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Immunosuppressive viruses in Chicken

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Review Article

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Abstract

Immunosuppression comprises ineffective antibody production as well as innate and cellular immunities. It was originally defined as "a state of temporary or permanent dysfunction of the immune response resulting from damage to the immune system and leading to increased susceptibility to disease" **Dohms and Seif (1984).** Immunosuppressive conditions can make flocks more vulnerable to infections and fatalities, decrease the efficiency of vaccines and feed conversion, and have an impact on the cost of production overall and condemnation at processing. They consequently have significant detrimental effects on the health, welfare, and production efficiency of poultry worldwide. Protecting health and productivity in the chicken business requires an understanding of the etiology of immunosuppressive illnesses.

The Research Topic aims to collect contributions on progresses made in understanding avian immunosuppressive diseases, especially virus-mediated immunosuppression and immunoevasion, persistent infection, pathogen-host interactions, innate immune response, signal transduction, cytokine expressions. It also aims to highlight challenges and opportunities for future research in novel vaccine development, diagnosis, and control of avian immunosuppressive diseases.

Keywords: *Immunosuppressive; viruses; infectious bursal diseases virus; chicken infectious anemia.*

Infectious bursal disease

The infectious bursal disease virus (IBDV) prefers bursal B cells over other cell types. Massive B cell degeneration in lymphoid organs is a symptom of infectious bursal disease (IBD), which also causes lymphopenia (immunesuppression) and secondary infection in afflicted birds **Lukert and seif (1997).** Dysfunction of the immune system, or immunosuppression, increases the risk of contracting diseases. **Schat and Skinner (2008).** One of the biggest issues posing a threat to the poultry business is immunosuppression disease's.

IBDV is divided into two different subtypes known as serotypes I and II **Lukert and Saif (1997).** Serotype I viruses cause disease in chickens, whereas serotype II viruses, which are isolated from turkeys and are not infectious to chickens, do not **McFerran *et al.* (1980).** The pathogenicity and bursal cell replication efficiency of IBDV serotype I isolates vary **Tsukamoto *et al.* (1995).** Serotype I virus vari-

ant strains started to appear in the US, Western Europe, and some regions of Southeast Asia around 1990. These strains were more virulent than traditional strains and resulted in fatality rates of over 50% **Lukert and Saif (1997), Murphy *et al*. (1999).** These variant strains, which are antigenically distinct from the classical strains and resistant to the most recent commercial vaccines, were obtained from flocks that had received vaccinations with the classical strains. When one of the classically virulent IBDV (vIBDV) strains, F52/70, was compared to the variant/very virulent (vvIBDV) strain, the mortality rate increased from 50% with vIBDV to 90% with vvIBDV, and the immunosuppression across the lymphoid organs became more severe.

Structure of IBD virus

IBDV belongs to the family Birnaviridae and the genus Avibirnavirus **Lukert and Saif (1997), Murphy *et al*. (1999).** Its genome is made up of two 6 kb long linear double-stranded RNA segments called A and B. Two partially overlapping open reading frames (ORF) are present in segment A, which is 3.2 kb in size. A polyprotein that is autocatalytically split into two structural proteins, VP2 and VP3, and a serine protease, VP4, is encoded by the biggest ORF **Birghan *et al*. (2000); Lejal *et al*. (2000).**

The primary antigenic location that triggers neutralising antibodies (Abs) is found in VP2, which is regarded as the main host-protective antigen **Fahey *et al*. (1998).** This polypeptide has at least two neutralising epitopes. The virus -neutralizing antibodies that VP2 produces shield susceptible chickens from vIBDV. It is in charge of viral virulence, tissue-culture adaptability, and antigenic variation **Brandt *et al*. (2001).**

VP2 is folded into the base, shell, and projection domains (respectively) **Bottcher *et al*. (1997); Coulibaly *et al*. (2005).** The VP2 N- and C-termini, which are conserved, combine to produce the base and shell domains. The hypervariable region of VP2 [AAs 206 to 350] **McFerran *et al*. (1980)** forms the projection domain. Two hydrophilic areas (A and B) inside the VP2 region were found. AAs 212 to 224 fall under area A, and AAs 314 to 325 fall under region B **Azad (1987).** The projection domain's outermost area, PBC and PHI (neutralising Ab-binding domains), is made up of these two loops **Letzel *et al*. (2007).** PDE and PFG, two more loops, were found in the projection domain **Coulibaly *et al*. (2005).** Aspartic acid at position 279, glutamine at position 253, and alanine at position 284 were found to be the probable AAs important for virulence and cellular tropism **Brandt *et al*. (2001).**

A 17-kD non-structural protein called VP5 is also encoded by Segment A from the short ORF **Lombardo *et al*. (2000).** A class II membrane protein called VP5 has an external C-terminal domain and a cytoplasmic N-terminus **Lombardo *et al*. (2000).** Among all serotype I IBDV strains, it is the most basic, cysteine-rich, and semi-conserved **Lombardo *et al*. (2000),** and it has been linked to the induced bursal disease **Yao *et al*. (1998).** Additionally, it contributes to the spread of viruses from infected cells **Lombardo *et al*. (2000).** The cell membrane becomes damaged as VP5 builds up there, reducing cellular viability. In vitro culture experiments have demonstrated that VP2 and VP5 cause apoptosis **Yao *et al*. (1998).**

