Journal of Zoonotic Diseases
2021, 5 (4): 12-23
doi: 10.22034/jzd.2021.14024
https://jzd.tabrizu.ac.ir/article_14024.html

Review Article

Immune responses to Newcastle disease virus as a minor zoonotic viral agent

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(Received 21 November 2021, Accepted 8 December 2021)

Summary
Newcastle is one of the leading diseases among poultry. The viral agent of this disease is classified in the genus avulavirus of the paramyxovirus family. Since the disease has a harmful impact on poultry production, it is one of the main economic problems that can be studied by virology scientists. Even though, Newcastle disease virus (NDV) has been extensively studied in recent years, our information on immune responses to this virus remains incomplete. NDV is a zoonotic agent that can cause infection in humans. The common transmission route of NDV is through contact of contaminated fingers with the eyes after careless handling infectious poultry samples. Like all infectious diseases, vaccination can enhance NDV control. Today, there are three types of NDV vaccines, including live inactive and vector-based vaccines. Since NDV is an economical concern to governments, its problem must be solved. To find effective solutions to this problem, our knowledge about immune responses to ND has to be completed. In this review, we discussed some aspects of these responses.
Keywords: NDV, Innate immunity, Cell-mediated immunity, Humoral immune system, Zoonotic disease, Vaccination

Introduction

Newcastle disease was first described in 1926. Since the disease has a harmful impact on poultry production by infected birds, it is one of the main economic problems that can be solved by virology scientists (Vickers 2017). Although, all strains of the Newcastle disease virus (NDV) are classified in a serotype, phylogenetic variations have been reported in assessments of genome similarity (Hollmén et al. 2002). Therefore, making genetic resistance to ND is very difficult because of the involvement of multifactorial mechanisms. Thus, developing immunity through vaccination is essential for ND control (Yurchenko et al. 2015). The effects of the immune system, including innate and acquired immunity on disease control are undeniable. Thus, it will be necessary to know the pathophysiology of the disease in order to produce a vaccine against it (Cardenas-Garcia et al. 2016).
This article reviews present data on immune responses to NDV. The review begins with a short explanation of the virological and clinical features of NDV infection and continues with a description of immune responses during NDV infection. Also, this paper will define the viral immune-evasion mechanisms.

Newcastle disease virus (APMV-1)

Newcastle is one of the leading diseases among poultry. The viral agent of this disease is classified in the genus avulavirus of the paramyxovirus family. Avian paramyxovirus type I serotype (APMV-1) is the responsible agent in this disease. NDV is an enveloped single-stranded RNA virus with negative polarity (Kapczynski et al. 2013). Its mRNA encodes six viral proteins such as nucleoprotein, matrix, fusion, hemagglutinin-neuraminidase, polymerase, and phosphoprotein. Among the structural proteins of the virus, F protein has an important role in viral proliferation due to the fusion properties of this protein during the entry of the virus through the plasma membrane and envelopment processes (Cardenas Garcia et al. 2013, Dimitrov et al. 2016). This protein is present as a precursor form (F0) and must be cleaved to F1 and F2, which is achieved by host cell proteases through providing the conditions for the virus entry (Gao et al. 2008). After virus entry, different types of pathotypes such as Viscerotropic velogenic NDVs, Neurotropic velogenic NDVs, Mesogenic NDVs, Lentogenic respiratory NDVs, and Asymptomatic enteric NDVs would be observed in the host's body. However, it is interesting to note that these different forms of the disease vary from one another in stimulating immune systems due to their clinical differences (Frank Jordan 2008, Goff et al. 2013). Even differences in the affected area can impact the symptoms of the disease. Infection with lentogenic and mesogenic forms leads to respiratory disease and lesions in the central nervous system, whereas infection with velogenic strains is without respiratory symptoms. Nevertheless, lesions with necrosis and bleeding are found in many organs of the body (Gupta et al. 2014). NDV infection at different levels of virulence causes changes in the expression of different cytokine genes in peripheral blood and spleen (Liu et al. 2012, Rue et al. 2011). Therefore, fluctuations in cytokine responses can affect the pathogenesis of the virus (Hu et al. 2012, Rasoli et al. 2014).

