UNIVERSITI PUTRA MALAYSIA

ROLES OF MITOCHONDRIA IN MODULATING CHICKEN INNATE IMMUNITY FOLLOWING NEWCASTLE DISEASE VIRUS INFECTION

HARYATI SHILA MOHAMAD WALI

IB 2021 4

ROLES OF MITOCHONDRIA IN MODULATING CHICKEN INNATE IMMUNITY FOLLOWING NEWCASTLE DISEASE VIRUS INFECTION

By

HARYATI SHILA MOHAMAD WALI

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Doctor of Philosophy

April 2019

DEDICATION

This thesis is dedicated to the pillars of my life;

My parents,
My husband, and
My beloved kids

With love, respect and a bunch of memories
Indeed, we belong to Allah and indeed to Him we will return.

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Doctor of Philosophy

ROLES OF MITOCHONDRIA IN MODULATING CHICKEN INNATE IMMUNITY FOLLOWING NEWCASTLE DISEASE VIRUS INFECTION

By

HARYATI SHILA MOHAMAD WALI

April 2019

Chair :Prof. Datin Paduka Dato' Aini Ideris, PhD
Faculty :Institute of Bioscience

Mitochondria have been established as having a vital role in innate immunity. Mitochondrial antiviral signalling (MAVS) protein is a mitochondrial protein proven to modulate the production of interferons and pro-inflammatory cytokines as well as initiating apoptosis in viral infection. Newcastle disease (ND) is a common threat to the poultry industry globally with genotype VII Newcastle disease virus (NDV) strains becoming one of the prominent virulent NDV strains. Antiviral innate immune response involve various pattern recognition receptors (PRR) such as Toll-like receptors (TLR), retinoic acid-inducible gene I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) to identify invading microorganism via their pathogen-associated molecular patterns (PAMP) like double-stranded RNA (dsRNA), bacterial lipopolysaccharide (LPS) and viral proteins. This leads to further downstream processes in the signalling cascade of the innate immune system. In this study, CARD adaptor inducing IFN-β (CARDIF), a prominent mitochondrial adaptor molecule linking RIG-I and MDA5 is amplified and exogenously expressed in two chicken cell lines prior to IBS002/11 strain (genotype VII NDV) infection. The gene expression experiment was conducted to assess whether the presence of CARDIF affected the production of type I interferons and pro-inflammatory cytokines in both cell lines following NDV strain IBS002/11 infection, besides its role in the induction of apoptosis. The contribution of mitochondrial DNA (mtDNA) in chicken innate immunity was also assessed following NDV infection. The assessments of cytokines expressions and mtDNA level were conducted via qPCR assay, while the determination of cell proliferation and apoptosis were conducted via MTS and JC-1 assays. Morphological evaluation was conducted by transmission electron micrography (TEM). All experiments were carried out on two cells lines; DF-1 and HD-11. The DF-1 cell line is a spontaneously transformed chicken embryo fibroblast while HD-11 is a chicken macrophage-like cell line. The CARDIF gene was successfully amplified via PCR and cloned into the pcDNA6V5-His B plasmid, a mammalian expression vector to produce the plasmid pcDNA6/CARDIF. Meanwhile, two truncated genes of the original CARDIF gene were also amplified and cloned into the expression

