# Differences in infectivities and genomic structures between oncogenic and non-oncogenic Marek's disease viruses

Sung-il Lee

*Laboratory of Infectious Diseases,*
*Department of Disease Control*
*Graduate School of Veterinary Medicine,*
*Hokkaido University, Sapporo 060-0818, Japan*

Marek's disease (MD) has been effectively controlled by vaccination, and considered as a model of protection immunity against herpesvirus-induced tumor. MD vaccine is one of the few vaccine, which can prevent infectious lymphomatous disorders among mammalian and avian species. However, the protection mechanism by MD vaccines has not been fully understood. Thus, current studies on Marek's disease virus (MDV) have focused on two major subjects. One is to clarify the protective mechanism of vaccine against MD. The other is to elucidate the mechanism of tumor induction by MDV serotype 1 (MDV 1) which is oncogenic. To approach both of the subjects, comparative studies among three MDV serotypes will be useful, because genetic dissimilarities between oncogenic MDV 1 and other two non-pathogenic serotypes, MDV serotype 2 (MDV 2) and herpesvirus of turkeys (HVT), are suggested to be related to viral oncogenicity, and unknown features shared by three MDV serotypes may play an important role in vaccine-induced immunity.

It is generally accepted that MD vaccination results in protection against both the viral infection and subsequent tumor formation by MDV. The main target for transformation by MDV is CD4$^+$ T cells, and it was shown that MDV preferentially infects CD4$^+$ rather than CD8$^+$ T cells. In addition, the differences in virus distributions in T cell subsets during the latent infection was found among different serotypes of MDV, Md5 (oncogenic MDV 1), CVI988 (non-oncogenic MDV 1) and SB-1 (non-pathogenic MDV 2). These differences in infectivities among MDV strains seem to be highly correlated with the oncogenic potentials of MDV. They also suggest the differences in the usage of viral receptors for different MDV strains. Furthermore, it was suggested that the reduction of the number of MDV-infected T cells could contribute to the protection mechanism induced by MD vaccines, since fewer viruses used for the challenge were re-isolated from vaccinated than unvaccinated chickens. Therefore, the exact mechanism for preferential infection of MDV to CD4$^+$ T cells should be studied in the future to understand the detailed molecular events induced by MD vaccines.

The molecular events during the MDV entry to host cells remains unknown due to its cell-associated nature. The herpesvirus entry to cells is mediated by various glycoproteins of the viral envelope. Following the attachment of virions, penetration is induced by fusion of the virion envelope with the cellular cytoplasmic membrane, resulting in release of the nucleocapsid and the tegument proteins into the cytoplasm. In order to find the candidates for viral receptors of oncogenic and non-oncogenic MDVs, an *in vitro* infection systems using cell-free MDVs has been established, and the cell-free MDV has been found to be

infectious to chickens. The finding of viral receptors should be a key role to define not only the virus-cell interactions but also the oncogenicity of MDV 1. Although different in infectivities to T cell subsets among different MDV strains, the candidate for the viral receptor for those MDV strains appears to be heparan sulfate, at least in the case of the cell-free condition. These results may help to provide a basis for elucidating the functions of various MDV glycoproteins that are essential for the MDV entry to host cells.

Which viral factors are responsible for different oncogenic potentials and for different infectivities among MDV strains ? In an attempt to determine those factors, changes in the viral genome were analyzed between oncogenic and non-oncogenic attenuated MDV 1. A novel change in the *meq* gene, which is a candidate for the MDV oncogene, has been found in the attenuated MDV 1. The *meq* gene of the attenuated MDV 1 was disrupted by the insertion of the 178-bp sequence. These observations suggest that this change could be responsible for differences in not only oncogenic potentials but also infectivities to T cell subsets of MDV 1 strains.

Complicated molecular events are undertaken during the MDV entry to target CD $4^+$ T cells in chickens, resulting in the variations in infectivities of MDV strains. To define the protection mechanism by MD vaccines, it would be necessary to search both viral ligands which can interact with cell surface heparan sulfate and other cellular receptors. Thus, the clarification of both mechanisms of anti-viral effects by MD vaccines and the molecular characteristics of attenuated MDV 1, especially the function of the elongated *meq* gene, could provide many useful information to develop immunotherapy against not only MDV, but also other virus-induced tumors.

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## Improvement of the alternative definitive host model for *Echinococcus multilocularis* and its application for *E. vogeli*

Kayoko Matsuo

*Laboratory of Parasitology,*
*Department of Disease Control,*
*Graduate School of Veterinary Medicine,*
*Hokkaido University, Sapporo 060-0818, Japan*

The alternative definitive host model for *Echinococcus multilocularis* using laboratory rodents was established and enables us to perform experimental infections of the tapeworm stage with minimum facilities for biosafety.

In chapter I, improvement of the alternative definitive host model for *E. multilocularis* was conducted by investigating various drug treatments and by using different host strains and protoscolex isolates. Prednisolone tertiary-butylacetate (PTBA) has been used in the present alternative definitive host model for *E. multilocularis* using Mongolian