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Review

Review of pathogenesis phases of Marek's disease in a susceptible host

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ABSTRACT

Marek's disease is caused by an oncogenic alphaherpesvirus, a common lymphoproliferative disorder-inducing agent usually characterized by mononuclear cellular infiltrates particularly T-cell lymphomas in various visceral organs and peripheral nerves. Natural infection of Marek's disease virus occurs through the respiratory mucosa inhalation of the virus shed from infected chickens (fecal-oral route). The respiratory tract of the chicken is the natural entry for Marek's disease virus. Marek's disease virus has long been of interest as a model organism, particularly concerning the pathogenesis and immune control of virus-induced lymphoma. Post inhalation of Marek's disease virus, the early cytolytic phase occurs in B cells of the bursa of Fabricius, spleen, and thymus. Marek's disease has four pathogenesis phases in the susceptible birds those are: an early cytolytic phase within 2 to 7 days post-infection which delineates as semi-productive lytic viral replication in lymphocytes. This phase is followed by a latency phase that occurs between 7 and 10 days post-infection in the CD4+ T cell subset resulting in systemic viral dissemination. Cutaneous viral infection can occur as early as 4 dpi and eventually results in fully productive viral replication and shedding. MDV reactivation in CD4+ T cells initiates a late cytolytic and immunosuppressive phase starting around 18 days of post-infection. Finally, a proliferative phase around 28 days post-infection is characterized by the formation of visceral tumors that originate from CD4+ T cells lymphoma. This review article aims to address the pathogenesis phase of Marek's disease infection, in susceptible birds.

Keywords: Marek's disease virus, pathogenesis, early cytolytic infection, latent infection, late cytolytic infection, transformation phase, CD4+ T cells lymphoma.

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INTRODUCTION

Marek's disease is a common, highly contagious, lymphoproliferative disease of chickens. The causative agent of Marek's disease is Marek's disease virus, a member of the genus *Mardivirus*, sub-family *Alphaherpesvirinae* in the family of *Herpesviridae* (Gimeno, 2014). Marek's disease is characterized by lymphoid infiltrations in peripheral nerves, visceral organs, eye, muscle, skin, and immunosuppression. The virus is classified into three different species: *Gallid herpesvirus 2 (*serotype 1), *Gallid herpesvirus 3 (*serotype 2), and *Meleagris herpesvirus 1 (*serotype 3 or HVT) (Reddy et al., 2017; Cui et al., 2016; Sharma et al., 2002). *Gallid herpesvirus 2 (MDV-1)* includes oncogenic viruses of variable virulence, *Gallid herpes virus 3* includes non-oncogenic viruses from chickens, and *Meleagrid herpes virus 1* includes non-oncogenic viruses from turkeys. Serotypes 2 isolated from chickens and serotypes 3 isolated from turkeys are nonpathogenic. Serotype 1 MDVs are further divided into path types, ranging from mild (**m**) to virulent (**v**) to very virulent (**vv**) and very virulent plus (**vv+**) strains (Cui et al., 2016).

Marek's disease is one of the most common lymphoproliferative diseases of chickens inducing an enlargement of the spleen, liver, kidney, proventriculus, lung, and gonads with diffuse lymphomatous involvement while enlargement of the peripheral nerve such as brachial and sciatic nerve also observed in classical MD which in turn consequence to spastic paralysis of wings and legs. Ocular form (blindness) was observed in poultry due to mononuclear cell infiltration in the iris (grey eye)

(Upadhayay and Ewam, 2012). Marek's disease is characterized by mononuclear cellular infiltrates, mostly T-lymphocytes in different visceral organs and peripheral nerves. The disease causes strong immunosuppression and neurological disorders, leading directly to death or health implications in susceptible domesticated and wild avian species (Mariappan et al., 2019). The transmission of MDV occurs by direct or indirect contact of infected chicken by the airborne route. The epithelial cells in the keratinizing layer of the feather follicle replicate the fully infectious virus and serve as a source of contamination of the environment. It may survive for months in poultry house litter or dust. Dust or dander from infected chickens is particularly effective in transmission (Chauhan et al., 2021).

Because chickens are exposed to the infection very early they must be protected by vaccination as soon as possible, therefore vaccination in hatcheries is practiced worldwide (Sharma et al., 2002; Witter and Schat, 2003). The disease has a tremendous economic impact, firstly because of the cost of vaccination and secondly because of continuing losses of chickens due to the disease (Tulman et al., 2000).

INFECTION PHASE OF MAREK'S DISEASE

The pathogenesis of MD in a susceptible host occurs in four distinct phases: (1) the early cytolytic phase with an initial amplification of the virus in the infected animal, (2) the latent phase with latency establishment predominantly in CD4+ T cells, (3) the late cytolytic phase, and (4) the transformation phase with a rapid lymphoma development and dissemination of these tumors preferentially into visceral organs and skeletal muscles (Mariappan et al., 2019; Bertzbach et al., 2018).

Early cytolytic infection phase

MDV infection of a naive host occurs via the respiratory tract following inhalation of dust containing the infectious Marek's disease virus from a contaminated environment (Osterrieder et al., 2006; Calnek et al., 2001). The virus can persist for extended periods in the environment and is so ubiquitous that virtually every chicken worldwide faces MDV challenges from its first day of life. Primary infection occurs when a virus particle breaks mucosal tolerance in the lungs, the site of entry into the epithelial cells. Local viral replication establishes infection and initiates viral immediate-early gene, viral Interleukin-8 (vIL-8), transcription and translation. Inflammatory responses in the underlying tissue recruit innate immune system cells which result in the uptake of infectious virus particles by macrophages. Viral Interleukin (vIL-8) plays an important role in pathogenesis as it allows the recruitment of B cells, which serve as primary targets for lytic replication. Infiltration of lymphocytes via the action of vIL-8 follows resulting in MDV infection of B-cells (Boodhoo et al., 2016; Bertzbach et al., 2018). The peak of virus replication in these cells is observed between two and seven days post-infection (Yang et al., 2020).