vector yielding pcDNA6/ΔCARD (putative CARDIF lacking the CARD domain) and pcDNA6/ΔTM (putative CARDIF lacking the TM domain). The effects of exogenous expression of CARDIF on the production of type I and II IFNs and pro-inflammatory cytokines in both cell lines following NDV infection were conducted via quantitative polymerase chain reaction (qPCR). Despite upregulated levels of type I IFN (IFN-α and IFN-β) following NDV infection observed in both cell lines as the effect of exogenous expression of CARDIF, the expression of IFN-α occurred at a much later time point (72 h) in both cell lines, showing that the production of IFN-α was less affected by the presence of the CARDIF gene in comparison to IFN-β. HD-11 cells exhibited a greater magnitude of IFN-β upregulation compared to DF-1 cells. The transfected CARDIF gene also upregulated the expression of IFN-γ (type II IFN) as well as IL-18 in HD-11 cells while the same molecules were downregulated in DF-1 cells. CXCLi2, a chemokine was upregulated in both cell lines while IL-1β was found to be upregulated in DF-1 cells. The presence of CARDIF resulted in the decreased number of viral copies over the treatment period in contrast to both truncated CARDIF genes. Both truncated genes caused an increase in the viral copy number over the treatment period. Subsequently, the mtDNA levels were detected to be higher ($P<0.05$) in infected cells compared to the control. Two mtDNA genes were used in the qPCR assay i.e. Cyt b and COIII whereby the higher level of mtDNA expression in infected cells means leakage of the mtDNA into the cytosol. In this study, the leakage of mtDNA to the surroundings assisted in triggering the production of pro-inflammatory cytokines as well as type I IFN. The proliferation percentage of the cells was assessed via the MTS assay in two conducts, the conventional and co-treatment method. A continuous decline of HD-11 cells in contrast to the DF-1 cells in the existence of the CARDIF gene was observed with the co-treatment method considered as a better approach in determining the percentage of cell proliferation following virulent NDV infection. The occurrence of CARDIF gene also initiated the onset of apoptosis as a measure to curb viral infection. The assessment was conducted via the mitochondrial membrane potential ($\Delta\psi$) assay (JC-1 assay). The results of JC-1 assay supported those of the MTS assay whereby the decline of cell proliferation percentage in the MTS assay is in agreement with the increased percentage of apoptotic cells in the JC-1 assay. The results of the cell proliferation and mitochondrial membrane potential assays were further confirmed by visual assessment of the cell morphology in TEM. Noticeable hallmarks of apoptosis such as convolution of nuclear membrane, condensed chromatin and the presence of lipid droplets were identified in both cell lines. Therefore, this study concluded that the presence of CARDIF, a mitochondrial adaptor molecule managed to prompt the production of type I and type II IFNs, as well other pro-inflammatory cytokines during infection with virulent NDV strain. The presence of the exogenous gene also showed better impact on the cell component of the immune system (HD-11 cells) compared to the stromal cell line (DF-1 cells). The exogenous gene managed to induce apoptosis in both cell lines, with HD-11 cells being more susceptible following NDV infection.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

PERANAN MITOKONDRIA DALAM PENGUBAHSUAIAN KEIMUNAN SEMULA JADI AYAM BERIKUTAN JANGKITAN VIRUS PENYAKIT NEWCASTLE

Oleh

HARYATI SHILA MOHAMAD WALI

April 2019

Pengerusi : Prof. Datin Paduka Dato' Aini Ideris, PhD
Fakulti : Institut Biosains

Mitokondria telah diperakui sebagai mempunyai peranan penting dalam sistem keimunan semula jadi. Protein pengisyaratan antivirus mitokondria (MAVS) adalah suatu protein mitokondria yang telah dibuktikan untuk mengubahsuai penghasilan interferon (IFN) dan sitokin pro-inflamasi di samping mencetuskan apoptosis pada jangkitan virus. Penyakit Newcastle (ND) merupakan ancaman biasa terhadap industri ayam secara global dengan virus penyakit Newcastle (NDV) genotip VII menjadi salah satu daripada strain virulen NDV yang penting. Tindak balas keimunan semula jadi antivirus melibatkan pelbagai penerima pengecaman pola (PRR) seperti penerima seumpama-tol (TLR), gen I asid retinoik-teraruhkan (RIG-1) dan protein 5 berkaitan-pembezaan melanoma (MDA5) bagi mengenalpasti mikroorganisma penyerang melalui pola molekular berkaitan-patogen (PAMP) seperti RNA bebenang ganda dua (dsRNA), lipopolisakarida bakteria (LPS) dan protein virus. Ini membawa kepada proses hiliran dalam lata pengisyaratan sistem keimunan semula jadi. Penglibatan suatu molekul penyesuai adalah penting di dalam laluan pengisyaratan antivirus. Di dalam kajian ini, penyesuai CARD mengaruh IFN-β (CARDIF), suatu molekul penyesuai mitokondria yang utama menghubungkan RIG-I dan MDA5 telah diperbanyakkan dan dizahirkan secara eksogenus dalam dua turunan sel ayam sebelum jangkitan strain IBS002/11 (NDV genotip VII). Eksperimen penzahiran gen telah dijalankan bagi menaksir sama ada kehadiran CARDIF memberikan kesan terhadap pengeluaran interferon (IFN) jenis I dan sitokin pro-inflamasi di dalam kedua-dua turunan sel selepas jangkitan NDV strain IBS002/11, di samping peranannya dalam mencetuskan apoptosis. Penyumbangan DNA mitokondria (mtDNA) dalam keimunan semula jadi ayam juga turut dinilai berikutan jangkitan NDV. Penilaian penzahiran sitokin dan tahap mtDNA telah dijalankan melalui asai MTS dan JC-1. Penilaian morfologi dijalankan dengan mikrografi transmisi elektron (TEM). Kesemua eksperimen dijalankan ke atas kedua-dua turunan sel; DF-1 dan HD-11. Turunan sel DF-1 ialah fibroblas embrio ayam terbitan spontan manakala HD-11 ialah turunan sel ayam seumpama-makrofaj. Gen CARDIF telah diperbanyakkan dengan

