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REVIEW ARTICLE **OPEN ACCESS**

Insights of Possible Mechanism of Immunity Against Marek's Disease- A Review

Somesh Banerjee[1*], Piyush Tomar[2], Manish Kumar[3] and Praveen Kumar[3]
[1]Department of Veterinary Microbiology
[2]Department of Public Health and Epidemiology
[3]Department of Veterinary Medicine
College of Veterinary Sciences
Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar
Correspondence[*]- tomarvety@gmail.com

ABSTRACT
Marek's disease (MD) is a lymphoproliferative disease of poultry caused by alpha herpes virus against which first antioncogenic viral vaccine was developed. MDV causes cytolytic infection affecting B and T lymphocytes. Sometimes it also causes latent infection in chicken. The disease is characterized by development of malignant T cell lymphoma in various organs like liver, spleen, lungs etc. Non oncogenic strain of the virus is used for the development of vaccine for commercial use which shows variable degree of immunity in field condition. Due to high cell associated nature of the virus, T cell mediated immunity confers protection in experimental condition but precise mechanism is still unknown. Role of different viral glycoproteins in inducing humoral immunity and neutralizing antibody (nAb) also studied and found protective in animal model but the correlates of protection against Marek's disease infection is still unknown. Further, use of different strain or strains in monovalent, bivalent and trivalent vaccine increases the virulency of the MDV in nature. Due to the above facts, in the present review we discuss about the various mechanisms associated with marek's disease infection and vaccine induced immunity.
Keywords: *Marek's disease, Non oncogenic strain, T cell mediated immunity, vaccine*

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INTRODUCTION

Marek's disease (MD) is a highly contagious malignant lymphoma of chicken caused by Marek's disease virus (MDV) which belongs to alpha-herpesvirus consisting of a linear, double stranded DNA of approximately 160-180 kbp size. Infected chickens are depressed, and many clinical signs including dullness, squat down and inverse feathers with progression of lymphoma development and paralysis or ataxia if lymphoma/lymphoblast cells infiltrate in peripheral nerves are observed [1]. The MDV group has been divided into three serotypes based on their biological properties viz. serotype 1,2 and 3[2]. Serotype 1 MDV is virulent and oncogenic whereas serotype 2 and 3 are non-pathogenic vaccine strains. Serotype 1 MDV strain viruses are further classified into pathotypes based on induction of lymphoproliferative lesions and severity of disease in vaccinated chickens (Table 1) [3] [21]. Later, a new classification system called 'neuropathotyping' is a statistical approach that was used for classification of Marek's disease virus on the basis of their neurotropism and neurovirulence [4]. The current review is made with the aim of various aspects of immunity against marek's disease infection and vaccine.

MDV INFECTION AND IMMUNOSUPPRESSION

The natural route of MDV transmission is direct or indirect contact between chickens by the airborne route [5]. The cell free virus particles after inhalation by the chicken transported to lymphoid organs where the virus particle remains as cell- associated form [6]. An exceptional of this is feather follicle epithelium (FFE) where the virus remains as cell free form and produces fully infectious virus [7].InInfectious viral particles in shed dander are first detected around 8 dpi and which further increases up to 28 dpi [8]. Viral genes US2, UL13, and glycoprotein C all have been found associated with horizontal