Pathogensis

Primary viraemia results from the virus's replication in gut-associated macrophages and lymphoid cells after oral infection before entering the portal circulation **Murphy *et al*. (1999).** The caecal macrophages and lymphoid cells may recognise the viral antigen as early as 4 hours after infection (hpi), the liver is infected by 5 hpi, and the Buras is infected by 11 hpi after initial viraemia **Murphy *et al*. (1999)**. After IBDV replication in the Bursa, the virus enters the bloodstream to generate secondary viraemia, which leads to the spread of the infection to other tissues.

The individual and active type of cell death known as apoptosis is distinguished by nuclear fragmentation and breakdown into apoptotic vesicles without external release of the cellular contents, and as a result, without inducing an inflammatory response **Cohen (1991).** The pathophysiology of IBDV and immunosuppression are significantly influenced by apoptosis. Peripheral blood lymphocytes from chickens infected with serotype I IBDV strain L display a significant level of apoptosis, and

these cells exhibit a high apoptotic index (nuclear fragmentation and cellular disintegration into apoptotic vesicles) **Vasconcelos and Lam (1994).**

Clinical signs

Anorexia, anorexia nervosa, diarrhoea, diarrhoea, shaking, and dehydration are signs of distress, depression, ruffled feathers at the end of the incubation phase, which is typically 2 to 3 days. Three to four days of the clinical illness are followed by a quick recovery in the surviving birds **Murphy *et al*. (1999).**

Diagnosis

IBDV field and vaccine strains must be distinguished from one another, and this can be done using a variety of methods, such as the enzyme -linked immunosorbent assay **Boot *et al*. (2000),** the reverse transcription polymerase chain reaction (RT-PCR) focused on single nucleotide polymorphisms in the VP2 region **Jackwood (2002),** and the restriction fragment length polymorphism method (RFLP), which analyses restriction enzyme sites specific to a particular viral genotype) **Biet (2000).**

Control

IBDV vaccines include live attenuated, inactivated/killed, and immune complex vaccines, which combine hyperimmune sera from hens infected with a given pathogen with live pathogens that have been modified for use in an embryo **Schijns *et al*. (2008).** The application method can be intramuscular injection, in ovo administration, or addition to water. Breeder hens are immunised by injecting inactivated vaccine in oil adjuvant soon before laying or by immunising breeding stock orally at 18 weeks of age with live virus to prevent infection of newly hatched chicks. This happens once more a year later. As a result, the neutralising Ab level is kept high and stable during the birds' whole laying lives. Chicks are effectively protected by maternal Abs for 4 to 7 weeks after hatching. At around 1-2 weeks of age, an attenuated virus vaccine is administered if the maternal Abs levels of the chicks are low or inconsistent. The egg yolk serves as a conduit for maternal abs from the mother to the chick. From the late stages of embryonic development until just after hatching, IgY starts to be absorbed from the yolk **Mast *et al*. (2001).**

Chicken Anaemia Virus (CAV)

Chicken infectious anemia (CIA) is a disease that af-fects poultry industry globally **Schat (2009).** It is caused by chicken anemia virus (CAV) which was firstly isolated in Japan in 1979 **Yuasa *et al*. (1979).**

Introduction

Chicken anemia virus (CAV) originally classified as the only member of the genus Gyrovirus within the family Circoviridae then reclassified in 2016 as the only recognized member of the genus Gyrovirus in the family Anelloviridae which is non-enveloped, icosahedral, negative sense single-stranded closed circular DNA.

Virus Genome

The genome of CAV is 2298–2319 nucleotides in length that encodes for three partially overlapping reading frames (ORF)1, 2, and 3 from which the three corresponding viral proteins, VP1, 2, and 3 are translated VP1 forms the capsid protein and is the only viral protein present in the virions. VP2 is critical for viral replication, and serving as a scaffold for the proper folding of VP1. VP3 is the major apoptosis-causing protein induces apoptosis of thymocytes in vivo and of cultured transformed avian cells in vitro. **Noteborn *et al*. (1991).** Also noncoding region shows complete promoter activity, containing conserved sequences related to replication and transcriptional regulation **Meehan *et al*. (1992).**

Transmission

Both vertical transmissions from breeders to the next generations while horizontal transmissions through feathers or oral contamination and feces **Da-vidson *et al*. (2008).**

Pathogenicity

In fact, chickens are susceptible to infection at all ages but the pathologic effect of CAV is most likely to be observed in 2 to 4-week-old broilers and layers that are void of the maternal antibodies within the first two weeks of age and cause severe damage to tissues and organs **Miller and Schat (2004), Bülow and Sebat (1997),** Virus infection enhance the lympho-

cyte depletion, hematopoietic deficiency, weight loss, anemia, intramuscular hemorrhage, lymphatic atrophy and bone marrow aplasia. While older ages showing subclinical symptoms of immunosuppression and being more sensitive to secondary pathogens, exhibiting poor vaccine responses **van Santen *et al.* (2001).** The degree of pathogenicity varies depending on the virulence of the virus, dose, and route of infection **Naish (1989).**