jayanya melalui PCR dan diklon ke dalam plasmid pcDNA6V5-His B, suatu vektor penzahiran mamalia bagi menghasilkan plasmid pcDNA6/CARDIF. Sementara itu, dua gen terpangkas daripada gen CARDIF asal juga telah diperbanyakkan dan diklon ke dalam vektor penzahiran menghasilkan pcDNA6/ΔCARD (CARDIF jangkaan tanpa domain CARD) dan pcDNA6/ΔTM (CARDIF jangkaan tanpa domain TM). Kesan penzahiran eksogenus CARDIF ke atas penghasilan interferon (IFN) jenis I dan II dan sitokin pro-inflamasi di dalam kedua-dua turunan sel berikutan jangkitan NDV telah dijalankan melalui tindak balas berantai polimerase kuantitatif (qPCR). Meskipun tahap pengawalaturan menaik IFN jenis I (IFN-α dan IFN-β) berikutan jangkitan NDV telah diperhatikan dalam kedua-dua turunan sel akibat kesan penzahiran eksogenus CARDIF, penzahiran IFN-α berlaku pada titik masa yang lebih lewat (72 j) pada kedua-dua turunan sel, menunjukkan bahawa penghasilan IFN-α kurang dipengaruhi oleh kehadiran gen CARDIF berbanding IFN-β. HD-11 mempamerkan magnitud yang lebih ketara dalam pengawalaturan menaik IFN-β berbanding sel DF-1. Pentransfeksian gen CARDIF juga meningkatkan pengawalaturan penzahiran IFN-γ (IFN jenis II) di samping IL-18 dalam sel HD-11 manakala molekul yang sama mengalami penurunan pengawalaturan dalam sel DF-1. CXCLi2, sejenis kemokin mengalami kenaikan pengawalaturan dalam kedua-dua turunan sel manakala IL-1β didapati mengalami kenaikan pengawalaturan dalam dalam sel DF-1. Kehadiran CARDIF menyebabkan penurunan bilangan salinan virus di sepanjang masa pengolahan berbeza dengan kedua-dua gen CARDIF terpangkas. Kedua-dua gen terpangkas menyebabkan kenaikan bilangan salinan virus di sepanjang masa pengolahan. Kemudian, tahap mtDNA dikesan lebih tinggi ($P<0.05$) dalam sel dijangkiti berbanding kawalan. Dua gen mtDNA telah digunakan dalam asai qPCR iaitu Cyt b dan COIII di mana tahap penzahiran mtDNA yang lebih tinggi di dalam sel dijangkiti bermaksud kebocoran mtDNA ke dalam sitosol. Di dalam kajian ini, kebocoran mtDNA ke persekitaran membantu mencetuskan penghasilan sitokin pro-inflamasi termasuk IFN jenis I. Peratus pembiakan sel telah ditaksirkan melalui asai MTS dalam dua kaedah, kaedah konvensional dan pengolahan bersama. Kemerosotan berterusan sel HD-11 berbanding sel DF-1 di dalam kewujudan gen CARDIF telah diperhatikan dengan kaedah pengolahan bersama dianggap sebagai pendekatan yang lebih baik di dalam penentuan peratus pembiakan sel berikutan jangkitan NDV virulen. Kehadiran gen CARDIF juga mencetuskan permulaan apoptosis sebagai suatu langkah untuk mengawal jangkitan virus. Pentaksiran telah dijalankan melalui asai potensi membran mitokondria ($\Delta\psi$, asai JC-1). Keputusan asai JC-1 menyokong keputusan asai MTS di mana kemerosotan peratus pembiakan sel di dalam asai MTS adalah bersesuaian dengan peningkatan peratus sel apoptotik dalam asai JC-1. Keputusan asai pembiakan sel dan potensi membran mitokondria telah dipastikan lebih lanjut melalui penilaian visual morfologi sel dalam TEM. Tanda-tanda apoptosis yang ketara seperti perlingkaran membran nukleus, penggumpalan kromatin dan kehadiran titisan lipid telah dikenal pasti pada kedua-dua turunan sel. Oleh itu, kajian ini menyimpulkan bahawa kehadiran CARDIF, suatu molekul penyesuai mitokondria berupaya mencetuskan penghasilan IFN jenis I dan II, di samping pelbagai sitokin pro-inflamasi semasa jangkitan dengan strain NDV virulen. Kehadiran gen eksogenus tersebut juga menunjukkan kesan yang lebih baik ke atas komponen sel keimunan (sel HD-11) berbanding turunan sel stroma (sel DF-1). Gen eksogenus tersebut mampu merangsang apoptosis di dalam kedua-dua turunan sel, dengan sel HD-11 sebagai lebih mudah dipengaruhi berikutan jangkitan NDV.

