MOLECULAR CHARACTERIZATION AND PATHOGENICITY STUDY OF SEROTYPE 8B FOWL ADENOVIRUS ISOLATED IN MALAYSIA

By

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Chair : Profesor Abdul Rahman Omar, DVM, PhD
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Inclusion body hepatitis (IBH) is an economic importance viral disease affecting broilers in many countries in this region including Malaysia. Depending on geographical locations, different serotypes of fowl adenovirus (FAdV) have been identified as the causative agent of IBH. The present study aimed to detect FAdV from suspected cases of IBH from commercial chicken farms in Malaysia based on amplification and sequencing of the hexon gene, to determine the phylogenetic tree of the identified FAdV isolates based on hexon gene sequence analysis, to determine the phylogenetic tree of serotype 8b FAdV isolate UPM/FAdV/420/2017 based on hexon and fiber gene sequence analysis and to determine the pathogenicity of serotype 8b FAdV isolate UPM/FAdV/420/2017 in specific-pathogen-free (SPF) chickens following inoculation of the virus via the oral route and intramuscular route. From the study, 16 cases of IBH from commercial chicken farms in Malaysia were detected positive for Fowl adenoviruses (FAdVs) by polymerase chain reaction (PCR). Result of phylogenetic analysis based on the hexon gene sequence confirmed the typing of all the 16 isolates into a single cluster of FAdV serotype 8b species E. One of the isolates, UPM/FAdV/420/2017 was opted for fiber gene sequencing and proceeded with phylogenetic analysis based on fiber gene sequence. The result of the fiber gene analysis supported the grouping of the isolate into FAdV species E. Subsequently, the pathogenicity of the isolate UPM/FAdV/420/2017 was characterized in 11-day old specific-pathogen-free (SPF) chickens following inoculation of the virus at 108.53 TCID50 via oral and intramuscular (IM) routes of inoculation. Infected chickens showed clinical signs of depression, ruffled feathers, huddling, inappetence, diarrhea and gross lesions characteristic of IBH such as enlarged, pale-yellowish liver with necrotic foci. Chickens infected via the IM route showed significantly higher clinical score values ($p<0.05$) and higher percent mortality than orally inoculated birds. Histopathologic examination of the liver in infected chickens showed the presence of intranuclear inclusion bodies with a higher degree of severity in IM-

infected groups ($p<0.05$). The amount and duration of virus shedding differ significantly between the two infected groups ($p<0.05$) with IM-inoculated chickens secreted higher amount of virus and the shedding last until the last sampling point at 28 dpi. Meanwhile, the amount of virus shedding of the oral group was lower and was detected until the 14-day pi. At day 5 post-inoculation, virus copy number (VCN) (> log10 9) was recorded highest in the liver and gizzard irrespective of inoculation. Although other organs namely cecal tonsils, bursa, kidney, spleen, and thymus were detected positive for FAdV, no significant gross and microscopic lesions were detected in these organs except the liver. The antibody response against FAdV showed a statistically significant difference ($p<0.05$) between oral and IM-inoculated groups. Higher values were recorded in IM-inoculated chickens throughout the experimental trial. Results of the study suggested that FAdV serotype-8b is a dominant serotype circulating in Malaysia and associated with outbreaks of IBH. This study also confirmed that Malaysian FAdV-8b isolate UPM/FAdV/420/2017 is a pathogenic virus and caused symptomatic IBH in SPF birds. The study approved that the extent of pathogenicity can be influenced by the route of inoculation. Further study is underway on the ability of inactivated FAdV vaccine in conferring protection against this virus.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Master Sains

