Int J Pharm Bio Sci 2013 Apr; 4(2): (B) 6 - 11

Review Article **Biotechnology**

International Journal of Pharma and Bio Sciences

ISSN 0975-6299

MAREK'S DISEASE: THE NEVER ENDING CHALLENGE –A REVIEW

SMITHA SUDHAKAR* AND Dr. A. JAYAKUMARAN NAIR

Department of Biotechnology University of Kerala, Thiruvananthapuram, India

ABSTRACT

Marek's disease virus is a highly oncogenic alpha-herpesvirus that induces Marek's disease, a lymphomatous disease in poultry which accounts for the huge economic loss every year. The virus has been an ever evolving strain with different pathotypes causing much concern because of possible interspecies transfer to humans. The existing vaccines may drive the pathogen to more and more virulence .So it is very particular that new recombinant vaccines or improved vaccines based on Herpes Virus of Turkey's, that can hinder viral replication and egression, should be developed. Marek's virus serves as a model for herpes virus induced cancer studies outside humans and when disarmed the virus itself is assumed to be the best vaccine against cancer of Herpes Simplex Viral origin.

Key Words: Marek's Disease, Marek's virus, Glycoproteins, Vaccines, Poultry, Herpes virus

SMITHA SUDHAKAR
Department of Biotechnology University of Kerala,Thiruvananthapuram, India

INTRODUCTION

Marek's Disease- Chronology and Incidence

At the beginning of the 20th century the flourishing poultry industry gave birth to a new pathogen, which as all Herpes viruses is unwieldy even today. This ever evolving virus caused Marek's disease. The triumphant evolutionary process was imparted to the virus by high animal densities, genetic monoculture, and intensive exchange of breeding material coupled with unhygienic poultry practices. Various workers have reported the incidence of Marek's disease (MD) but the pioneering report by Jozef Marek (1868 - 1952) a Hungarian veterinarian and scientist, published in 1907 of manifestation in roosters, was the first account of the disease that now bears the author's name. The thickening of sacral plexus and spinal routes that were infiltrated by mononuclear cells were documented and he termed the disease 'Neuritis interstitials' or 'Polyneuritis gallinarium'. Further studies showed that apart from the nerve lesions, lymphoid tumor formation was evident in MD infection .By the time the visceral lympho-proliferative manifestation of the disease was also well understood besides the nervous implication. In 1950s amidst chicken of 8-10 weeks of age, high incidence of visceral lymphomatosis was reported in USA. This condition was also noted in Great Britain and was termed 'Acute leucosis'. Consequently Acute Leucosis was found to coincide with the conditions described by Joseph Marek in 1907 and the disease was termed 'Acute Marek's Disease'. MD occurs in all breeds of chicken, pheasants, turkeys and occasionally quail at 3–4 weeks of age or older and is most common between 12 and 30 weeks of age, but birds die near the onset of egg production. Morbidity up to 50% and mortality up to 100% typically continues at a moderate or high rate for quite a few weeks in an affected flock. The incidence is quite variable in commercial flocks and depends on various parameters like strain and dose of virus, age at exposure, maternal antibody, host gender and genetics, other concurrent diseases, and several environmental factors including stress.Since the 1960s poultry production has become a major global industry operating in very high population densities under highly intensive management conditions aimed at higher rates of growth and productivity. As per the estimates of the Food and Agriculture Organization (FAO) a total of 45 bn broilers and 57 mtons of eggs with an approximate value of US$100 bn were produced in the year 2002. Under the present scenario it is calculated that yearly loss due to MD accounts for at least US$1 bn. In India reports of MD outbreaks from Orissa, Punjab, Assam, Uttar Pradesh, Andhra Pradesh, Arunachal Pradesh and Tripura, Gujarat appeared periodically and the annual loss accounts for Rs.4 Crores. Morocco, Nigeria, Russia, Peru and many other countries have faced serious economic loss during the turn of the century due to frequent MD outbreaks.

Marek's Disease Virus (MDV) and its Serotypes

MDV is a member of the genus Mardivirus and is morphologically and biochemically similar to other herpes viruses. MDV is composed of (i) an inner core, (ii) the capsid with 256 capsomeres, and (iii) an outer envelope.MDV has been classified into three serotypes based on the virulence and antigenic properties; MDV-1, MDV-2 and MDV-3/HVT (herpes virus of turkeys) also known as gallid herpes virus 2 (GaHV-2), gallid herpes virus 3 (GaHV-3) and meleagrid herpes virus 1 (MeHV-1), respectively. MDV serotypes are 50-80% similar at the DNA sequence level, but MDV-1 is the only serotype that is known to be pathogenic or oncogenic in chickens.