ACKNOWLEDGEMENTS

With the name of Allah, the Most Gracious and the Most Merciful

All praises and thanks to Almighty Allah, for His blessings and mercy, to allow me to complete this manuscript.

First of all, I would like to extend my heartfelt gratitude to my supervisor, Prof. Datin Paduka Dato' Dr. Aini Ideris for her unconventional support and help to get me through this arduous journey of becoming a PhD scholar. Notably, a massive thank to my co-supervisor-cum-mentor, Prof. Dr. Abdul Rahman Omar for his invaluable contributions and guidance in every technical aspect of this journey. I would also like to convey my sincere gratitude to Prof. Mohd. Hair Bejo as my co-supervisor for his contributions and support in this journey of mine. I am very honoured and blessed for the opportunity to be acquainted and to work with them.

I am very much obliged to the staff of the Laboratory of Vaccines and Immunotherapeutics (LIVES), Institute of Bioscience for the conducive yet professional ambience of the lab. Special thanks to Dr. Tan Sheau Wei and Dr. Yeap Swee Keong for their professional guidance during my study. Professionalism aside, the friendship nurtured is worth mentioning. Deepest gratitude goes out to the staff-cum-friends from LIVES; Mrs. Norhafiza Azwa, Mrs. Nancy Liew, Mrs. Noor Nadia, Mrs. Norhaszalina and Mrs. Nur Azah Nazihah. I am also grateful for the assistance and co-operation of staff from the other departments of IBS.

Words are not enough to express my highest gratitude and appreciation to the sisters I came to know since I started this formidable odyssey. These beautiful souls helped me through with their kindness, sincerity, prayers and words of encouragement; Shafinaz, Amy, Parvaneh, Nor Yasmin, Farah, Suwaibah, Shafika and many more. May Allah bless all of you.

I shall always be indebted to my parents, my paradise. Thank you for always trusting me, showering me with their unconditional love and for the continuous prayers. What more can I say except Alhamdulillah.

Last but not least, my little family deserves my utmost appreciation. To my loving husband, thank you for all the sacrifices, the support and prayers. To my precious prince and princess, thank you for the constant support and co-operation. Thank you for understanding me, for allowing me the time I needed and for the constant prayers. This is our journey together.

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

Aini bt. Ideris, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Chairman)

Abdul Rahman bin Omar, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

Mohd. Hair bin Bejo, PhD
Professor
Faculty of Veterinary Medicine
Universiti Putra Malaysia
(Member)

ZALILAH MOHD SHARIFF, PhD
Professor and Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 6 May 2021

Declaration by graduate student

I hereby confirm that:

- this thesis is my original work;
- quotations, illustrations and citations have been duly referenced;
- this thesis has not been submitted previously or concurrently for any other degree at any other institutions;
- intellectual property from the thesis and copyright of thesis are fully-owned by Universiti Putra Malaysia, as according to the Universiti Putra Malaysia (Research) Rules 2012;
- written permission must be obtained from supervisor and the office of Deputy Vice-Chancellor (Research and Innovation) before thesis is published (in the form of written, printed or in electronic form) including books, journals, modules, proceedings, popular writings, seminar papers, manuscripts, posters, reports, lecture notes, learning modules or any other materials as stated in the Universiti Putra Malaysia (Research) Rules 2012;
- there is no plagiarism or data falsification/fabrication in the thesis, and scholarly integrity is upheld as according to the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) and the Universiti Putra Malaysia (Research) Rules 2012. The thesis has undergone plagiarism detection software.