transmission of MDV though their exact mechanism are yet not understand [9]. The oncogenic MDV have four overlapping infection phases [10]. Chicken infected with virulent MDV undergoes early productive replication between 3 and 7 dpi in which the virus replicates in macrophages, B and T lymphocytes [11, 12, and 13]. Latent (non-replicating) infection is established around 7 d post-infection (dpi). The third and fourth phases of infections are secondary productive replication stage and transformation in the infected chicken [14, 15]. MDV stays non-productive and no viral antigens are produce during latent period [16] but between 14 and 21 dpi, latently-infected T lymphocytes can undergoes transformation resulting development of lymphomas in visceral organs [13, 15, 17]. Immunosuppression caused by MDV involves both humoral and cell-mediated immune response [18]. This is mainly associated with cytolysis of both B and T lymphocytes leading to lymphopaenia and infection with MDV [3]. Understanding the mechanism of immunosuppression, rapid apoptosis and depletion of CD 4+ T lymphocytes in periphery and CD 4+ CD 8+ double positive thymocytes leading to thymic atrophy in infected chicken [19]. In addition with apoptosis, down regulation of expression of surface CD 8 molecule and major histocompatibility complex leads to the deficiency of functional effector cells [20]. Interestingly, the virulence of different pathotypes of oncogenic MDV correlates with the degree of bursal and thymic atrophy, supported by the data of relative organ weights and histological examination [3]. The variability in immunosuppression and atrophy in relation to degree of virulence of various pathotypes demands further investigation in the disease mechanism for locating the underlying factor, precisely.

IMMUNE RESPONSE TO MDV INFECTION:

Immune response to MD requires activation of both innate and adaptive arm of immune system. The interaction between MDV and different components of host immune system determine the appropriate immunity against MD infection. Previously it was thought that there was distinct border between innate and adaptive immune response of host against MD infection. Later it was found that virus-host interaction was very complex and involve different cytokines, antibodies, macrophages, natural killer (NK) cells, T helper (TH) cells, cytotoxic T lymphocytes (CTLs) and soluble factors such as nitric oxide (NO) suggesting there is no such distinct border between them [22]. Replication of MDV mostly occurs in macrophages, B and T lymphocytes [23].One of the mechanisms of MDV immune evasion is reduce expression of major histocompatibility complex B glycoproteins [24]. During latency, down regulation of surface expression of viral gene and lack of integration into host telomeres also contribute to the evasion of immune system of the host which might be associated with tumorigenesis, although the precise mechanism is still unknown. [25] [26] [27].Host telomere integration of MDV suggested a key feature of cellular transformation in early and late MD infections [28]. When birds are challenged with mutated telomeric MDV strains, the development of lymphomas significantly reduce suggesting a link in between host telomere integration and tumorigenecity [29].

Host innate immune response have found a critical regulator of the MDV infection when studies in inbred chicken line with variable resistance [30]. As the MDV replication occurs within the macrophages, the role of macrophages in MD pathogenesis and immunity has shown both in vitro and in vivo studies [31, 32, 33]. Macrophage is a potent phagocytic cell which may exert their antiviral activity through phagocytosis of the MDV infected cell or through release of pro inflammatory cytokines like NO. In MD infected chicken, up regulation of inducible nitric oxide synthase (iNOS) gene has found on the surface of spleen, lung and brain and higher concentration of NO directly correlates with the greater inhibition of the MDV replication inside the macrophages [34, 35, 36].Another important cell of innate immune response which has potent antiviral activity against herpes virus is NK cells [37]. The NK cells mediate their antiviral activity either by Fas-FasL mediated apoptosis of the infected cells or release of granzyme and perforin mediated pathway. In MD viral infection, higher expression level of granzyme A and perforin was observed in study suggesting its role in limiting the MDV infection. The role of NK cells during cellular transformation have been also studied have result suggest that NK cells target the MDV transformed cells and cause apoptosis. Altogether, NK cells activity during early cytolytic infection stage is very crucial and it can generate a protective immune response against infection [38, 39].

Cytokines play an important role in viral infection and one of the important among these is type I interferon which has potent antiviral activity. Detection of virus pathogen by the pattern recognition molecules elicited and appropriate innate immune response. These pattern recognition molecules recognize conserved molecular patterns known as pathogen-associated molecular patterns (PAMPs) via TLRs, NLRs and others. Avian TLRs have well characterized and TLR3 and TLR 7 found have role in MDV infection [40]. Both these TLRs have been found over expressed in an aerosol-based chicken infection model. These TLRs recognized viral nucleic acids and caused activation of transcription factor known as interferon regulatory factors (IRF) and finally induction of type I interferons [41, 42].

