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The Differences of Serum IFN-β and Antibodies Concentrations in Chickens at Early and Late ALV-J Infection Stage

Yue Yin, Xi Lan, Kai Tian, Tian-Jie Li, Qing Zhu, Yi-Ping Liu,
Xiao-Ling Zhao, Hua-Dong Yin, Yao-Dong Hu and Yan Wang
Key Laboratory of Sichuan Province, Farm Animal Genetic Resource Exploration and Innovation,
Sichuan Agricultural University, Ya'an, 625014 Sichuan, People's Republic of China

Abstract: Interferon-β (IFN-β) and immunoglobulin M (IgM), immunoglobulin G (IgG) are essential in anti-retrovirus progress. ALV-J is a kind of ubiquitous retrovirus in chicken. To investigate whether natural Avian Leukosis Virus strain J (ALV-J) infection has effect on the concentrations of serum IFN-β, IgM and IgG, two important time points after hatching, 3 and 18 weeks age which represent the early and late stages of ALV-J infection, respectively were decided to study. The results reveal that the serum IFN-β, IgM and IgG increase at the early stage of ALV-J infection while decrease at the late stage compared with the control chickens which indicate that ALV-J infection boosts the immune response and up-regulates IFN-β and antibody while long-term infection suppresses immune function and down-regulates IFN-β and antibody.

Key words: ALV-J, IFN-β, immunoglobulin, ALV-J infection stage, chicken

INTRODUCTION

Avian Leukosis Viruses (ALVs) are subfamily of the retroviruses of the genus *alpretrovirus* which correlated with malignancy tumor including myeloid leukosis, hemangioma and lymphoid have a profound impairment of immune functions, production performance in host birds (Payne *et al*., 1992). ALVs are classified into ten subgroups and placed in exogenous and endogenous categories (Coffin, 1992). The J subgroup of Avian Leukosis Viruses (ALV-J) was relatively novel which belongs to the exogenous subgroups (Bai *et al*., 1995; Rasgon *et al*., 2005; Payne *et al*., 1991). It's notorious for the highly infectivity, oncogenicity which causes more adverse damage in mortality, morbidity, disease condemnations and feed conversions (Payne and Nair, 2012).

For controlling virus infection, host cells secrete pro-inflammatory cytokines (such as type I interferon) to restrict virus replication and modulate adaptive immunity. IFN-β is the first member of the type I interferon to be launched, particularly in anti-retroviral immune responses (Griffin, 2003). The secreted IFN-β induce multiple of antiviral genes transcription through the JAK/STAT signaling pathway causing the so-called antiviral state. Those signaling cascades ultimately result in apoptosis of infected cells, prevention of viral replication and limitation of viral spread (Holtzman *et al*., 2011). Addition, IFN-β was sufficient to enhance the primary antibody response and induce isotype switching of IgG in dendritic cells causing the adaptive immune responses to retroviruses (Akhtar *et al*., 2010; Gessani *et al*., 1994).

Antibody response is one of the most predominant portion of adaptive immune responses. The importance of antibodies in the immune system to resist the viruses invading has been highlighted because neutralizing antibodies restrict spread of virus infection. Besides, the recent study indicated that the antibodies can potentiate the IFN-β response (Le Bon *et al*., 2001). There are three distinct immunoglobulins in chicken which were designated as IgA, IgM and IgG (also known as IgY in birds) (Leslie and Clem, 1969) and each of them exhibits a unique profile of effector functions. IgA mainly presents on mucosal surfaces (Cerutti *et al*., 2011) and only represents <4% of total chicken immunoglobulins while IgM, IgG constitute the major components of the natural antibodies in blood (Lebacq-Verheyden *et al*., 1974). In mammal, IgM is the frontline defense antibody generated in anti-infection with polyreactivity, high valence and IgG is the prime antibody of secondary immune response during the virus infection (Ehrenstein and Notley, 2010). In addition, IgM may trigger an amplified IgG response (Baumgarth *et al*., 2000; Diamond *et al*., 2003a, b). In clinical tests, the two antibodies levels are the most common factors to represent the primary immune response (Bonilla *et al*., 2005).