NDV epidemiologic characteristics as a zoonotic agent

NDV is considered a biological agent that can cause infection in humans. The first report of human infection by NDV was documented in 1942 in Australia (Martella et al. 2011). So far, the most reported incidence of ND in humans is through accidental inoculation of high-titer NDV-contaminated egg fluid or touching NDV-contaminated fingers into the eyes after careless handling infectious poultry samples. Therefore, the major transmission route of ND infection from birds to humans is limited to close contact with infected birds or materials (Kuiken et al. 2018). In these cases, most of the time, conjunctivitis appears as a sign in workers that were involved in the diagnosis, euthanasia, and disposal of NDV-related dead birds. Also, in immunocompromised individuals, ND can be enumerated hazard due to defective immunity (Nolen 2003). These pathogens also would be transmitted by inhalation of airborne excreta and dried feces, ocular discharges, and crop milk (Phan et al. 2013). The duration and severity of infection take 6–8 days. Following the incubation period (1–2 days), unilateral or bilateral conjunctivitis or influenza-like symptoms are observed (Shabbir et al. 2021).

The clinical symptom consists of fever of more than 100°F, headache, eye itching, redness, lacrimation, mucopurulent discharge, chilliness, sore throat, depressed appetite, pain, malaise, little photophobia, pharyngitis, slight unproductive cough, and marked insomnia with apathy. Identification of NDV genome from blood cells and blood serum is a marker to support viremia events in the body. Regardless of bird-to-human transmission, there is no evidence about the human-to-human transmission (Nolen 2003). Most of the time, reported NDV in humans is self-limiting, nonlife-threatening, and usually restricted not for more than 4–5 days. However, three causalities of immunocompromised patients by pneumonia symptom has been observed due to respiratory failure (Ul-Rahman et al. 2021). In this regard, two cases of this infectious disease caused deaths in Netherland during 2003, and one death

was observed during 2007 in the United States (Goebel et al. 2007).

NDV vaccines from the past to present

Like all infectious diseases, vaccination follows three basic goals to help control ND: I) reduction or elimination of clinical disease; II) reduction of the virus shedding; and III) increasing the infectious dose of the ND virus (Miller et al. 2013). Biosafety is an essential program of keeping the community away from the NDV to achieve a protective immunity, effective vaccine, or ideally avoiding any contact. The NDV vaccination is always successful, if a minimum of 85% of the poultry community takes an appropriate dose and achieves herd immunity. Globally, the most generally utilized ND vaccines are live vaccine types (Rue et al. 2010).

Viruses circulating in birds are usually the source of the B1, LaSota, and VG/GA vaccines. All of the mentioned viruses fit in genotype II and are genetically extremely close (>98% phylogenetic identity; (Diel et al. 2012b). The major variances among vaccine types are the tropism and the replication capability in chickens that is maximum in LaSota, leading to the production of more neutralizing antibodies in comparison with other strains (Diel et al. 2012a). Other common traditional vaccines are those originated from class II genotype I (V4, I2, and PHY-LMV42) that are a virulent and securely utilized in chickens. Among these strains, the I-2 has better thermo-stability compared to the V4 vaccine strain, which is utilized in regions with higher temperatures (Zhao et al. 2014).

Inactivated ND vaccines have revealed the weakness of requiring a withdrawal course before vaccinated chickens could be used as food for human and each vaccine needs separate administration (Bublot et al. 2006). Although, chickens vaccinated with inactivated vaccines were revealed to have higher levels of humoral immunity, they did not develop a robust cellular immunity and shed more wild viruses in comparison with those vaccinated with live ND vaccines (Le Gros et al. 2009). In 1990, the Fowlpox virus (FPV) vector-based vaccines with the NDV F or HN protein expression were confirmed to keep birds from a wild NDV.

However, some studies have revealed that maternal protection to the Flu A virus hemagglutinin (HA) protein may inhibit recombinant FPV (rFPV) vaccines with HA expression; others have demonstrated that protection to FPV from previous FPV vaccinations is the problem (Faulkner et al. 2013). The Meleagrid alphaherpesvirus 1, usually recognized as turkey's herpesvirus (HVT) or a serotype 3 Marek's virus, is a common applied vector in recombinant vaccine construction. The efficacy of HVT vector-based vaccines in birds to protect from NDV and Marek's disease was established in early 1990 (García 2017). Some of the characteristics of NDV vaccines are listed in Table 1.

Table 1- Characteristics of different NDV vaccines (Mass: Spray, aerosol, drinking. Individual: eye drop, injection).

Vaccine types	Adjuvants	Administration route	Duration of immunity	Response to the vaccine	Protection onset	Cost
live	no	Mass and individual	short	Systemic and local	2–3 weeks	less expensive
inactivated	yes	injection	long	systemic	3–4 weeks	more expensive
vectored	no	Mass and individual	long	Systemic and local	4–5 weeks	Variable

The innate immune system in NDV

Intrinsic immunity includes factors with a rapid response against a microbial agent, including 1) physical and chemical barriers such as epithelia, skin, and mucosal secretions; 2) phagocytic cells such as macrophages and NK cells; 3) complement system and inflammatory mediators; and 4) cytokines. The first inherent immune response is applied by pattern recognition receptors (PRRs) (Kapczynski et al. 2013). PRRs are factors that identify pathogenic molecular patterns (PAMPs) and thus enhance the innate and acquired immune response against the pathogen (Takeuchi & Akira 2010).