Humoral response in MDV:

Due to the highly cell-associated nature of the MDV, the precise mechanism of development of antibody mediated immune response has not been clearly understood. However, role of neutralizing Antibodies against various glycoproteins of MDV for example gB, gE and gI has been studied and found protective [43, 44]. Virus neutralizing antibody via blocking the entry of virus, antibody-dependent cell-mediated cytotoxicity (ADCC) all has been described in understanding the mechanism of humoral response [45]. The role of maternal antibodies in reducing the virus replication and tumor formation has been described. These antibodies may also interfere with cell-free virus HVT vaccines by neutralizing the vaccine virus reducing the vaccine efficacy [46].

Cellular response in MDV:

The role of CD8+ T cells in marek's disease was found by depleting using monoclonal antibodies, resulting in a high MDV titer within CD4+ T cells [47]. The cytotoxic activity of CD8+ T cells against cells expressing MDV antigens such as pp38, meq, ICP4 and gB was identified [48]. In another study the CTL was characterized as CD8+TCR2+cells and showed that CD4+ and TCR1+ cells are not important for the MDV antigen- expressing cells elimination [49]. An increase in expression of granzyme A and CD8a genes after MDV infection was also found using a microarray approach, which suggest up-regulation in CTL activity after MDV infection [50]. It was also tried to identify the epitopes within the MDV antigens and observed that some of these epitopes are close to the C-terminal domain of the gB antigen [51]. In several studies the peptides presented by MHC haplotypes of chickens were examined with the intention of predicting and identifying T cell epitopes of MDV [52, 53]. The Marek's disease tumor-associated surface antigen (MATSA) was also recognized [54]. Removal of MATSA from MD tumor cell lines did not change the lyses of these cells by CTL [55]. MATSA can also be expressed on spleen cells after stimulation with mitogens and than culturing in ''conditioned medium'' (CM) or by directly culturing normal spleen cells in CM [56].

MAREK'S DISEASE VACCINE

The vaccine against Marek's disease is the first vaccine against oncogenic virus which use for commercial purpose. Initially, the non-oncogenic serotype 3 MDV (HVT) was introduced for commercial breeder (egg-laying and broiler parent flocks) and layer flock with a high rate of success. As the virulency of the MDV increase within 10 years, a second type of vaccine containing non-oncogenic serotype 2 (SB1) was introduced in USA with gives protection against vvMDV field challenge. Later the efficacy of bivalent vaccine containing both SB1 and HVT found more compare to monovalent vaccine against vvMDV. Later, around 1990 a more pathogenic pathotypes vv (+) MDV were being isolated in SB 1 and HVT vaccinated flock. Later, in 1994, a oncogenic serotype 1 rispen strain of MDV (CVI988) was introduced particularly for the area associated with MD outbreaks in vaccinated flocks. CVI988 mostly used in association with SB1 and HVT as a trivalent form [57]. Many considered CVI988 strain as a gold standard vaccine for protection against MD in challenged condition but, never the less, evidence is there that some new emerging strain of MDV may able to break the protective effect of CVI988 vaccine [58]. These reports indicated that the protective effects of HVT vaccine were mediated through T cell responses. Glycoprotein B (gB) is one of the candidates which induces the protective effects by the vaccine, because this antigen is shared by all three serotypes of MDV. Recently, it has been reported that recombinant fowlpox virus expressing glycoprotein B (gB) significantly reduced the level of cell-associated viremia and induced protective immunity against MD [46, 58]. The recombinant fowlpox virus vaccine induces both humoral and cellular immunity via CD8+T cells, indicating that immune responses against gB might be essential for the protective effects induced by the vaccines. Gene expression through RT-qPCR can be employed for elucidating the mechanisms of vaccine causing protection. It was observed that there was significantly less IL-6, IL-10, and IL-18 transcripts in the spleen of vaccinated protected chickens compared to unvaccinated-infected chickens [59]. It is also found that IL-10 significantly increased in response to infection [59]. Expression of interferon regulatory factor 3 (IRF3) and iNOS was higher in response to vaccination at the later time points but lower at the earlier time points [60].