Signature: _____ Date: _____

Name and Matric No.: Haryati Shila binti Mohamad Wali, GS30984

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

AIV	Avian influenza virus
BCR	B cell receptors
CARD	Caspase activation and recruitment domains
CARDIF	CARD adaptor inducing IFN-β
CLR	C-type lectin receptors
CPE	Cytopathic effects
DAMP	Danger-associated molecular pattern
DC	Dendritic cells
DF-1	Chicken embryo fibroblast
DMEM	Dulbecco's Modified Eagle's Medium
HA	Hemagglutination assay
HD-11	Chicken macrophage-like cell
IFN	Interferon
ISG	Interferon-stimulated gene
JC-1	5,5',6,6'-tetrachloro-1,1',3,3'-tetraethylbenzimidazolcarbocyanine iodide
LB	Luria-Bertani
LD	Lipid droplets
LGP2	Laboratory of genetics and physiology 2
MAVS	Mitochondrial antiviral signaling
MDA5	Melanoma differentiation-associated protein 5
MTS	3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
MTT	(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide)
NDV	Newcastle disease virus

NK cells	Natural killer cells
NLR	Nucleotide oligomerization domain (NOD)-like receptors (NLRs)
NOD	Nucleotide oligomerisation domain (NOD)
PAMP	Pathogen-associated molecular pattern
PBS	Phosphate-buffered saline
PRR	Pattern recognition receptors
RE	Restriction enzyme
RIG-I	Retinoic acid-inducible gene I
RLR	Retinoic acid-inducible gene I (RIG-I)-like receptors
ROS	Reactive oxygen species
$TCID_{50}$	Tissue culture infective dose
TCR	T cell receptors
TEM	Transmission electron microscopy
TLR	Toll-like receptors
TM	Transmembrane
VDAC	Voltage dependent anion channel
cRBC	Chicken red blood cells
dsRNA	Double-stranded RNA
mDAMP	Mitochondrial danger-associated molecular pattern
mtDNA	Mitochondrial DNA
qPCR	Quantitative PCR
ssRNA	Single-stranded RNA
$\Delta\psi$	Mitochondrial membrane potential

CHAPTER 1

INTRODUCTION

1.1. Background

Commonly known as the powerhouse of the cell, mitochondrial function is no longer restricted to energy production. Recent research have shown that mitochondria possess a distinct role in innate immunity with functions in apoptosis, danger signalling, induction of type I interferons (IFN) and pro-inflammatory cytokines and viral clearance (Pichlmair & Reis e Sousa, 2007; Galluzzi et al., 2012; Wang & Fish, 2012; West & Shadel, 2017). Being a multifunctional organelle, it became the target of invading viruses for the ease of controlling the whole cell while in the same time promoting/blocking apoptosis in accordance to the need (Reshi & Hong, 2017; Zemirli et al., 2018). Mitochondrial proteins have been established as having an important role in innate immunity. Mitochondrial antiviral signalling protein (MAVS), which is the first mitochondrial protein identified in the innate immune system play key roles in modulating interferon and pro-inflammatory cytokines following virus infection (Castanier et al., 2010; Scott, 2010). Sun et al. (2006) demonstrated the evidence of MAVS signalling in various kinds of cells including fibroblasts, macrophages and dendritic cells (DC). Mitochondrial DNA (mtDNA), the mitochondria's own genetic material, is similar to its bacterial antecedent. The leakage of mtDNA to the cytosol and its surroundings initiates damage-associated molecular patterns (DAMP), which leads to inflammation (Chen & Nunez, 2010; Tang et al., 2012; Fang et al., 2016). Meanwhile, the incidence of mtDNA stress stimulates antiviral priming response. Therefore, altered mtDNA homeostasis is not only an indicator of viral infection, it also serves as the platform for further antiviral reactions (Kugelberg, 2015).

It has been well established that viral infections are normally resolved by the organisms' innate and adaptive immunity. Previous studies showed that the mammalian innate immunity is activated via pathogen-associated molecular pattern (PAMP) proteins such as Toll-like receptors (TLR) and retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) that interact with mitochondrial antiviral signalling (MAVS) proteins (Yoneyama et al., 2004; Seth et al., 2005; Liu, 2001; Koshiba et al., 2011; Santhakumar et al., 2017). The role of TLR in animals including chickens has been well studied. However, little is known on the role of chicken RLR and MAVS in immunity against virus infection. MAVS is also known by other names such as IPSI, VISA, and CARDIF (Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005).