Characteristic lesions of Marek's Disease

Table 1

MACROSCOPIC LESIONS	MANIFESTATION
Neural involvement	Frequent
Bursa of Fabricius	Diffused enlarged or atrophied
Tumours in skin, muscle and pro- ventriculus, 'grey eye'	Seldom

Table 2

MICROSCOPIC LESIONS	MANIFESTATION
Neural involvement	Yes
Liver tumours	Perivascular
Spleen tumors	Diffuse
Bursa of Fabricius	Interfollicular tumour or atrophied follicles
Central nervous system	Yes
Lymphoid proliferation in skin and feather follicles	Yes

Vaccination strategies against MDV

Live vaccines are opted as an auxiliary control measure with good hygiene management as a basic practice at day one. All vaccines require 7-14 days to produce effective immunity and hence it is vital to reduce exposure during the first week of post-hatching. Presently freeze-dried and wet live vaccines are available. SB-1 was the first serotype2 MDV strain that was licensed to be used as a vaccine. The intensity of protection conferred by serotype 2 vaccines single-handedly is low, but they display protective synergism when used in combination with serotype 3 strains in bivalent vaccines. Naturally occurring non oncogenic turkey herpes virus (serotype 3), also known as HVT and combinations of HVT and serotype 2 strains, and the serotype 1 strain CVI988 have replaced orthodox vaccines. Various strategies have been practiced to develop MD vaccines based on recombinant techniques.

Current challenges for MDV vaccines

Generally vaccination is still used as the major strategy against MD, but the evolution of MDV strains towards greater virulence is an issue of major concern to the poultry industry and scientists. The first trend of evolution in the late 1950s shifted the virus from "mMDV" (mild Marek's disease virus) to "vMDV" (virulent Marek's disease virus). Due to ever scaling industrial practices, "vMDV" became "vvMDV," and now the world is dealing with "vv+MDV. Recently isolated MDV strains of high virulence appeared to have increased pathogenicity for adult chickens. Although not directly associated with vv+ strains the appearance of MD as a clinical disease of turkeys in France and Israel was simultaneous with the emergence of the pathotype. In the present scenario MDV will continue its evolution towards more virulence and more efficacious MD vaccines and sustainable strategies will be needed. Use of adjuvant and immune-modulators, double vaccination, alternating vaccines, management strategies inducing genetic resistance etc can be practiced. Present day MD vaccines that protect against the development of the disease, but not against the infection or transmission, can be only a temporary solution that might drive the pathogen to higher virulence and will likely spread not only to other animals but also to humans. The detection of MDV DNA in human sera has raised doubts about interspecies transmission of the virus between poultry and human beings. The emergence of epidemics like avian influenza strongly suggests the probability of such a doubt and it is the need of

the hour that effective vaccination strategies against poultry viral diseases like Marek's have to be designed. Experts are assuming that due to consumption of diseased chicken meat such viruses enter the human biological system and play a crucial role in causing malignant tumors in humans. These viruses remain in the blood for long intervals until the malignancies surface.

Novel MDV vaccines

Research proves that several MDV genes could be expressed in transgenic chickens to gain the potential to increase resistance to MDV. The glycoprotein D (gD) gene of HSV when transfected in cultured cells resulted in resistance to HSV infection presumably due to envelope blockage. Recently vaccine efficacy experiments using a Meq-null virus, rMd5 Delta Meq (in which the oncogene meq was deleted) showed that in chickens vaccinated with rMd5 Delta Meq virus or a preparation of CVI988/Rispens, rMd5 Delta Meq provided superior protection than traditional vaccines.

How to tackle MDV?