CONCLUSION

In conclusion, there is a considerable gap in understanding the mechanism of immunity; dynamicity of T cell mediated immune response against MDV. Though the molecular and cellular mechanism of immunity was studied by various groups, knowledge regarding molecular determinants associated with the MDV is not fully understood. An important aspect of development of Marek's disease in poultry is that increasing in the virulence of field virus due to sustainable vaccination, which is a threat to poultry production. A keen knowledge regarding molecular and cellular mechanism involve in immunity, identification of potential determinants and vaccine induce immunity will help us to circumvent the problem associated with precipitation of MD in poultry.

Table 1: Different MDV serotypes and their respective pathotypes or strains (Adopted from M. C. McPherson and M. E. Delany, 2016 [21])

MDV serotypes	Status	Genome size (kb)	Pathotypes or strains
Serotype 1	Pathogenic or oncogenic strains	174-178.3	Very virulent plus (vv+): 648A Very virulent (vv): Md/5, Md/11, RB-1B, Ala-8 Virulent (v): HPRS-16, JM GA Mild (m) virulent: HPRS-B14, conn A Weakly virulent: CU-2, CV 1988
Serotype 2	Naturally occurring non-pathogenic, non-oncogenic or avirulent strains	165.9	SB-1, HRPS-24, 301B/1, HN-1
Serotype 3	Naturally occurring non-pathogenic, non-oncogenic or avirulent strains	160	Herpes virus of turkey (HVT) FC-126, PB-1