Newcastle disease (ND) is an important disease in poultry and exerted substantial economic impact on the poultry industry (Yusoff & Tan, 2001). Studies have shown that NDV-infected cells undergo cell death via apoptosis and necrosis (Khan et al., 2015; Abdolmaleki et al., 2018). Current measures to curb NDV outbreaks are by vaccination using live and attenuated ND vaccines. However, despite the vast application of vaccines, ND is still endemic in majority of the countries in the world. Newcastle disease

virus (NDV) is a nonsegmented RNA virus classified under the family Paramyxoviridae (Yusoff & Tan, 2001). The virus causes a systemic infection in chickens that are associated with high morbidity and mortality. The current control measure is by vaccination using genotype II lentogenic vaccine, meanwhile majority of outbreaks in various countries are due to genotype VII virulent NDV (Miller et al., 2009, 2010). Despite vaccination with existing commercial vaccines, infection of genotype VII shed more viruses compared to other virulent genotypes (Samuel et al., 2013; Susta et al., 2014; Roohani et al., 2015; Satharasinghe et al., 2016). The mechanisms associated with genotype II NDV vaccine failure is not clear but probably associated with the ability of virulent genotype VII to modulate acquired immune responses especially antibody responses (Miller et al., 2007). Several groups reported that velogenic NDV strains are able to initiate strong innate immune response by the upregulation of various genes related to the innate antiviral and inflammatory responses (Mase et al., 2002; Ebrahimi et al., 2012; Rasoli et al., 2014; Satharasinghe et al., 2016). These intense innate responses are postulated to contribute to the severe pathological damage and high mortality of infected chickens (Rue et al., 2011; Liu et al., 2012).

Although extensive studies regarding the role of MAVS signalling involve human cells, the importance of MAVS in chickens is not clear. A few research groups demonstrated that the presence of exogenous MAVS provides protection to cell lines in vitro against the infection of RNA and DNA viruses such as coxsackievirus B3, influenza A virus, viral haemorrhagic septicaemia virus 23/75 (VHSV), spring viremia of carp virus Fijan (SVCV) and others (Biacchesi et al., 2009; Liniger et al., 2012c; Zhang et al., 2012).

1.2. Problem statement

Despite intensive research involving the role of MAVS and mitochondrial DNA (mtDNA) in innate immunity and inflammation carried out on humans and various types of viruses, its role in avian virus infection especially NDV in chicken is still unclear. Currently, the role of MAVS genes and mtDNA on NDV-induced inflammation, virus clearance and their effect in the induction of apoptosis of NDV-infected cells are not known. The association of MAVS genes with mitochondrial-related damages such as inflammation and apoptosis following NDV infection as well as information on mtDNA level during NDV infection are lacking. Additionally, the question on how MAVS modulate innate immunity during NDV infection was also addressed in this study. Therefore, this study intends to explore the effects of exogenous MAVS gene presence in the regulation of inflammation, cytokine production as well as induction of apoptosis in NDV-infected cells, besides assessing the effects of NDV infection on mtDNA level.

The questions answered will further support the hypothesis that chicken MAVS possess a distinct role in innate immunity against NDV infection by assisting in inflammation, cytokine production and inducing apoptosis. Secondly, the knowledge gained from the analysis of mtDNA level in uninfected and infected cells will contribute to better understanding of its role in NDV infection. Information acquired from this study is hoped to be able to contribute to the possibility of exploiting the knowledge to develop novel

antiviral therapies against RNA viruses particularly Newcastle disease. Therefore, this study embarked on the following objectives:

To amplify MAVS (CARDIF) gene via polymerase chain reaction (PCR) and construct plasmid containing chCARDIF in mammalian expression vector.

To assess the effects of the plasmids pcDNA6/CARDIF, pcDNA6/ ΔCARD, and pcDNA6/ΔTM on the production of type I interferons and the plasmid pcDNA6/CARDIF on pro-inflammatory cytokines in two types of chicken cell lines (DF-1 and HD-11) following genotype VII NDV infection.

To investigate the involvement of mitochondrial DNA (mtDNA) in chicken cell lines by comparing mtDNA level in uninfected and infected chicken cell lines following genotype VII NDV infection.

