, R.A., 2001. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* 413, 732-738. doi: 10.1038/35099560. PMID: 11607032.

Kuchipudi, S.V., Nelli, R.K., Gontu, A., Satyakumar, R., Surendran, N.M., Subbiah, M., 2021. Sialic Acid Receptors: The Key to Solving the Enigma of Zoonotic Virus Spillover. *Viruses* 13(2), 262-269. doi:10.3390/v13020262.

Morgan, B., Ly, H., 2019. Comparative Structure and Function Analysis of the RIG-I-Like Receptors: RIG-I and MDA5. *Frontiers in Immunology* 10, 1586-1595. doi:10.3389/fimmu.2019.01586.