REFERENCES

1. Payne, L.N. (1985). Pathology. pp.43-75. In: Marek's Disease (Payne, L. N. ed.), Martinus Nijhoff, Boston.
2. Witter, R.L. (1998). The changing landscape of Marek's disease. Avian Pathology., 27:S46–S53.
3. Calnek, B.W., Harris, R.W., Buscaglia, C., Schat, K.A. and Lucio, B. (1998). Relationship between the Immunosuppressive Potential and the Pathotype of Marek's Disease Virus Isolates. Avian Diseases., 42:124-132.
4. Gimeno, I.M., Witter, R.L. and Neumann, U. (2002). Neuropathotyping: A new system to classify Marek's disease virus. BIOONE online journal: Avian Dis., 46(4):909-918.
5. Carrozza, J.H., Fredrickson, T.N., Prince, R.P., Luginbuhl, R.E. (1973). Role of desquamated epithelial cells in transmission of Marek's disease. Avian Dis., 17:767–781.
6. Schat, K.A. and Nair, V. (2008). Marek's disease. Pages 452–514 in "Diseases of Poultry", 12th ed., Y. M. Saif et al., eds. Blackwell Publishing, Iowa.
7. Calnek, B.W., Adldinger, H.K. and Kahn, D.E. (1970). Feather follicle epithelium: a source of enveloped and infectious cell free herpesvirus from Marek's disease. Avian Dis., 19:473–482.
8. Jarosinski, K.W. (2012). Marek's Disease Virus Late Protein Expression in Feather Follicle Epithelial Cells as Early as 8 Days Post infection. Avian Dis., 56:725–731.
9. Jarosinski, K.W., Margulis, N.G., Kamil, J.P., Spatz, S.J., Nair, V.K. and Osterrieder, N. (2007). Horizontal Transmission of Marek's Disease Virus Requires US2, the UL13 Protein Kinase, and gC. J. Virol., 8119:10575–10587.
10. Calnek, B.W. (2001). Pathogenesis of Marek's disease virus infection. Curr. Top. Microbiol. Immunol., 255:25–55.
11. Arumugaswami, V., Kumar, P.M., Konjufca, V., Dienglewicz, R.L., Reddy, S.M., and Parcells, M.S. (2009). Latency of Marek's disease virus (MDV) in a reticuloendotheliosis virus-transformed T-cell line. II: expression of the latent MDV genome. Avian dis., 53:156–165.
12. Baigent, S.J. and Davison, F. (2004). Marek's disease virus: biology and life cycle. In Marek's disease, an evolving problem. Elsevier Academic Press. (pp. 62–77).
13. Trapp, S., Parcells, M.S., Kamil, J.P., Schumacher, D., Tischer, B.K., Kumar, P.M., Nair, V.K. and Osterrieder, N. (2006). A virus encoded telomerase RNA promotes malignant T cell lymphomagenesis. J. Exp. Med., 203:1307–1317.
14. Nair, V. (2005). Evolution of Marek's disease–a paradigm for incessant race between the pathogen and the host. Vet. J., 170:175–183.
15. Osterrieder, N., Kamil, J.P., Schumacher, D., Tischer, B.K. and Trapp, S. (2006). Marek's disease virus: from miasma to model. Nat. Rev. Microbiol., 4:283–294.
16. Calnek, B.W., Shek, W.R. and Schat, K.A. (1981). Latent infections with Marek's disease virus and turkey herpes virus. J. Natl. Cancer Inst., 66:585– 590.
17. Burgess, S.C. and Davison, T.F. (2002). Identification of the neoplastically transformed cells in Marek's disease herpesvirus-induced lymphomas: recognition by the monoclonal antibody AV37. J. Virol., 76:7276–7292.
18. Islam, A.F.M.F., Wong, C.W., Walkden-Brown, S.W., Colditz, I.G. , Arzey, K.E. and Groves, P.J. (2002). Immunosuppressive effects of Marek's disease virus (MDV) and herpesvirus of turkeys (HVT) in broiler chickens and the protective effect of HVT vaccination against MDV challenge. Avian Pathol., 31(5): 449-461. DOI: 10.1080/0307945021000005824
19. Morimura, T., Hattori, M., Ohashi, K., Sugimoto, C. and Onuma, M. (1995). Immunomodulation of peripheral T cells in chickens infected with Marek's disease virus: involvement in immunosuppression. J. Gen. Virol., 76: 2979–2985.
20. Morimura, T., Ohashi, K., Kon, Y., Hattori, M., Sugimoto, C. and Onuma, M. (1996). Apoptosis and CD8-down-regulation in the thymus of chickens infected with Marek's disease virus. Arch. Virol., 141: 2243–2249.
21. McPherson, M. C. and Delany, M. E. (2016). Virus and host genomic, molecular, and cellular interactions during Marek's disease pathogenesis and oncogenesis. Poultry Science 00:1–18. http://dx.doi.org/10.3382/ps/pev369
22. Schat, K.A. and Markowski-Grimsrud, C.J. (2001). Immune responses to Marek's disease virus infection. Curr. Top. Microbiol. Immunol., 255:91–120.
23. Calnek, B.W., Schat, K.A., Ross, L.J., Shek, W.R. and Chen, C.L. (1984). Further characterization of Marek's disease virus-infected lymphocytes. I. *In vivo* infection. Int. J. Cancer. 33:389–398.