TLR3, 7, 8, 9 , RIG-I, MDA5, and LGP2 are among the sensors that detect the nucleic acid of the virus and stimulate the response of IFN-I, IFN-II, inflammatory cytokines, and chemokines that are effective in promoting immunity against the virus (Bowie & Unterholzner 2008). NDV infection widely stimulates the production of inflammatory cytokines IFN-α, IFN-β, IL-1β, and IL-6 (Kapczynski et al. 2013). As a result of infection, immune response increases in various tissues such as spleen, lymph nodes, and peripheral blood, and is associated with increased mRNA expression of inflammatory cytokines and chemokines such as IFN-γ, IL-12α, IL-18, IL-1β, and IL-6 (Figure1) (Ecco et al. 2011, Hu et al. 2015, Li et al. 2016a). Also, the important role of related genes, including IRF3 and IRF7, is undeniable. It has been shown that eliminating these two factors increases the susceptibility of macrophages to NDV infection (Munir et al. 2005). Infection with NDV causes the expression of IFN effector genes, which are related to PKR (Protein kinase R) and OAS (2'-5'-oligoadenylate synthetase). Other cytokines such as K203 and ah221, CXCL13 / BCA-1, CCL21, and MIP-1β are also secreted. Most of these cytokines, such as MIP-3α and MIP-1β, activate the cell-dependent response (Wei et al. 2015). There is a study on a factor called S1PR1 (sphingosine-1-phosphate receptor-1), which is a protein-bound to G protein and acts as an activator of inflammatory response. To investigate the effect of this factor, its inhibitor, called W146, was used to observe that by inhibiting this factor, the production of pre-inflammatory cytokines is stopped (Walsh et al. 2014). On the other hand, excessive expression of this factor also causes excessive expression of IL-1β (Li et al. 2016b). In general, IL-1β and IL-6 play an important role in the inflammatory response of the host, so the production of these cytokines and their function act as key mechanisms in controlling inflammation (Wei et al. 2015). Factors such as NF-KB, NLRP3, MAPKs, and MYD88 are involved in the IL-1β signaling pathway (Harikumar et al. 2014). It should be noted that all factors related to chemokines, pre-inflammatory cytokines, IFN-I, and IFN-II are in the initial phase of the innate immune response against the virus. What is important is the difference in the activity of factors related to innate immunity in different strains of NDV (Wang et al. 2014). This means that many other genes in the initial phase of response to the infectious agent in the host spleen infected with NDV-CA20 such as IL-6, IFIT-5, and MIP-3a are expressed, but the expression of these genes for the same agent is not observed in the lentogenic strains of NDV (Vénéreau et al. 2015).

In a study of two different strains of NH10 and SS10 in PEKING ducks, it was found that high levels of RIG1, MDA5, TLR3, TLR7, and LGP2 were observed in the first three days of NDV infection (Qian et al. 2017). Seventy-two hours after infection, TLR3 and TLR7 expression was regulated. While in infected ducks with NH10 strain of NDV, the expression of RIGI, TLR3, and TLR7 reached the highest level in 24 hours, and their expression was still high two days after infection (Kang et al. 2015). As we know, cytokines are important in intrinsic immunity. But, if expressed in large amounts in the host body, cytokine stroma can cause damage to host tissues, such as in ND strains called JS5 / 05 and JS3 / 05 and F480E8 and Herts / 33 are expressed (Hu et al. 2012). However, what has been said about

interferon-gamma is slightly different, because it is thought to be a factor in helping the pathogenesis of the viral agent (Susta et al. 2015). In addition to its antiviral activity, this factor, if overexpressed, increases the levels of mortality and morbidity in NDV-infected hosts (Liu et al. 2012). On the other hand, in addition to the high rate of expression, the time of expression of this factor affects its performance (Susta et al. 2013). In the meantime, NDV infection can produce nitric oxide (Ahmed et al. 2007), which is produced by macrophages (Schijns et al. 2014). Accordingly, excessive expression of toxic effects in the host will occur (Smith 2004).