To assess the role of MAVS genes and mtDNA in the induction of apoptosis in chicken cells following NDV infection and to determine the ultrastructural changes of the affected chicken cell lines following NDV infection.

REFERENCES

Abbas, A. K., & Lichtman, A. H. (2005). *Cellular and molecular immunology* (5th ed.). Elsevier Oxford.

Abdolmaleki, M., Keong Yeap, S., Wei Tan, S., Amila Satharasinghe, D., Bashir Bello, M., Zareian Jahromi, M., … Ideris, A. (2018). Effects of Newcastle disease virus infection on chicken intestinal intraepithelial natural killer cells. *Frontiers in Immunology*, *9*, 1386. http://doi.org/10.3389/fimmu.2018.01386

Abolnik, C., Horner, R. F., Bisschop, S. P. R., Parker, M. E., Romito, M., & Viljoen, G. J. (2004). A phylogenetic study of South African Newcastle disease virus strains isolated between 1990 and 2002 suggests epidemiological origins in the Far East. *Archives of Virology*, *149*(3), 603–619. http://doi.org/10.1007/s00705-003-0218-2

Ahamed, T., Hossain, K. M., Billah, M. M., Islam, K. M. D., Ahasan, M. M., & Islam, M. E. (2004). Adaptation of Newcastle disease virus (NDV) on vero cell line. International *Journal of Poultry Science*, *3*(2), 153–156. http://doi.org/10.3923/ijps.2004.153.156

Ahmed, K. A., Saxena, V. K., Ara, A., Singh, K. B., Sundaresan, N. R., Saxena, M., & Rasool, T. J. (2007). Immune response to Newcastle disease virus in chicken lines divergently selected for cutaneous hypersensitivity. *International Journal of Immunogenetics*, *34*(6), 445–455. http://doi.org/10.1111/j.1744-313X.2007.00722.x

Aldous, E. W., Mynn, J. K., Banks, J., & Alexander, D. J. (2003). A molecular epidemiological study of avian paramyxovirus type 1 (Newcastle disease virus) isolates by phylogenetic analysis of a partial nucleotide sequence of the fusion protein gene. *Avian Pathology*, *32*(3), 239–256. http://doi.org/10.1080/0307945031000097783

Alexander, D. J. (1991). Newcastle disease and other avian paramyxovirus infections. In B. W. Calnek, H. J. Barnes, C. W. Beard, W. M. Reid, & J. Yoder, H. W. (Eds.), *Diseases of Poultry* (9th ed, pp. 496–519). Ames, Iowa: Iowa State Univ. Press.

Alexander, D. J. (2001). Newcastle Disease. *British Poultry Science*, *42*(1), 5–22. http://doi.org/10.1080/713655022

Alexander, D. J., Bell, J. G., & Alders, R. G. (2004). FAO Technology Review: Newcastle disease with special emphasis on its effect on village chickens. *FAO Animal Production and Health*, *4*(ISSN 0254-6019), 55.

Alexander, D. J., Manvell, R. J., Lowings, J. P., Frost, K. M., Collins, M. S., Russell, P. H., & Smith, J. E. (1997). Antigenic diversity and similarities detected in avian paramyxovirus type 1 (Newcastle disease virus) isolates using monoclonal antibodies. *Avian Pathology*, *26*(November 2014), 399–418. http://doi.org/10.1080/03079459708419222

Alexander, D. J., & Senne, D. A. (2008). Newcastle disease, other avian paramyxoviruses, and pneumovirus infections. In Y. M. Saif (Ed.), *Diseases of poultry* (12th ed.). Iowa State University Press.

Alexopoulou, L., Holt, A. C., Medzhitov, R., & Flavell, R. A. (2001). Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature*, *413*(6857), 732–8. http://doi.org/10.1038/35099560

Anand, S. K., & Tikoo, S. K. (2013). Viruses as modulators of mitochondrial functions. *Advances in Virology*, *2013*. http://doi.org/10.1155/2013/738794

Arai, K. I., Lee, F., Miyajima, A., Miyatake, S., Arai, N., & Yokota, T. (1990). Cytokines: Coordinators of immune and inflammatory responses. *Annual Review of Biochemistry*, *59*, 783–836. http://doi.org/10.1146/annurev.bi.59.070190.004031

Arnoult, D., Soares, F., Tattoli, I., & Girardin, S. E. (2011). Mitochondria in innate immunity. *EMBO Reports*, *12*(9), 901–10. http://doi.org/10.1038/embor.2011.157

Ashkar, A. A., & Rosenthal, K. L. (2002). Toll-like receptor 9, CpG DNA and innate immunity. *Current Molecular Medicine*, *2*(6), 545–556.