24. Hunt, H.D., Lupiani, B., Miller, M.M., Gimeno. I., Lee, L.F. and Parcells, M.S. (2001). Marek's disease virus down-regulates surface expression of MHC (B complex) class I (BF) glycoproteins during active but not latent infection of chicken cells. Virology., 282:198–205.
25. Schat, K.A. (2004). Marek's disease immunosuppression. In: Nair, V., Davison, F. (Eds.), Marek's Disease: An Evolving Problem. Elsevier, Great Britain, pp. 142–155.
26. Desfarges, S. and Ciuffi, A. (2012). Viral integration and consequences on host gene expression, in G. Witzany, Ed: Viruses: Essential Agents of Life. XVI (pp. 147–175) Springer, Berlin.
27. Nair, V. (2013). Latency and tumorigenesis in Marek's disease. Avian Dis. 57:360–365.
28. Robinson, C.M., Cheng, H.H. and Delany, M.E. (2014). Temporal Kinetics of Marek's Disease Herpesvirus: Integration Occurs Early after Infection in Both B and T Cells. Cytogenet Genome Res., 144:142–154.
29. Kaufer, B.B., Jarosinski, K.W. and Osterrieder, N. (2011). Herpesvirustelomeric repeats facilitate genomic integration into host telomeres and mobilization of viral DNA during reactivation. J. Exp. Med., 208:605–615.
30. Kaiser, P. (2010). Advances in avian immunology—prospects for diseasecontrol: a review. Avian. Pathol., 39:309–324.
31. Barrow, A.D., Burgess, S.C., Baigent, S.J., Howes, K. and Nair, V.K. (2003). Infection of macrophages by a lymphotropic herpesvirus: a new tropism for Marek's disease virus. J. Gen. Virol., 84:2635–2645.
32. Djeraba, A., Bernardet, N., Dambrine, G. and Quéré, P. (2000). Nitric oxide inhibits Marek's disease virus replication but is not the single decisive factor in interferon-gamma-mediated viral inhibition. Virology., 277:58–65.
33. Gimeno, I.M., Witter, R.L., Hunt, H.D., Lee, L.F., Reddy, S.M. and Neumann, U. (2001). Marek's disease virus infection in the brain: virus replication, cellular infiltration, and major histocompatibility complex antigen expression. Vet. Pathol., 38:491–503.
34. Abdul-Careem, M.F., Haq, K., Shanmuganathan, S., Read, L.R., Schat, K.A., Heidari, M. and Sharif, S. (2009b). Induction of innate host responses in the lungs of chickens following infection with a very virulent strain of Marek's disease virus. Virology., 393: 250–257.
35. Jarosinski, K.W., Njaa, B.L., O'Connell, P.H. and Schat, K.A. (2005). Pro-inflammatory responses in chicken spleen and brain tissues after infection with very virulent plus Marek's disease virus. Viral Immunol., 18:148–161.
36. Xing, Z. and Schat, K.A. (2000b). Inhibitory effects of nitric oxide and gamma interferon on in vitro and in vivo replication of Marek's disease virus. J. Virol., 74:3605– 3612.
37. Paludan, S.R., Bowie, A.G., Horan, K.A. and Fitzgerald, K.A. (2011). Recognition of herpesviruses by the innate immune system. Nat. Rev. Immunol., 11:143–154.
38. Sarson, A.J., Abdul-Careem, M.F., Read, L.R., Brisbin, J.T. and Sharif, S. (2008). Expression of cytotoxicity-associated genes in Marek's disease virus-infected chickens. Viral Immunol., 21:267–272.
39. Garcia-Camacho, L., Schat, K.A., Brooks Jr, R. and Bounous, D.I. (2003). Early cell-mediated immune responses to Marek's disease virus in two chicken lines with defined major histocompatibility complex antigens. Vet. Immunol. Immunopathol., 95:145–153.
40. Boyd, A., Philbin, V.J. and Smith, A.L. (2007). Conserved and distinct aspects of the avian Toll-like receptor (TLR) system: implications for transmission and control of bird-borne zoonoses. Biochem. Soc. Trans., 35:1504–1507.
41. Jenkins, K.A., Lowenthal, J.W., Kimpton, W. and Bean, A.G. (2009). The in vitro and in ovo responses of chickens to TLR9 subfamily ligands. Dev. Comp. Immunol., 33:660– 667.
42. Abdul-Careem, M.F., Javaheri-Vayeghan, A., Shanmuganathan, S., Haghighi, H.R., Read, L.R., Haq, K., Hunter, B.D., Schat, K.A., Heidari, M. and Sharif, S. (2009a). Establishment of an aerosol-based Marek's disease virus infection model. Avian Dis., 53:387–391.
43. Davison, T.F. and Kaiser, P. (2004). Immunity to Marek's disease. In: Nair, V., Davison, F. (Eds.), Marek's Disease: An Evolving Problem. Elsevier, Great Britain, pp. 126–139.
44. Schat, K.A. and Markowski-Grimsrud, C.J. (2001). Immune responses to Marek's disease virus infection. Curr.Top. Microbiol. Immunol., 255:91–120.
45. Ross, L.J.N. (1980). Mechanisms of protection conferred by HVT. In: Biggs, P.M. (Ed.),Resistance and Immunity to Marek's disease. Commission of the European Communities, Berlin, pp. 289–297.
46. Calnek, B.W. (1986). Marek's disease – a model for herpesvirus oncology. Crit. Rev.Microbiol., 12:293–320.
47. Morimura, T., Ohashi, K., Sugimoto, C. and Onuma, M. (1998). Pathogenesis of Marek's disease (MD) and possible mechanisms of immunity induced by MD vaccine. J.Vet. Med. Sci., 60:1–8.
48. Omar, A.R. and Schat, K.A. (1996). Syngeneic Marek's disease virus (MDV)-specific cell mediated immune responses against immediate early, late, and unique MDV proteins. Virology., 222:87–99.
49. Omar, A.R. and Schat, K.A. (1997). Characterization of Marek's disease herpesvirus specific cytotoxic T lymphocytes in chickens inoculated with a non-oncogenic vaccine strain of MDV. Immunology., 90:579–585.
50. Sarson, A.J., Zhou, H. and Sharif, S. (2006). Transcriptional analysis of host responses to Marek's disease viral infection. Viral Immunol., 19:747–758.
51. Schat, K.A. and Xing, Z. (2000). Specific and nonspecific immune responses to Marek'sdisease virus. Dev. Comp. Immunol., 24:201–221.
52. Cumberbatch, J.A., Brewer, D., Vidavsky, I. and Sharif, S. (2006). Chicken major histocompatibility complex class II molecules of the B haplotype present self and foreign peptides. Anim. Genet., 37:393–396.
53. Sherman, M.A., Goto, R.M., Moore, R.E., Hunt, H.D., Lee, T.D. and Miller, M.M. (2008). Mass spectral data for 64 eluted peptides and structural modeling define peptide binding preferences for class I alleles in two chicken MHC-B haplotypes associated with opposite responses to Marek's disease. Immunogenetics., 60:527–541 (Erratum in: Immunogenetics 62, 419).