Purified HVT (MDV-Serotype-3) stocks, inactivated HVT preparations, membrane fractions of HVT-infected chick embryo fibroblasts, all are found to be equally effective in immunization against Marek's disease as cell-associated viruses. From numerous studies conducted it may be concluded that immunologic prevention of MD with HVT is mediated by antibodies against viral envelope and virus-specific membrane antigens. Several studies have proved the efficiency of envelope specific glycoproteins of HVT to induce neutralization of pathogenic MDV1, MDV2 and HVT strains.This unique neutralization property of some candidate glycoproteins of HVT viz., B, C, D and I can be harnessed, based on the principle that the heterologous expression of HVT or MDV related proteins or peptides in different expression systems can be exploited, for mass production of immunogenic molecules. These recombinant proteins when combined or singly can one day prove to be an effective MDV eradication strategy

MDV serves as a model for human cancer studies

MDV and HVT are direct cousins and the genetic variations between them may serve as a parameter for distinguishing oncogenic and non-oncogenic viruses of mammalian origin. Although pathogenicity or safety tests in humans have not been performed, it is assumed that MDV can act as candidate live virus for the prevention of herpes virus-induced cancer in humans. The MD model has not formed the basis of human cancer studies but the scientific intelligentsia hopes that the problems in using the virus for such tests may be facilitated, if the oncogenic virus produces an acute manifestation against which the vaccine will safeguard.

CONCLUSION

Marek's disease virus, the causative agent of Marek's disease, is an oncogenic alpha-herpesvirus that induces T-cell lymphoma in poultry. Present day MD vaccines can be only a temporary solution that might induce higher virulence and will likely spread not only to other animals but also to humans. The trend of evolution of the virus from "mMDV" to "vMDV" then to "vvMDV," and finally to "vv+MDV" is a matter of concern. Recent advances in MDV genetics and the revelation of the chicken genome sequence using functional genomics have dramatically increased our understanding of lytic MDV replication and also of the factors and mechanisms leading to latency and tumor formation. This helps to elucidate cellular signalling pathways that have undergone convergent evolution and emphasizes the value of MDV as a comparative biomedical model in cancer research. The great potential of using killed MDV as vaccines against human cancer is yet to be exploited.

REFERENCES

1. Adldinger, H. K., and Calnek, B. W. Pathogenesis of Marek's Disease: Early Distribution of Virus and Viral Antigens in Infected Chickens. J. Natl. Cancer Inst., 50. 1287-1298, 1973.
2. Afonso. C. L, Lu. Z, Zsak. L, Rock. D.L and Kutish. G. F. "The genome of turkey herpes virus" Journal of Virology 75: 971-978, 2001
3. Akiyama, Y., Naito, M., and Kato, S. Cell Surface Antigen and Viral Antigen of Marek's Disease Virus in Lymphoid Cells of the Spleen from Chickens Inoculated with Virulent Strains. 16: 91, 1973.
4. Benda, V. and Holzanek, I., Effect of large doses of turkey herpesvirus on antibody response in chickens, Folia Biol. 21, 184-188, 1975.
5. Biggs, P. M., Marek's disease. In The Herpesviruses Kaplan A. S., (ed.), pp. 557-594. Academic Press, New York, 1973.
6. Brown A.C, Baigent S.J, Smith LP, Chattoo JP, Petherbridge LJ, Hawes P, et al. Interaction of MEQ protein and C-terminal-binding protein is critical for induction of lymphomas by Marek's disease virus. Proc Natl Acad Sci USA; 103(6):1687–92, 2006
7. Bulow, V. von and Biggs, P.M. Differentiation between strains of Marek's disease virus and turkey herpes virus by immunofluorescence assays. Avian Pathology, 4: 133-146, 1975
8. Calnek, B. W. and Adldinger, H. K., Some characteristics of cell-free preparations of Marek's disease virus, Avian Dis. 15, 508-517 ,1971.
9. Cheng, Y.Q, Lee, L.F, Smith. E.J. and Witter, R.L. An enzyme linked immunosorbent assay for the detection of antibodies to Marek's disease virus. Avian Diseases, 28: 900-911, 1984.
10. Cho, B. R., Horizontal transmission of turkey herpesvirus to chickens. IV. Viral maturation in the feather follicle epithelium, Avian Dis. 19- 13, 141, 1975.
11. Churchill, A. E., and Biggs, P. M. Agent of Marek's Disease in Tissue Culture. Nature, 215: 528-530, 1967.
12. Churchill. A. E, Payne. L. N., "Immuni-zation against Marek's disease using a live attenuated virus." Nature 221: 744-747, 1969
13. Davison .A. J."Evolution of the herpes viruses." Veterinary Microbiology 86: 69-88, 2002
14. Frank Fehler. No. 25 / 2001, page 1, Marek's Disease: History, actual and future perspectives. Lohmann Information
15. Gomase. V.S. and Chitlange. N.R. Antigen protein from Schistosoma mansoni: New paradigm of synthetic vaccine development. International Journal of Pharma and Bio Sciences.1,3.1-7,2010
16. Griffin, B. E. & Xue, S. A. Epstein-Barr virus infections and their association with human malignancies: some key questions. Annals of Medicine 30, 249-259, 1998.
17. Holmes, G. P., Chapman, L. E., Stewart, J. A., Straus, S. E., Hilliard, J. K. & Davenport, D. S. Guidelines for the prevention and treatment of B-virus infections in exposed persons. C. I. D 20, 421-439, 1995
18. Isabel M. Gimeno (Vaccine 268), C31–C41,Marek's disease vaccines: A solution for today but a worry for tomorrow?, 2008
19. Jaganti.V, Das. S and Sampath.T. S .A Review on Cancer Vaccines, International Journal of Pharma and Bio Sciences .2,3.p 86-97,2011
20. Jarosinski. K. W, Margulis. N. G, Kamil. J, Nair.V. K and Osterrieder. N, Horizontal transmission of MDV requires US2, UL13 protein kinase, and gC, J.Virol.81, 19.10575–10587, 2007.
21. Jeurissen S.H.M, Janse E.M, Wagenaar F, de Boer G.F. The role of splenic ellipsoid associated reticulum cells in the pathogenesis of Marek's disease. 19th World's Poultry Congress, vol. 1. p. 211–215, 1995