Recently, a factor called high mobility group box 1 (HMGB1) has been mentioned as a key member of DAMPs that plays an important role in systemic inflammation but also has a pathogenic role in cases of viral and bacterial infections (Barqasho et al. 2010). Newcastle disease causes a severe inflammatory response in the host body, resulting in extensive tissue damage and cellular apoptosis, and the HMGB1 factor is referred to as the inflammatory factors (Andersson & Tracey 2011). This is an important factor in activating the NF-KB pathway and inflammation. HMGB1 stimulates the production of inflammatory cytokines through TLR4, TLR2, and RAGR receptors (Chen et al. 2016). The reaction between HMGB1 and RAG activates the ERK1, 2 / JNK path. If this is not the case, there will be no change in virus replication, but the production of inflammatory cytokines and pathogenic changes will be reduced. On the other hand, it will increase the host's survival (Duan et al. 2014). The functional response is through IFN and also affects MDA5 and RIG1, while also preventing the activation of signaling pathways by these two factors, thus preventing the activation of all antiviral responses and pre-inflammatory factors (Huang et al. 2003). But NDV V protein blocks the IFN's functional response and also affects MDA5 and RIG1, preventing the signaling pathways from activating. It thus prevents all antiviral responses and inflammatory factors from being activated (Solomon et al. 2010).

Humoral immune system

Antibodies are important factors in protecting the host against the virus by clearing and neutralizing the pathogens in two ways: 1) by binding to the infected cell, which prevents the production of a virus; 2) by connecting to the progeny virus, which prevents the spread of the virus (van Boven et al. 2008). Antibodies' ability to protect against the virus can be measured by the Neutralization Test (NT) (Zhao et al. 2016b). Due to ELISA, the production of different classes of antibodies in protection against NDV was investigated, and it was concluded that IgM and IgG are among the dominant antibodies (Zhao et al. 2016a). IgM reaches its maximum in the first four days, and then IgA and IgG increase. Serum antibodies act on the infection in the respiratory mucosa, while secreted antibodies reduce the proliferation of the virus in the epithelium (Al-Garib et al. 2003b).

Several studies have confirmed the protective effects of antibodies to the NDV virus. The presence of antibodies is detected by HI and NT tests, and their role in protecting the host against the virus is investigated (Samuel et al. 2013). On the other hand, in some cases, inactive antibodies are used to protect against the virus, which is successful, but it is noteworthy that antibodies are not effective against any protein because the use of inactive antibodies is anti-HN / F protects against the NDV virus, while inactive antibodies against NP / P, M do not protect against the virus (Rauw et al. 2010a, Rauw et al. 2010b, Rauw et al. 2015). In general, it can be said that humoral immunity is an effective key factor in protecting the host against the viral agent (Reynolds & Maraqa 2000b). On the other hand, in the case of producing inactive antibodies before NDV infection within four days of incubation in the trachea, the virus causes an increase in antibody titer, which indicates the importance of local antibodies (Basavarajappa et al. 2014, Huang et al. 2004, Li et al. 2014, McGinnes et al. 2010, Miller et al. 2009). Regarding the performance of antibodies against NDV, it can be said that what protects the host from the virus are antibodies against the F and HN glycoproteins of the virus, and on the other hand,

the use of local antibodies plays a significant role in protecting against the virus (Palya et al. 2012, Reynolds & Maraqa 2000a). At the same time, there are some non-conserved residues on viral mRNA, which might be effective on alterations in viral glycoproteins that would be captured by neutralizing antibodies. Therefore, this can be an intelligent strategy for the virus to avoid the host's neutralizing antibodies (Palya et al. 2014).

