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Review

Marek's disease: Genetic regulation of gallid herpesvirus 2 infection and latency

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ABSTRACT

Gallid herpesvirus-2 (GaHV-2) is an oncogenic α-herpesvirus that causes Marek's disease (MD), a T cell lymphosarcoma (lymphoma) of domestic fowl (chickens). The GaHV-2 genome integrates by homologous recombination into the host genome and, by modulating expression of viral and cellular genes, induces transformation of latently infected cells. MD is a unique model of viral oncogenesis. Mechanisms implicated in the regulation of viral and cellular genes during GaHV-2 infection operate at transcriptional, post-transcriptional and post-translational levels, with involvement of viral and cellular transcription factors, along with epigenetic modifications, alternative splicing, microRNAs and post-translational modifications of viral proteins. Meq, the major oncogenic protein of GaHV-2, is a viral transcription factor that modulates expression of viral genes, for example by binding to the viral bidirectional promoter of the pp38-pp24/1.8 kb mRNA, and also modulates expression of cellular genes, such as Bcl-2 and matrix metalloproteinase 3. GaHV-2 expresses viral telomerase RNA subunit (vTR), which forms a complex with the cellular telomerase reverse transcriptase (TERT), thus contributing to tumorigenesis, while vTR independent of telomerase activity is implicated in metastasis. Expression of a viral interleukin 8 homologue may contribute to lymphomagenesis. Inhibition of expression of the pro-apoptotic factors JARID2 and SMAD2 by viral microRNAs may promote the survival and proliferation of GaHV-2 latently infected cells, thus enhancing tumorigenesis, while inhibition of interleukin 18 by viral microRNAs may be involved in evasion of immune surveillance. Viral envelope glycoproteins derived from glycoprotein B (gp60 and gp49), as well as glycoprotein C, may also play a role in immune evasion.

Introduction

Marek's disease (MD) is a contagious lymphoproliferative disease of domestic fowl (chickens) first described in 1907 by Jozsef Marek. The disease is caused by an oncogenic α-herpesvirus, gallid herpesvirus type 2 (GaHV-2), and is characterised by formation of T cell lymphosarcomas (lymphomas) and paralysis (Cauchy and Coudert, 1986; Burgess et al., 2004). MD is present worldwide and has a major economic impact on the poultry industry. Until the 1950s, the disease was associated with a polyneuritis syndrome, with a low rate of mortality (Fig. 1). Concomitant with increasing industrialisation in the 1960s, an acute form of the disease appeared, with a higher mortality rate (10–30%) (Biggs and Nair, 2012). This acute form was characterised by visceral tumours in addition to nervous system lesions described initially.

In the classical (paralytic) form, the disease has an incubation time of 3–9 weeks. The first clinical signs are locomotor dysfunction, followed by the onset of paralysis; the chicken usually dies of starvation (Cauchy and Coudert, 1986). The acute (lymphomatous) form leads to the death of the chicken after 4 weeks and is characterised by multiple T cell tumours arising in visceral organs.

In the late 1960s, GaHV-2, also known as MD virus type 1 (MDV-1), was identified as the causative agent of MD (Churchill and Biggs, 1967; Churchill, 1968). Currently, herpesviruses belonging to the gender Mardivirus are divided into three viral species, designated GaHV-2, GaHV-3 and meleagrid herpesvirus type 1 (MeVH-1) (Table 1) (Bulow and Biggs, 1975a and b). The GaHV-2 group contains all the oncogenic viruses and includes four pathotypes: moderate (m; strain CU-2), virulent (v; strain HPRS-16), very virulent (vv; strains RB-1B or Md5) and very virulent + (vv+; strain RK-1) (Witter, 1997).

In the late 1960s, two vaccines against MD were generated; the first was based on the GaHV-2 oncogenic strain HPRS-16, attenuated by more than 30 passages in chicken kidney cell cultures (Table 1) (Churchill and Chubb, 1969). A few years later, this vaccine

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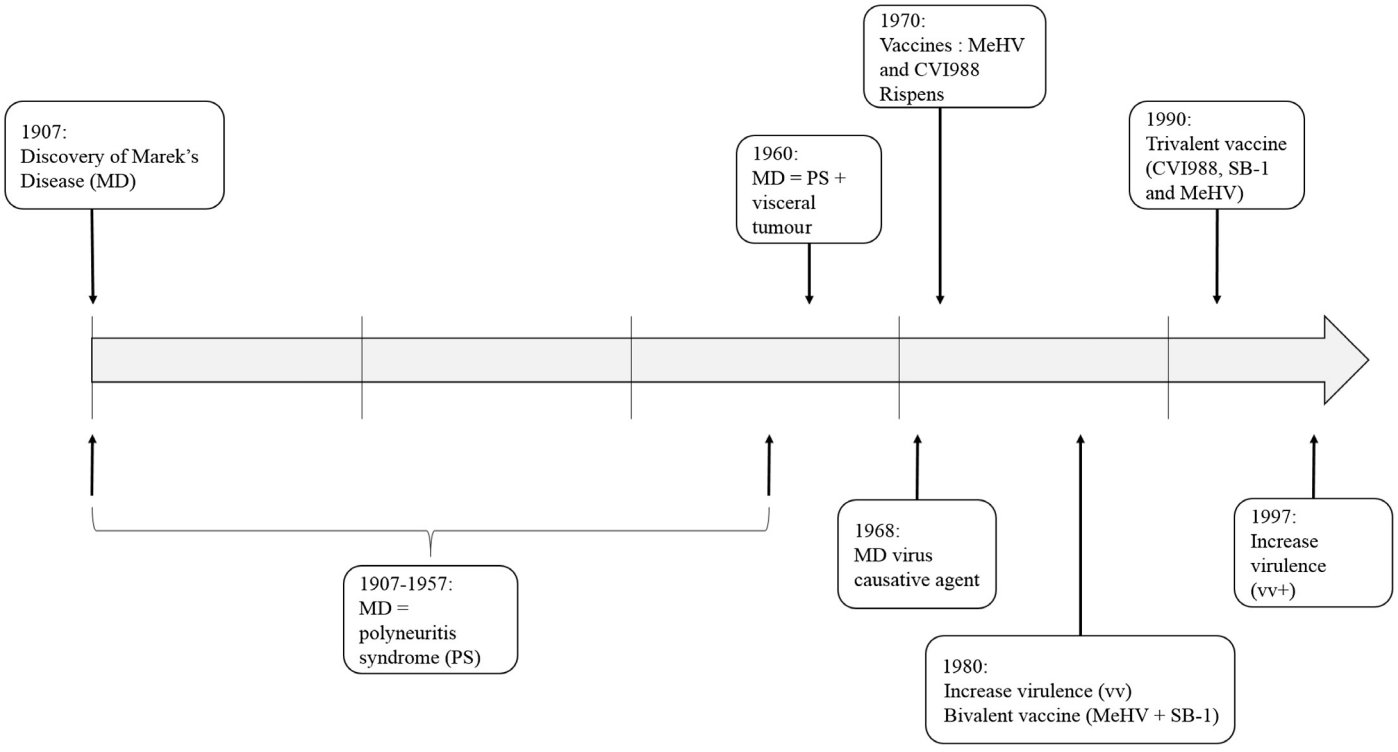