22. Johnson.R.M and Spear.P.G, Herpes simplex virus glycoprotein D mediates interference with herpes simplex virus infection, resulted in resistance to HSV infection. J Virol 63, 1989
23. Kingham, B. F., Kopacek. J, Majerciak. V, Ney. E and Schmidt .C. J. "The genome of herpesvirus of turkeys: comparative analysis with Marek's disease viruses, J of Gen Virology 82: 1123-1135, 2001
24. Lee L.F., Liu X. & Witter R.L. (1983). Monoclonal antibodies with specificity for three different serotypes of Marek's disease virus in chickens. J. Immunol., 130, 1003–1006, 1983
25. Lee .L.F, Kreager KS, Arango J, Paraguassu A, Beckman B, Zhang H, Fadly A, Lupiani B, Reddy SM. Comparative evaluation of vaccine efficacy of recombinant MDV vaccine lacking Meq Feb 3; 28(5):1294-9,2010
26. Malkinson, M., Davidson, I and Y. Weisman,1996. Marek's disease in turkeys.Vet. Rec. 139:504–504.
27. Mallick A. R, Sarma.A.D and Ghosh.A. K. H5N1 Virus: A Pandemic Threat International Journal of Pharma and Bio Sciences. 1,3.1-11,2010.
28. Nair, V. Evolution of Marek's disease-a paradigm for incessant race between the pathogen and the host. Veterinary Journal. 83, 170-175. 2005
29. Nazerian, K., Solomon, J. J., Witter, R. L., and Burmester, B. R. Studies on the Etiology of Marek's Disease. Proc. Soc. Biol. Med., 127: 177-182, 1968.
30. Okazaki, W., Purchase, H. G. and Burmester, B. R., Protection against Marek's disease by vaccination with HVT, Avian Dis. 14, 413 429,1970
31. Payne, L. N., Frazier, J. A. and Powell, P. C., Pathogenesis of Marek's disease, Int. Rev. exp. Pathol. 16, 59-153, 1976.
32. Payne, L. N. Marek's disease-scientific basis and methods of control. Martinus Nijhoff Publishing, Boston, 1985
33. Purchase, H. G. and Sharma, J. M., Amelioration of Marek's disease and absence of vaccine protection in immunologically deficient chickens, Nature 248, 419 421,1974
34. Rosenberger, J. K., Cloud. S. S and Olmeda Miro, N. Epizootiology and adult transmission of Marek's disease. Pages 30–32, 1997
35. Solomon, J. J., Witter, R. L., Stone, H. A. and Champion, L. R., Evidence against embryo transmission of MDV, Avian Dis. 14, 752-762 ,1970
36. Witter, R. L. and Solomon, J. J., Epidemiology of HVT: possible sources and spread of infection in turkeys, Infect. Immun.4, 356-361, 1971
37. Witter, R. L., Turkey herpesvirus: lack of oncogenicity for turkeys, Avian Dis. 16, 666-67, 1972
38. Witter, R. L., Sharma, J. M. and Offen becker, L.,HVT infection in chickens: induction of lymphoproliferative lesions and characterization of vaccinal immunity against Marek's disease, Avian Dis. 20, 676-692,1976