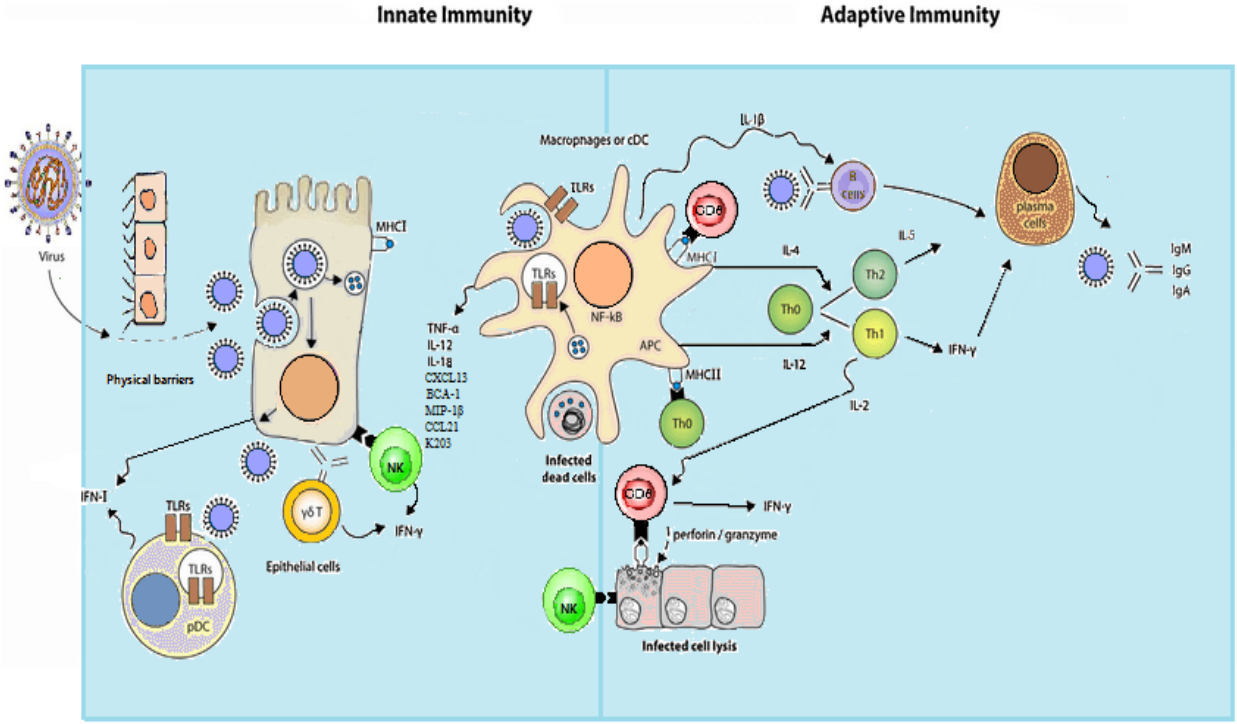

Fig. 1. NDV is detected by PRR and is presented for APCs. After activation of APCs two pathways is started 1: APC-induced production of cytokines; 2: appearing of CD markers as ligands for CTLs and B cells and activation of these cells as adaptive immunity response (Crisci et al. 2013).

Cell-mediated immunity

Cellular immunity is considered an important factor in protecting the host against the NDV virus (Sachan et al. 2015, Xiao et al. 2012, Yu et al. 2013). Its activation will occur 2 to 3 days after infection. In some literature, it has been shown that cellular immunity is more important than humoral immunity. Thus, according to some strategies, this feature has been investigated for NDV infection (Tseng et al. 2009). Two strategies were used to investigate this characteristic: first, sodium dodecyl sulfate was used to change the neutralizing epitopes, in which the hemagglutinin inhibitor antibodies are no longer stimulated, and only cellular immunity is activated (Rehmani et al. 2015). In the second strategy, the humoral immune response was depleted, and only the cellular immune response remained. Consequently, without antibodies, the immune response could not protect the host against the NDV. In other words, the presence of HI and neutralizing antibodies are necessary to fight the virus (Reynolds & Maraqa 2000b).

In the NDV infection, leukocyte infiltration is seen in places such as the respiratory tract and Harderian gland (HG), where the virus proliferates. As a result of viral entry, leukocytes, macrophages, T CD4, and T CD8 cells were stimulated (Perozo et al. 2012). However, T lymphocytes and B lymphocytes are normally present in HG, and their levels increase by 2 to 3 times during exposure to lentogenic and mesogenic strains of NDV. After

phagocytosis and antigen processing by antigen-processing cells, T CD4 cells are activated, leading to the release of cytokines that can destroy the target cells or use non-specific cells such as macrophages to destroy the target cell (Al-Garib et al. 2003a). On the other hand, activating B cells by T CD4 cells lead to proliferate and differentiate in antibody production, and also memory B cells are produced (Ramakrishnan et al. 2015).

Conclusion

Even though NDV has been extensively studied in recent years, our information on the immune responses to this virus remains incomplete. However, since NDV is a zoonotic disease with an economic concern to governments, learning about its pathophysiology is of critical importance. To find effective solutions to this problem, we must focus on learning how the virus impacts its host. In this study, we reviewed some of the physiological systems that are involved in infection and immunity to the NDV. Future research should focus on applying the theoretical physiological of our study using *in vivo* animal models to further expand our knowledge on this virus. By gaining a deeper understanding of host defense systems against the virus, future research will assist in vaccine development and it can help minimize the economic impacts of the virus through improvements in treatments and control of the disease.

Abbreviations

NDV: Newcastle disease virus, APMV-1: Avian paramyxovirus type I serotype, PRRs: pattern recognition receptor

Acknowledgements

Not applicable.

Ethics approval

Not applicable.

Conflict of interest statement

The authors declare no conflicts of interest.

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