PENCIRIAN MOLEKULAR DAN KAJIAN KEPATOGENAN PENCILAN ADENO-UNGGAS SEROTIP 8B DI MALAYSIA

Oleh

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Badan inklusi hepatitis (BIH) merupakan penyakit virus berkepentingan ekonomi yang menjejaskan ayam daging di banyak negara di rantau ini termasuklah Malaysia. Bergantung pada lokasi geografi, serotip virus adeno-unggas yang berbeza telah dikenalpasti sebagai agen penyebab bagi penyakit BIH. Kajian ini bertujuan untuk mengesan virus adeno-unggas dari kes yang disyaki BIH daripada ladang ayam komersial di Malaysia berdasarkan amplifikasi dan penjujukan gen hexon, untuk menentukan pokok filogenetik virus adeno-unggas serotip 8b dikenalpasti berdasarkan analisis gen hexon, untuk menentukan pokok filogenetik serotip 8b virus adeno-unggas pencilan UPM/FAdV/420/2017 berdasarkan analisis gen hexon dan gen fiber dan untuk menentukan kepatogenan serotip 8b virus adeno-unggas pencilan UPM/FAdV/420/2017 dalam ayam-bebas-patogen-spesifik (SPF) selepas inokulasi virus melalui laluan oral dan intra-otot. Dari kajian ini, 16 kes BIH daripada ladang ayam komersial di Malaysia telah dikesan positif virus adeno-unggas oleh tindak balas rantai polimerase (PCR). Keputusan analisis filogenetik berdasarkan jujukan gen hexon mengesahkan penjenisan kesemua pencilan ke dalam kelompok virus adeno-unggas serotip 8b spesis E. Salah satu daripada pencilan, UPM/FAdV/420/2017 telah dipilih untuk analisis jujukan gen fiber dan diteruskan dengan analisis pokok filogenetik berdasarkan jujukan gen fiber. Keputusan dari analisis menyokong pengelompokan pencilan ke dalam virus adeno-unggas spesis E. Kemudiannya, kepatogenan pencilan UPM/FAdV/420/2017 telah dicirikan dalam ayam-bebas-patogen-spesifik (SPF) yang berusia 11 hari selepas inokulasi virus pada dos 108.53 TCID50 melalui laluan inokulasi oral dan intra-otot. Ayam yang dijangkiti virus menunjukkan gejala klinikal seperti depresi, bulu kusut, saling berkerumun, hilang selera makan, cirit birit dan tanda perubahan kasar pada organ yang menunjukkan ciri-ciri jangkitan badan inklusi hepatitis seperti bengkak dan kuning kepucatan pada tisu hepar berserta fokus nekrosis. Ayam yang dijangkiti melalui laluan intra-otot mencatat perbezaan ketara skor klinikal lebih tinggi ($p<0.05$) dan mencatat peratusan kematian lebih tinggi berbanding burung yang dijangkit

secara oral. Pemeriksaan histopatologi tisu hepar ayam terjangkit mendapati kehadiran badan inklusi intra-nuklear pada tahap keparahan yang lebih tinggi dalam ayam yang dijangkit intra-otot ($p<0.05$). Jumlah dan durasi penumpahan virus berbeza dengan ketara antara kedua-dua kumpulan yang dijangkiti ($p<0.05$) dengan ayam yang dijangkit intra-otot menyebarkan jumlah virus yang lebih tinggi dan penumpahan virus kekal sehingga titik pensampelan terakhir iaitu pada hari ke-28 selepas jangkitan. Manakala, jumlah penumpahan virus bagi kumpulan oral adalah lebih rendah dan dikesan sehingga pada hari ke-14 selepas jangkitan. Pada hari kelima selepas jangkitan, jumlah kepulihan virus (> log10 9) direkodkan paling tinggi dalam tisu hepar dan hempedal tanpa mengira laluan inokulasi. Walaupun organ lain seperti tonsil sekum, timus, bursa, ginjal dan limpa dikesan positif virus adeno-unggas, tiada lesi kasar dan lesi mikroskopik yang ketara dapat dikesan pada organ-organ ini melainkan pada tisu hepar. Gerak balas antibodi terhadap virus adeno-unggas menunjukkan perbezaan statistik yang ketara ($p<0.05$) di antara kumpulan inokulasi oral dan intra-otot. Nilai yang lebih tinggi direkodkan dalam ayam dijangkit intra-otot sepanjang percubaan eksperimen. Keputusan kajian ini mencadangkan bahawa virus adeno-unggas serotip 8b adalah serotip dominan yang beredar di Malaysia dan dikaitkan dengan wabak IBH. Kajian ini juga mengesahkan bahawa virus adeno-unggas Malaysia serotip 8b pencilan UPM/FAdV/420/2017 adalah virus patogenik dan menyebabkan gejala BIH pada burung SPF. Kajian ini menyetujui bahawa skala kepatogenan boleh dipengaruhi oleh laluan jangkitan. Kajian lanjut masih dijalankan bagi melihat keupayaan vaksin nyah-aktif virus adeno-unggas dalam memberikan perlindungan bagi menentang virus ini.