Corresponding Author: Yan Wang, Key Laboratory of Sichuan Province,
Farm Animal Genetic Resource Exploration and Innovation, Sichuan Agriculture University,
Xinkang Road 46#, Ya'an, 625014 Sichuan Province, China

As the IFN-β and antibodies IgM and IgG are the most influential components in response to virus infections, previous studies have revealed the induction of the three factors in retroviruses infection in mamalian model. Moreover, the three factors may affect one another, no data is yet available on the production of the three factors in the same research. Whether ALV-J infection can lead the similar changes in avian and the three factors will vary with infection stages are still unclear. In this study, researchers quantified the serum IFN-β concentrations, IgM, IgG levels between ALV-J-infected and uninfected chicken at the early (3 weeks age) and late (18 weeks age) infection stages, researchers conclude that: ALV-J virus infection can promote immune response but it is transient, eventually ALV-J overcomes this protective immune response through an unknown mechanism results in immune response impairment.

MATERIALS AND METHODS

Ethics statement: All research involving in animals and sample collection were conducted according to the guidelines approved by the Sichuan Agricultural University Institutional Animal Care and Use Committee.

Recruitment of case and control animals: Birds used in this study had been selected from a locally raised pure-line Chinese breed called HeiKang (HK) a fine crossbreed of Erlang Moutain chicken♀ and Heikang chicken♂ (the second generation) and all the chickens were raised in poultry farm of Sichuan Agricultural University. All the cohort populations hatched on the same day and housed on the deep-litter bedding then moved to the growing pens at the age of 7 weeks. All birds accessed to feed and water *ad libitum*. Before initiation of the study, researchers extracted blood samples randomly in the cohort at two phases (3 and 18 weeks age) to detect the natural infection of ALV-J by Polymerase Chain Reaction (PCR) Method and collected serum samples for further study. According to results of PCR, researchers screened 100 individuals, 50 infected and 50 non-infected.

DNA isolation: Blood samples collected in EDTA from wing vein of chickens, randomly. And genomic DNAs were isolated from blood by the standard phenol-chloroform protocol then stored at -20°C for PCR. Concentration and purity of DNAs were assessed by UV spectrophotometry using Nanodrop System (Nanodrop 2000C, Thermo Scientific, USA). All these processes were performed under sterile condition.

Oligonucleotide primers: To detect ALV-J, PCR was employed with primers H5/H7 which were specific for ALV-J according to the previous study performed by Smith *et al.* (1998). The primers derive from the prototypes sequence of HPRS-103 strain (GenBank Accession No. Z46390) and details of the primers sequence are listed in Table 1.

Polymerase Chain Reaction: PCR was carried out in a total volume of 10 μL mixture as the following: 20 mM Tris-HCI (pH 8.3), 100 mM KCI; 3 mM $MgCl_2$; dNTP each at 500 uM; 0.5 units of Taq DNA polymerase (Takara, Dalian, China); primers (20 mM each) and 100-150 ng of genomic DNA. Cycling conditions were initial denaturation at 94°C for 5 min then the DNA was amplified during 34 cycles of 94°C for 45 sec, 55°C for 30 sec and 72°C for 1 min. A final elongation step was conducted at 72°C for 10 min.

Electrophoresis of PCR products: PCR samples of 10 μL each were mixed with gel loading buffer (0.25% bromophenol blue tracking dye in 40% sucrose). Electrophoresis was carried out in 1% agarose gels with ethidium bromide, 0.5 μg mL^{-1} in 1×Tris-Borate-EDTA buffer (TBE) at 120 Volts. The molecular weight marker for DNA gel analysis was a 1 kb DNA ladder (Takara, Dalian, China). The electrophoresis results were photographed by gel documentation system (UVITEC, Cambridge, UK). Ultimately, DNA sequences from the positive clones was purified and sequenced by a commercial company (BGI, Shenzhen, China). Results were blasted against the sequence of the ALV-J prototype HPRS-103 strain (GenBank Accession No. AY360088).

