Preview

NDV Induced Immune-Pathology in Chickens

Hu Zenglei[1] and Xiufan Liu[1,2*]

[1]Animal Infectious Disease Laboratory, School of Veterinary Medicine; [2]Jiangsu Co-innovation Center for Prevention and Control of Important Animal Infectious Diseases and Zoonoses, Yangzhou University, Yangzhou, Jiangsu 225009, China.

Abstract | Virulence and pathogenicity of Newcastle disease virus (NDV) is one of the major determinants for the clinicopathological manifestations in infected hosts. Recent studies showed that the host innate immune responses to infection play important role in the pathogenesis of NDV, and correlate with the severity of the clinical disease. Virulent strains of different genotypes induce distinct pathological manifestations in chicken organs, especially in lymphoid tissues. Genotype VIId of NDV, which is currently endemic in many countries of Asian and Middle East, replicates at a significantly higher level, induces more potent innate antiviral and inflammatory response, and causes more severe damages in lymphoid tissues when compared with virulent viruses of other genotypes. Therefore, severe pathology in immune organs, caused by genotype VIId of NDV, is associated with high levels of virus replication and an intense innate immune response.

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***Correspondence** | Xiufan Liu, Yangzhou University, 48 East Wenhui Road, Yangzhou, Jiangsu, China; **E-mail** | xfliu@yzu.edu.cn
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Newcastle disease virus (NDV) varies greatly in their virulence or pathogenicity for chickens and based on this difference NDV strains are classified into three pathotypes: velogene, mesogene and lentogene (Alexander, 2003). The virus is rapidly evolving, and several new velogenic genotypes have been discovered in the past two decades. Both the severity of disease and the pathological changes induced by NDV are dependent on multiple factors associated with pathogen, host and environment, while the most important factor is the virulence of the infected strain. It is generally accepted that the cleavage site in the fusion (F) protein is the primary molecular determinant of NDV virulence (Dortmans et al., 2011; Peeters et al., 1999). However, more recent studies have shown that virulent strains of different genetypes sharing similar F cleavage site associated with high virulence produce distinct pathological manifestation in chickens, especially in lymphoid tissues (Ecco et al., 2011; Merino et al., 2011; Susta et al., 2011; Wang et al., 2012).

Furthermore, results from independent studies have shown that velogenic NDV strains induce strong innate immune response evidenced by up-regulation of groups of genes associated with the innate antiviral and inflammatory responses which correlates to the high mortality or severe pathological damage, indicating its contribution in the pathogenesis (Liu et al., 2012; Rue et al., 2011). Comparative studies with different pathotypes of NDVs showed that the magnitude of innate immune response is mainly related to virulence.

As mentioned above, virulent NDV strains of different genotypes may induce distinct pathological changes. For instance, genotype VIId virus which is currently endemic in many countries (Ebrahimi et al., 2012; Liu et al., 2003; Mase et al., 2002; Qin et al., 2008) induce more severe damage in lymphoid tissues featured by severe lymphocytic depletion, histiocytic accumulation and necrosis of the spleen and thymus when compared with virulent viruses of other

genotypes (Susta et al., 2011; Wang et al., 2012; Hu et al., 2015). More recent studies demonstrated that the high level of virus replication and intense innate immune response contribute to the severe pathology in lymphoid tissues caused by NDV of genotype VIId (Ecco et al., 2011; Hu et al., 2012; Hu et al., 2015). A common finding from these studies is that the extent of the innate immune response which correlates with the efficiency of virus replication in target organs. Most likely, genotype VIId strains of NDV replicate at higher levels in lymphoid tissues and release more viral components that would be recognized by pattern recognition receptors (PRRs), resulting in the over-activated innate immune response. Strong antiviral and pro-inflammatory responses induced by genotype VIId of NDV, or immunopathology, is an indispensable part of its pathogenesis, very similar to the "cytokine storm" in the pathogenesis of highly pathogenic avian influenza viruses (Baskin et al., 2009; Tisoncik et al., 2012).

Recently, Cornax et al. (2013) demonstrated that the fusion (F) and haemagglutinin-neuraminidase (HN) proteins are major determinants of NDV responsible for the replication capacity in macrophages. In addition, using gene-swapping strategy, we have recently identified that the matrix (M), F and HN genes together determine the high level of replication and intense innate response, and thus the severe pathology, in the spleen caused by genotype VIId strains of NDV (Hu et al. unpublished data). To further elucidate viral replication and innate immune response in the pathogenesis of NDV infection, it is necessary to characterize the interaction between individual viral proteins or their functional domain and the factors involved in the innate immune pathway.

Furthermore, the innate immune response may also affect NDV pathology through its interplay with apoptosis. NDV infection induces directly apoptosis resulting in the histologic changes such as lymphocyte depletion or necrosis in lymphoid tissues (Harrison et al., 2011; Kommers et al., 2003; Kommers et al., 2002). In our studies, genotype VIId strains of NDV induce more apparent apoptosis in chicken splenocytes (Hu et al., 2012) and up-regulate genes associated with apoptosis in the spleen when compared to genotype IV strains of NDV (Hu et al., 2015), suggesting the involvement of apoptosis in NDV pathology. On the other hand, in addition to the function in antiviral activity, some cytokines, such as interferons (IFNs), also serve as key mediators of apoptosis. Many factors in IFN signaling pathway, including IFN regulatory factor, protein kinase R and 2',5-oligoadenylate/RNaseL system, contribute to apoptosis through different mechanisms (Barber, 2001). The IFNs can also activate tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) that initiates the death receptor-mediated cell death (Barber, 2001). Thus, one possible secondary effect of the hyper-induction of the innate immune response may be the enhanced apoptosis, which may further deteriorate NDV pathology. Therefore, the relationship between the innate response, apoptosis and pathological manifestation caused by NDV deserve additional studies. Understanding these complex host pathogen interactions would help to underpin some of the key cellular interactors that are fundamental to the pathogenesis of NDV. Once highlighted, these specific pathways may pave the way for defining future control strategies of NDV and may help to reduce the economic burden caused by this deadly disease especially in the countries where biosecurity is not up-to-date and the disease is endemic.

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