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This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

aa	Amino acid
AdV	Adenovirus
AdV	Adenovirus
BLAST	Basic Local Alignment Search Tool
bp	Base pair
BSA	Bovine Serum Albumin
CEE	Chicken embryonated egg
CMI	Cell-mediated immunity
CPE	Cytopathic effect
DMEM	Dulbecco's Modified Eagle's Medium
DNA	Deoxyribonucleic acid
dpi	Day post-inoculation
dsDNA	Double-stranded deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FAdV	Fowl adenovirus
HAdV	Human adenovirus
HHS	Hydropericardium syndrome
IACUC	Institutional Animal Care and Use Committee
IBH	Inclusion body hepatitis
ICTV	International Committee on Taxonomy of Viruses
Ig	Immunoglobulin
IM	Intramuscular
INIB	Intranuclear inclusion bodies
ITR	Inverted terminal repeats
L1	Loop 1
LIVES	Laboratory of Vaccine and Immunotherapeutic
MEGA	Molecular Evolutionary Genetics Analysis
MHC	Major histocompatibility complex
NCBI	National Centre for Biotechnology Information
nt	Nucleotide

OIE	World Organization of Animal Health
ORF	Open reading frame
PAMPs	Pathogen associated molecular patterns
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
pi	Post inoculation
qPCR	Quantitative polymerase chain reaction
rpm	Revolutions per minute
SPF	Specific-pathogen free
$TCID_{50}$	50% tissue culture infectious dose
TP	Terminal proteins
UPM	Universiti Putra Malaysia
VCN	Virus copy number
VN	Virus neutralization
w/v	Weight/volume

CHAPTER 1

INTRODUCTION

The poultry industry is one of the key components in the Malaysian livestock sector. Currently, production of local poultry is self-sufficient to meet the domestic demand and exporting enough to become the major net exporter of chickens among ASEAN nations. Nevertheless, the growth of the industry is continuously threatened by potential endemic viral disease of opportunistic pathogens. These infectious agents may act alone or in concert with other encouraging factors to cause a disease strikes which directly impact the profit and loss of the industry. One of the common viruses found in the local poultry farm is fowl adenovirus (FAdV). In Malaysia, the virus is first detected in the field in 2005 (Hair-Bejo, 2005) and since then, a steady reported case of FAdV has been reported for past 5 years, affecting primarily broilers and breeders (De la Torre et al., 2018; Marek et al., 2016; Xia et al., 2017).

FAdV is a non-enveloped double-stranded DNA virus which belongs to family Adenoviridae (Zhao et al., 2015). The virus has characteristics icosahedral shape with approximately 70-100 nm capsid diameter and formed by three major structural protein namely the hexon, fiber, and penton. Presently, FAdV can be classified into five species (FAdV A to E) as determined by its molecular structure and 12 serotypes (FAdV-1 to -8a, -8b to -11) based on virus neutralization test (Hess, 2000). Circulation of FAdV is widespread, covering most geographical location and appeared to infect not only chickens but also various kind of avian species (Adair & Fitzgerald, 2008). A feature of the virus epidemiology is the unusually large number of serotypes that can be isolated on a farm. In many cases, it is also common to isolate different FAdV serotypes from the same diseased bird which suggested a lack of cross-protection among serotypes (Pereira et al., 2014).

The pathogenic role of FAdV under field conditions remains unclear since the virus is ubiquitous in nature and can be isolated in both sick and healthy birds. Heterogeneity of FAdV serotypes in term of genetic makeup has led to a discrepancy in regard to disease behavior and producibility of clinical signs between different serotype or different isolates of similar serotype (Gaba et al., 2010). Previously, FAdV is indicated to cause disease when they act in concert with an immunosuppressive agent such as chicken anemia virus or mycotoxins (Toro et al., 2002). However, several studies have revealed emerging virulent strains of FAdV that able to elicit severe infections alone without immunosuppression as a co-factor. In this case, results of the disease often come with a high degree of mortality depending

on the virulence of the strains, susceptibility of the birds or animal-related management of the farm. Then again, there is no strong evidence to support the probability of synergistic effect toward the severity of the disease due to infection of mixed serotypes (Changjing et al., 2016).