Serum isolation: Blood samples were centrifuged at 3000 r min^{-1} for 10 min at 4°C, the serum were carefully obtained and stored at -80°C until use.

Enzyme-Linked Immunosorbent Assay (ELISA): Concentrations of IFN-β, IgM and IgG in serum were determined by corresponding Quantikine ELISA kits (R&D Systems, Minneapolis, MN). All the specimens were treated in strict accordance with manufacturer's instructions and absorbance values were measured at 450 nm by Thermo Scientific Varioskan Flash Multiplate Reader (Thermo scientific, USA). Each specimen was measured in 10 min for 3 times and results were expressed in ng/mL or μg/mL.

Table 1: PCR primer sequences of the ALV-J

Target	Primers	Sequence(5'-3')	Product size (bp)	Location
ALV-J	H5	GGATGAGGTGACTAAGAAAG	545	5258-5277
	H7	CGAACCAAAGGTAACACACG	-	5783-5802

Statistical analysis: Differences of serum IFN-β, IgM and IgG concentrations between the ALV-J infected and uninfected individuals in two group (3 and 18 weeks age group) were analyzed with the Student t-test and expressed as mean±Standard Deviation ($\bar{X} \pm SD$). Values of $p<0.05$, $p<0.01$ were considered statistically significant and extremely significant, respectively.

RESULTS AND DISCUSSION

PCR: To screen the natural ALV-J virus infected birds, PCR was performed with the most sensitive primers H5/H7 (Smith *et al*., 1998) which could amplified a 545 base pair (bp) fragment only from genomic DNAs of infected birds (Fig. 1). In order to confirm the reliability of PCR results, PCR productions were sequenced by a commercial company and blasted against the ALV-J prototype HPRS-103 strain (GenBank Accession No. AY360088). Results demonstrated that the 545 bp fragment belongs to the ALV-J gp85.

ELISA: All average absorbance values of serum IFN-β, IgM and IgG between the two groups in different time converted into ng/mL or μg/mL to represent their concentrations and summarized in Table 2. Results show that in the 3 weeks age group ALV-J infected individuals present much higher average concentration of serum IFN-β, IgM and IgG than uninfected individuals and fold change can be 1.544-2.905 times. Differences of these three immune factor's concentrations between uninfected and infected individuals are extremely significant ($p<0.01$). In contrast the uninfected individuals in the 18 weeks age group have significant higher ($p<0.05$) levels of IgM and IgG than infected individuals. What's more the infected individuals have extremely low ($p<0.01$) level of IFN-β. Fold change can be 0.486-0.585 times (Fig. 2).

Fig. 1: ALV-J virus infected birds: 1, 2, 3, 4, 5, 6; control: 7. The 545 bp fragment belongs to the ALV-J gp85

In China, ALV-J was first detected in broiler chickens (Du *et al*., 1999). Due to the highly contagious and no effective prophylactic vaccine, subsequent infections were expanded rapidly in other chicken species such as layer chickens (Xu *et al*., 2004) and local breeds (Sun and Cui, 2007). There is a long asymptomatic latent period in ALV-J infected population and ALV-J primarily causes late-onset myeloma leukosis (Cui *et al*., 2003) and immunosuppression. As ALV-J can decrease production performance and increase the subsequent mortality, it has become a new challenge to the poultry industry. Early infection of ALV-J is dificult to be detected and the Polymerase Chain Reaction (PCR), a rapid specific and sensitive method for diagnosis ALV-J used in this study can only detect the positive individuals as early as 14 days after infection (Smith *et al*., 1998; Lin *et al*., 2013). According to Mitra *et al*. (2013) research, blood is more sensitive for ALV detection. In this study, blood DNA specimens were employed to detect ALV-J by PCR and sequences of PCR productions can be blasted to the ALV-J prototype HPRS-103 strain.