54. Murthy, K.K. and Calnek, B.W. (1979). Marek's disease tumor-associated surface antigen (MATSA) in resistant versus susceptible chickens. Avian Dis., 23:831–837.
55. Schat, K.A. and Murthy, K.K. (1980). In vitro cytotoxicity against Marek's disease lymphoblastoid cell lines after enzymatic removal of Marek's disease tumor associated surface antigen. J. Virol., 34:130–135.
56. McColl, K.A., Calnek, B.W., Harris, W.V., Schat, K.A. and Lee, L.F. (1987). J. Natl. Cancer Inst., 79:991–1000.
57. Bublot, M. and Sharma, J.M. (2004). In: Marek's Disease:An Evolving Problem. Davison F, Nair VK (Eds). Elsevier, London, UK, 168–185.
58. Davison, F. and Nair, V. (2005). Use of Marek's disease vaccines:could they be driving the virus to increasing virulence? Expert Rev. Vaccines., 4(1):77–88.
59. Abdul-Careem, M.F., Hunter, B.D., Parvizi, P., Haghighi, H.R., Thanthrige-Don, N. and Sharif, S. (2007). Cytokine gene expression patterns associated with immunization against Marek's disease in chickens. Vaccine., 25:424–432.
60. Kano, R., Konnai, S., Onuma, M. and Ohashi, K. (2009). Cytokine profiles in chickens infected with virulent and avirulent Marek's disease viruses: interferon-gamma is a key factor in the protection of Marek's disease by vaccination. Microbiol. Immunol., 53:224–232.

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