Fig. 1. Time line representing the history of increase virulence and usage of vaccines against gallid herpesvirus-2 (GaHV-2). Black bars represent every 20 years. MeHV, meleagrid herpesvirus.

was replaced by a vaccine based on MeHV-1 (strain FC-126) (Table 1). Since vaccine failures were still encountered when using HPRS-16 or FC-126, a new vaccine was developed based on a naturally attenuated GaHV-2 strain, CVI988-Rispens, which exhibits low pathogenicity (Table 1).

In the 1980s, the virulence of GaHV-2 increased further with the emergence of a vv strain. The vaccine strategy was modified; a bivalent vaccine composed of FC-126 (MeHV-1) and SB-1 (GaHV-3) was introduced (Table 1) (Calnek et al., 1982; Witter and Lee, 1984). Ten years later, there was a further increase in the incidence of MD due to the emergence of hypervirulent (vv+) GaHV-2 (Table 1). In response, the three species of Mardivirus were combined into a trivalent vaccine composed of CVI988 (GaHV-2), SB-1 (GaHV-3) and FC-126 (MeVH-1). Currently, the disease is controlled with this updated vaccine strategy. Vaccination prevents the development of MD, but not virus transmission or infection, so there is a risk that increases in virulence may occur in the future (Gimeno, 2008). New strategies, such as recombinant virus, e.g. GaHV-2 ΔMarek EcoQ (Meq), might be needed in the future to control infection (Lee et al., 2008, 2012).

The aim of this review is to examine the genetic regulation of viral and cellular genes during the infectious cycle of GaHV-2 and to explore how the virus modulates gene expression.

Table 1
Description of the gender Mardivirus.

Species	Pathotype	Oncogenicity	Strains
GaHV-2	Hypervirulent (vv+)	+++	RK-1, 584A, 648A
	Very virulent (vv)	++	RB-1B, Md5, Md-11
	Virulent (v)	+	GA, HPRS-16, JM
	Mildly virulent (m)	No	Rispens, CU-2, HPRS17
GaHV-3	Mildly virulent (m)	No	SB-1, HPRS-24, HN-1
MeHV-1	Mildly virulent (m)	No	FC-126, WTHV, HPRS-26

GaHV, gallid herpesvirus; MeVH, meleagrid herpesvirus.

Infectious cycle of gallid herpesvirus type 2 in vivo

The infectious cycle of GaHV-2 contains four phases: (1) the early productive phase; (2) the latent phase; (3) the late productive phase; and (4) the transformation phase (Fig. 2). Infection begins by inhalation of dust or dander containing infectious particles released from feather follicles. Within the lung, the virus is phagocytosed by macrophages and transported to secondary lymphoid tissue, such as the spleen, thymus and bursa of Fabricius (Barrow et al., 2003). In these organs, the early productive phase, with active replication of virus, takes place mainly in B lymphocytes (Shek et al., 1983). In the latent phase, the virus persists in target cells, mainly $CD4^+$ T lymphocytes, without replicating; genome expression is limited to specific genes required to maintain latency, no progeny virions are produced and the latent virus remains undetected by the immune system (Baigent and Davison, 2004).

The GaHV-2 genome integrates by homologous recombination into the host genome within specific telomeric regions in chromosomes of any size (macro- and micro-chromosomes) (Robinson et al., 2010). The GaHV-2 linear genome possesses telomeric repeats identical to host telomere sequences $(TTAGGG)_n$ (Kaufer et al., 2011). Viral integration appears to enhance cellular transformation and tumour formation. The late productive phase consists of reactivation of the virus in a subpopulation of latently infected cells (Fig. 2). During this phase, viral replication occurs within epithelial cells in feather follicles and is associated with horizontal transmission of the virus. Finally, the transformation phase appears within latently infected cells, which spread in peripheral nerves and visceral organs, causing T cell lymphoma and paralysis (Davison and Nair, 2004).

During the viral replication cycle, transcriptional modification and epigenetic changes (DNA methylation, histone post-translational modifications and non-coding RNAs), along with post-transcriptional and post-translational modifications, regulate expression of cellular and viral genes (Fig. 3). These allow GaHV-2 to switch between the productive and latent phases, and to induce transformation of infected cells.