Epidemiological control of FAdV is tricky because they can set up latent infections and caused the infected birds to become a lifetime carrier of the virus. Upon reactivation of the latent virus, birds can vertically transmit the FAdV through the embryonated eggs and chicks may shed the virus in feces upon hatching. Apparently, chicks can reactivate the virus once their maternal antibody declines and during this time, usually between four to six weeks, virus shedding is at maximum and cease when the birds develop local immunity. Presence of virus in excretions inevitably lead to horizontal transmission of FAdV in the flocks. In addition, lateral spread also occurs through direct contact with infected birds and contaminated fomites or personnel. Chances of aerosol transmission are minimal though and work at a very short distance (McFerran & Smyth, 2000).

In the field, FAdV has been isolated in various clinical conditions. They are most notable as primary pathogens of inclusion body hepatitis (IBH), hepatitis-hydropericardium syndrome (HHS) and avian gizzard erosion (AGE) (Schachner et al., 2017). Serotypes of FAdV isolated from these cases are varied and more often than not, particular FAdV serotypes are predisposed to certain clinical conditions and geographical locations (McFerran & Smyth, 2000). For example, IBH outbreaks in New Zealand are associated with serotype 1, 8 and 12 although in Korea the culprits mostly from serotype 3, 9 and 11 (Lim et al., 2011). Meanwhile, HHS is mostly implicated with FAdV belong to serotype 4 and disease outbreak is more widespread in Asia (Harrach, 2014).

Classically, detection of FAdV is achieved by virus isolation in embryonated eggs or cell culture. Since this virus replicates inside the nucleus, the presence of the virus in cell culture is identified by the demonstration of intranuclear inclusion bodies or manifestation of cytopathic effect. Further confirmation is made by immunofluorescence and electron microscopy validated by the presence of virus particles. Presently, the traditional routine diagnostic test has been superseded by molecular tools of PCR detection and sequencing of the FAdV hexon gene. PCR is a powerful molecular tool that allows highly specific and sensitive detection of the FAdV genome, with cost-benefit advantages. This method also robust and allow differentiation of species and serotypes of FAdV to replace the traditional serological method of virus neutralization test for serotyping of isolates. FAdV hexon gene is targeted because it is the longest gene and contains the hypervariable loop 1 (L1) region that holds the most sequence variability between serotypes and thus can accurately classify FAdV serotypes apart (Meulemans et al., 2004).

In Malaysia, FAdV has been implicated in sporadic outbreaks of IBH. The outbreaks occurred mostly in meat-producing chicken characterized with sudden onset of mortality that peaks after three to four days and gradually cease after day 6 (Norina et al., 2016). Liver of affected chickens is swollen, pale and presence of inclusion bodies in the hepatocytes. FAdV infections often resulted in a low degree of morbidity, but mortality rates can range between 5% to 10% and in severe cases may up to 30%. High mortality accompanied by poor growth performance of survived chickens in the infected house has an indirect effect on the sustainability of chicken-meat supply and turnover of the poultry industry as a whole. In an effort to put the FAdV's outbreaks under control, it is vital to identify the serotypes of the FAdV involved along with its pathogenic behaviour especially when vaccination to be implemented as a major approach against outbreaks. In Malaysia, proper epidemiological surveys on its FAdV's serotype distribution and its pathogenic characterization are still lacking which demand further exploration. The hypothesis of this study is, IBH cases in Malaysia is associated with a single FAdV serotype that is pathogenic in chickens. Findings from this experiment will provide updated information on Malaysian FAdV for development of control strategies to counter the FAdV outbreaks including the development of inactivated FAdV vaccine based on the circulating FAdV serotypes.

Therefore, the objectives of the present study were:

1. To detect FAdV from suspected cases of IBH from commercial chicken farms in Malaysia based on amplification and sequencing of the hexon gene.
2. To determine the phylogenetic tree of the identified FAdV isolates based on hexon gene sequence analysis.
3. To determine the phylogenetic tree of serotype 8b FAdV isolate UPM/FAdV/420/2017 based on hexon and fiber gene sequence analysis.
4. To determine the pathogenicity of serotype 8b FAdV isolate UPM/FAdV/420/2017 in specific-pathogen-free (SPF) chickens following inoculation of the virus via the oral route and intramuscular route.

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