In innate immune response to retroviral infections, generation of IFN-β is an inaugural event following the production of type I IFN (Griffin, 2003). Human Immunodeficiency Virus (HIV) and Simian Immunodeficiency Virus (SIV) are the best documented for the moderate effect of IFN-β in the host immune response to retroviral infection. Several studies using macrophages as cell model had shown that the antiviral effect of IFN-β militates both at the early and late stages of the HIV infectious cycle, low constitutive production of IFN-β can inhibit viral replication and improve innate immune functions (Cremer *et al*., 1999, 2000). Moreover, with the infection of HIV-1 and SIV, IFN-β levels was elevated in plasma (Kristina *et al*., 2005; Boasso and Shearer, 2008) which illustrate that IFN-β is a key mediator of the host innate immune response to retroviral infection.

Antibodies are essential components in protection against virus infection in adaptive immune

Table 2: Comparisons of the serum IFN-β, IgM and IgG concentrations with ALV-J infection and uninfection birds at 3 and 18 weeks age

Age (weeks)	Groups	Sample size	IFN-β (ng mL^{-1})	IgM (μg mL^{-1})	IgG (μg mL^{-1})
3	ALV-J$^-$	44	91.90±6.24^A	16.96±4.93^A	166.55±17.75^A
	ALV-J$^+$	41	141.85±7.51^B	34.76±6.32^B	483.75±17.39^B
18	ALV-J$^-$	42	199.53±8.55^A	34.98±6.03^a	486.30±20.00^a
	ALV-J$^+$	45	98.15±7.43^B	20.48±4.99^b	236.45±11.63^b

Different small letters within the same column shoulder standard mean siginificant difference ($p<0.05$); Different capital letters within the same column shoulder standard mean extremely significant difference ($p<0.01$)

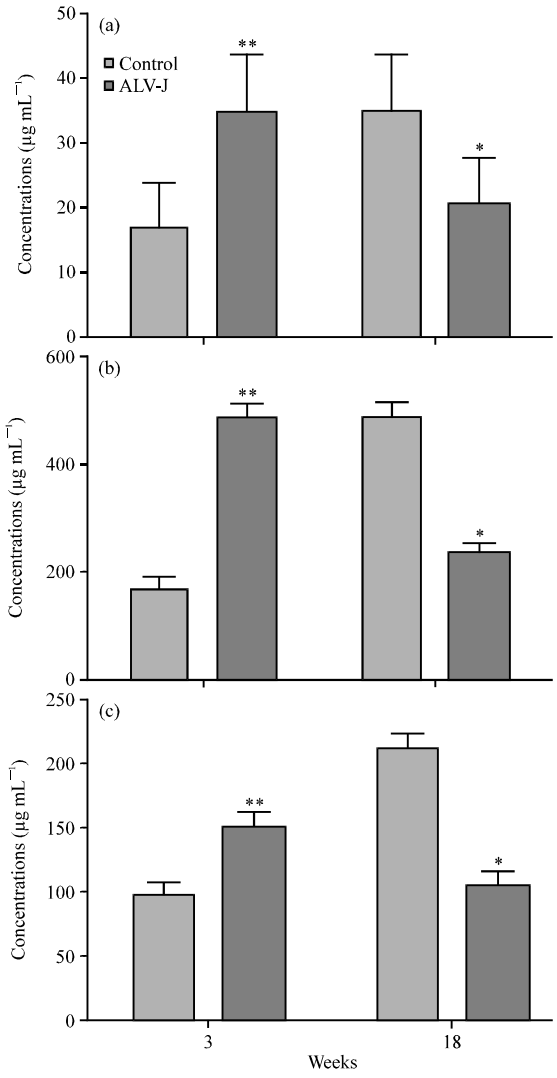

Fig. 2: Comparisons of the serum: a) IgM; b) IgG and c) IFN-β concentrations with ALV-J infection and control birds at 3 and 18 weeks age. Asterisks (*) and (**) above the bars show significant ($p<0.05$) or exstremely significant ($p<0.01$) differences compared to the ALV-J infection group with the same condition