Latent infection phase

Following the early cytolytic phase of infection, the latent infection starts wherein the MDV becomes latent in activated T cells at 6 to 7 days post-MDV infection, and the virus spreads throughout the entire body by the MDV-infected lymphocytes resulting in cell-associated viremia (Mariappan et al., 2019). Herpes virus latency is a common feature that is defined by the persistence of the viral genome in infected cells without replication or production of infectious virus (McPherson and Delany, 2016). By 6 to 7 days post-infection, the MDV lytic antigen expression subsides in lymphoid organs and switches from the early lytic phase to the latency phase starts (Baigent and Davison, 2004; Cui et al., 2004). The host immune response to lytic infection has been shown to play an essential role in switching from cytolysis to latency. The role of host factors in latency is supported by the findings that immunosuppression before infection with MDV leads to prolonged early lytic infection, and chemically induced immunosuppression after latency leads to reactivation and cytolytic infection. Latency maintaining factor (LMF) and host cytokines, as well as soluble mediators (nitric oxide, NO), are involved in maintaining latency (Yang et al., 2020). In addition, unlike the early lytic phase, the predominant infected cells in latency are CD4+ TCR αβ+ T cells, which can be detected as early as 3 dpi. During latency, transcription of the viral genome is limited to latency-associated transcripts (LATs), a complex family of spliced RNAs localizing to the nucleus that is abundant in MDV transformed cells, but reduced upon MDV reactivation. Meqprotein also plays a role in maintaining latency by blocking apoptosis of CD4+ cells trans activating latent gene expression and suppressing the promoters of MDV lytic genes infected cell peptide4(ICP4) and phosphoprotein 38/14 (pp38/pp14) (Nair, 2013; McPherson and Delany, 2016).

Late cytolytic infection/immunosuppression phase

The late cytolytic infection occurs in the feather follicular epithelium, which disseminates infectious cell-free virus to the environment via feather follicle debris and dander. Few latently infected T cells consequently are transformed, leading to the development of lymphoma in peripheral nerves and visceral organs (Schermuly et al., 2015; Mariappan et al., 2019). Latently infected T cells transport the virus to the skin and feather follicle epithelia,

where cell-free MDV is generated (Bertzbach et al., 2020). The Infection of feather follicle epithelium enables fully productive viral replication. MDV productively replicates is occurred in B-cells that transfer the virus to T-cells (Kheimar et al., 2017). Viral replication results in syncytia formation and infection of feather epithelium leads to the secretion of mature virion in skin danders and dust that acts as the major source of infectious materials. Horizontal transmission is the only recognized form of environmental persistence and infection in field conditions (Boodhoo et al., 2016).

Transformation phase

The neoplastic transformation of latently infected lymphocytes to lymphoblastoid tumor cells is the ultimate consequence of the interaction of MDV with the host cell. Fully latent MDV-Transformed CD4+ T-cells proliferate in all sites where immune systems cells are involved in primary and secondary lines of defense [4]. During the secondary cytolytic phase, the transformation phase of infection becomes apparent, in which latently-infected CD4+ T cells proliferate and give rise to lymphomas. The spleen is a primary site for lymphomas formation; but cannot be the only source of transformable target cells, as splenectomized birds still develop neoplastic MD lesions (Lian et al., 2012). Three weeks post-infection the splenic T-dependent areas become hyperplastic, and following this diffusely distributed T cells, presumed to be precursors of neoplastically transformed cells, are seen throughout the spleen. From 3 to 4 weeks post-infection, non-productively infected lymphocytes pro- aggressively migrate into the visceral organs and peripheral nerves, where, under the influence of as yet undetermined factors, they proliferate to form lymphomas (Baigent and Davison, 2004). Lymphocytes continually circulate from the blood to the lymphatics via lymphoid and non-lymphoid tissue, and migration through endothelial cell monolayers requires the production of matrix-degrading enzymes- an ability that increases in activated T cells such as those latently infected with MDV.

Fully latent neoplastic MDV-Transformed CD4+ T cells infiltrate and establish a reservoir of MDV genome in peripheral nerve fibers interspace. These cells have a CD4+ CD25+ Treg phenotype although additional cell surface markers have yet to be determined. The expression of viral neurovirulence factor, phosphoprotein 14 (pp14), promotes neuropathy and cell survival. Neuropathy is presented as transient acute paralysis of the legs, wings, and neck, with vision impairment and weight loss depending on the MDV-1 virulence factor. Birds infected with serotype-1 eventually succumb to death from paralysis. Reactivation from latency enables the second phase of replication whereby viral oncogenic protein *Meq* acts on T cell signaling pathways causing uncontrolled cellular proliferation leading to disseminated lymphoma formation in visceral organs, peripheral and central nervous system, musculoskeletal systems, skin, and eyes. Severe lymphoma eventually causes death in birds. Highly pathogenic viruses (serotype-1,vv+ MDV) kill birds before they reach the lymphoproliferative phase of the disease (Boodhoo et al., 2016).

CONCLUSION

The pathogenesis of Marek's disease is complex with many effective factors and with many possible expressions of the pathological lesion. The underlying mechanisms by which many of these various factors affect the events comprising the pathogenesis of the disease are still needed investigation. In this review, I highlighted the four pathogenesis phases of MD disease in susceptible hosts and it is important to pathotype the virus and host genotype to determine the likelihood of lymphoma development.

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