Genetic diversity and phylogenetics of CAV strains

In Chile, from thymus samples of 9-week old White Leghorn breeders CAV was isolated for the first time **Toro *et al.* (1994).** Although there aren't any antigenic variations identified between different CAV strain in cross-neutralization and cross-immunofluorescence tests, the incidence of anemia induced by different isolates of CAV was ranged between 0 and 88%, indicating the virulence **Yuasa *et al.* (1979); Bülow *et al.* (1986).**

Despite on that CAV has a conserved genome VP1 is known to be the less conserved protein. The variability of VP1 gene among CAV isolates has been reported and it has influenced diversity of different CAV isolates **Schat (2003); Eltahir *et al.* (2011); Kye *et al.* (2013).** Genetic characterization of CAV genome reveals that the hypervariable region (position 139 to 151) of VP1 protein, of which position 139 and 144 are known to play key role in the growth and spread of the virus **Renshaw *et al.* (1996).** Likewise,Yamaguchi *et al*. texted that even a single change in the residue 394 of VP1 was critical for the pathogenicity of CAV and if the amino acid at this position is glu-tamine viral infection will be pathogenic **Yamaguchi *et al.* (2001).** Based on the diversity of viral proteins, different clades of CAV strains have been reported with no consistent classification among CAV strains of different origins **Zhang *et al.* (2013).**

The immunosuppressive quality of CAV

CIAV replicates in hemocytoblasts in the bone marrow and thymocytes in the cortex of the thymus, causing apoptosis of these cells. Hemocytoblasts are the precursors for red blood cells, thrombocytes, and heterophils, whereas thymocytes are the precursors for CD4 Th lymphocytes and CD8 CTLs. Apoptosis of the hemocytoblasts by CIAV can result in anemia, hemorrhages and increased susceptibility to bacterial infections, while apoptosis of thymocytes affects Th functions, which are essential for immunoglobulin Y (IgY) and IgA antibody production and CTL functions. The B cells are not susceptible to CAV directly but indirect impact on B cells has been associated with damage to cyto-kines and other molecules **Adair (2000).** A lot of studies have assured the reduction of cytokines such as interleukin 2 (IL -2) with downstream impact on neutrophils, macrophages and the phagocytic activity of the immune system, which is the main cause of the immunosuppressive effect of CAV **Natesan *et al.* (2006); Oluwayelu *et al.* (2010).** Suppression of the immune molecules, interferon gamma (IFN-γ) has been noticed to increase at first few days of in-fection, followed by gradual decrease **Natesan *et al.* (2006).** Recent study by **Wani *et al.* (2016)** evaluated the impact of viral load of CAV on immunocytological and histopatho-logical parameters. The studies confirmed the highest viral load in blood, thymus and spleen at 15 days post infection with minimal expression in liver, bone marrow and bursa. Drastic reduction of cytokines (IL-2, IL-1, IL-12) at all doses with a 3–15-fold initial increase of IFN- γ at the early stage of infection was also established. The reduction of CD4+ and CD8+ in CAV infected chicks has also been reported **Adair (2000); Kuscu and Gurel (2008); Wani *et al.* (2016).**

Perspective in the control of CAV

Vaccination combined with good poultry management, has been the only available control measure for preventing the vertical transmission of CAV from breeder hens to their progenies. Progenies of vacci-nated breeders get the maternal antibodies, which protect them from severe clinical signs of chicken infectious anemia **Todd (2000).** Despite the availability of maternally derived antibodies, which wane after three weeks of age, chickens are still susceptible to this infection though with subclinical symptoms **Hoerr (2010).** Several traditional vaccines have proven to be effective against this virus, but their limitation has led to the

emergence of myriads of modern vaccines with potential protection ability, though many are still on clinical considerations. Live attenuated vaccine provides good protection against CAV with high immune response, but the big fear that the vaccine virus be able to revert to its virulent nature and the risk of horizontal transmission of the virus to chickens **Sawant *et al.* (2015).** Commercialized vaccines are banned in China as they have been suggested to cause subclinical symptoms **Fang *et al.* (2023)**. Inactivated vaccine has been regarded as safe because it is stable, though with low immune response, which could be addressed with appropriate vaccine adjuvants.

Conclusion

The danger of immunosuppressive viruses lies not only in their morbidity and mortality rates within chicken flocks, but their greater risk is in contributing to the production of immunologically incompetent generations that are unable to resist any other secondary infections affecting the herd. On the other hand, these viruses leave the bird with a compromised immune system, incapable of forming a suitable and rapid an immunoresponse against the vaccination process. Therefore, it is necessary to resort to certain measures and precautions on the farm to control these diseases which are as follows: Providing a clean and healthy environment for poultry, reducing exposure to immunosuppressive viruses through good hygiene practices, using effective and appropriate vaccines for immunosuppressive viruses, improving nutrition and health management of poultry. And Implementing monitoring and early detection measures for immunosuppressive diseases and taking necessary actions to control them.

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