(Diamond *et al*., 2003a, b). Therein lies two well-studied antibodies, IgM and IgG. IgM mainly binds to blood group antigens (Jefferis and Kumararatne, 1990) and can set up the immune response by promoting phagocytosis, activing complement (Austen Jr. *et al*., 2003) and boosting the unequivocal initiation of IgG (Diamond *et al*., 2003a, b; Boes, 2000). IgG is the secondary class of secreted Ig (Ratcliffe, 2006) which is the predominant isotype present in blood. IgG provides comprehensive systemic immune protection by directly neutralizing receptor binding and complement-mediated lysis of virus or infected cells (Diamond *et al*., 2003a, b). At present IgM and IgG have been used in several applications such as detection of chronic or virus infection immune disease and using as immunotherapeutic agents (Pas *et al*., 2013; Lennon *et al*., 2004; Ibrahim *et al*., 2008). The study of Dou manifested that maternal antibodies could provide effective protection against viremia and immunosuppressive lesions caused by ALV-J infection (Dou *et al*., 2013). All of those studies prove that antibodies are crucial for confronting retroviral infection.

IFN-β, IgM and IgG are key roles in both innate and adaptive antiviral immune responses. The effect of ALV-J infection on the activity of IFN-β, IgM and IgG is uncertain. A previous study has shown that Specific Pathogen-Free (SPF) chickens infected with ALV-J engenderd strong immune response at 2 weeks age while the response decreased quickly after 4 weeks age (Wang *et al*., 2011). The result indicates that it is critical and sensitive for detecting of ALV-J and determining the serum IFN-β, IgM and IgG concentration at 3 weeks age which can represent the early stage of ALV-J infection. In the study, serum IFN-β concentration of infected individuals were significantly up-regulated and ~1.5 fold to the control group at the early stage of ALV-J infection. This observation is in agreement with previous findings that HIV induces low levels of IFN-β in macrophages (Gessani *et al*., 1994) and IFN-β levels in the brain increase between 7 and 21 days after infected with SIV (Barber *et al*., 2004). Early infection with ALV-J usually led to production of antibodies (Payne and Nair, 2012) which quite consistent with the results in the research that IgM and IgG concentrations of ALV-J infected group were significantly higher than the control group at the early stage of ALV-J infection. To summarize, the research demonstrates that early infection of ALV-J launch a strong immune response and enhance the serum IFN-β, IgM and IgG levels.

With long-term chronic virus infection such as HIV-1, immune dysfunction and cognitive impairment may happen to the host because of prolonged immune challenge, neither the cellular nor the humoral arms of the immune system can control the infection (De Milito *et al*., 2004). Similar results elucidated in ALV-J infection: ALV-J caused damage of immune organs and decrease of immune responses. What's more, pathogenesis of immunosuppression caused by ALV-J appears to be associated with both T and B cells (Wang *et al*., 2011) which may cause profound damage to the immune response. The results manifest that long-term ALV-J infection induces the low level of serum IFN-β, IgM and IgG and the conclusion reaches a consensus with the study of White Leghorn chickens (Williams and Sellers, 2012).

A major function of IFN-β is to link innate and adaptive immunity and IFN-β is a symbol to resent virus invading (Le Bon and Tough, 2002). Results of present studies suggest that IFN-β is implicated in the production of several immunomodulatory cytokines. Because of the strong immunomodulatory effects of dendritic cells and B cells, IFN-β potently affects adaptive immune responses mainly via inducing antibody production and increasing the antibody-secreting cells (Coro *et al*., 2006). In return, antibodies potentiate the IFN-β response by increasing expression of three IFN-β-regulating miRNAs (Witwer *et al*., 2010). Previous research results manifest that there are interactions between IFN-β and antibodies and are consistent with our findings that increase of serum IFN-β accompanied up-regulation of IgM and IgG at the early stage of ALV-J infection while serum IFN-β levels decreased with a descending of IgM and IgG simultaneously at the late stage of ALV-J infection.

CONCLUSION

The results indicate that early ALV-J infection up-regulates the serum IFN-β, IgM and IgG concentrations. Conversely, late ALV-J infection down-regulates the three factors significantly. Furthermore, the concentrations of IFN-β, IgM and IgG present highly consistency in the two different stages of ALV-J infection which indicates that there may be interplay among IFN-β, IgM and IgG.

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