Baggiolini, M. (1998). Chemokines and leukocyte traffic. *Nature Immunology*, *392*, 565–568. http://doi.org/10.1038/ni.f.214

Ballagi-Pordany, A., Wehmann, E., Herczeg, J., Belak, S., & Lomniczi, B. (1996). Identification and grouping of Newcastle disease virus strains by restriction site analysis of a region from the F gene. *Archives of Virology*, *141*, 243–261.

Baltimore, D. (1971). Expression of animal virus genomes. *Bacteriological Reviews*, *35*(3), 235–241.

Barber, M. R. W., Aldridge, J. R., Webster, R. G., & Magor, K. E. (2010). Association of RIG-I with innate immunity of ducks to influenza. *Proceedings of the National Academy of Sciences*, *107*(13), 5913–5918. http://doi.org/10.1073/pnas.1001755107

Belgnaoui, S. M., Paz, S., & Hiscott, J. (2011). Orchestrating the interferon antiviral response through the mitochondrial antiviral signaling (MAVS) adapter. *Current Opinion in Immunology*, *23*(5), 564–572. http://doi.org/10.1016/j.coi.2011.08.001

Beller, M., Thiel, K., Thul, P. J., & Jäckle, H. (2010). Lipid droplets: A dynamic organelle moves into focus. *FEBS Letters*, *584*(11), 2176–2182. http://doi.org/10.1016/j.febslet.2010.03.022

Benedict, C. A., Norris, P. S., & Ware, C. F. (2002). To kill or be killed: Viral evasion of apoptosis. *Nature Immunology*, *3*(11), 1013–1018. http://doi.org/10.1038/ni1102-1013

Beug, H., von Kirchbach, A., Döderlein, G., Conscience, J.-F., & Graf, T. (1979). Chicken hematopoietic cells transformed by seven strains of defective avian leukemia viruses display three distinct phenotypes of differentiation. *Cell*, *18*(2), 375–390. http://doi.org/10.1016/0092-8674(79)90057-6

Biacchesi, S., LeBerre, M., Lamoureux, A., Louise, Y., Lauret, E., Boudinot, P., & Bremont, M. (2009). Mitochondrial antiviral signaling protein plays a major role in induction of the fish innate immune response against RNA and DNA viruses. *Journal of Virology*, *83*(16), 7815–7827. http://doi.org/10.1128/JVI.00404-09

Bon, A. Le, & Tough, D. F. (2002). Links between innate and adaptive immunity via type I interferon. *Current Opinion in Immunology*, *14*, 432–436.

Boren, J., & Brindle, K. M. (2012). Apoptosis-induced mitochondrial dysfunction causes cytoplasmic lipid droplet formation. *Cell Death and Differentiation*, *19*(9), 1561–1570. http://doi.org/10.1038/cdd.2012.34

Boya, P., Roumier, T., Andreau, K., Gonzalez-Polo, R. A., Zamzami, N., Castedo, M., & Kroemer, G. (2003). Mitochondrion-targeted apoptosis regulators of viral origin. *Biochemical and Biophysical Research Communications*, *304*(3), 575–581. http://doi.org/10.1016/S0006-291X(03)00630-2

Broquet, A. H., Hirata, Y., McAllister, C. S., & Kagnoff, M. F. (2011). RIG-I/MDA5/MAVS are required to signal a protective IFN response in rotavirus-infected intestinal epithelium. *The Journal of Immunology*, *186*(3), 1618–1626. http://doi.org/10.4049/jimmunol.1002862

Bruns, K., Studtrucker, N., Sharma, A., Fossen, T., Mitzner, D., Eissmann, A., … Schubert, U. (2007). Structural characterization and oligomerization of PB1-F2, a proapoptotic influenza A virus protein. *Journal of Biological Chemistry*, *282*(1), 353–363. http://doi.org/10.1074/jbc.M606494200

Bulua, A. C., Simon, A., Maddipati, R., Pelletier, M., Park, H., Kim, K.-Y., … Siegel, R. M. (2011). Mitochondrial reactive oxygen species promote production of proinflammatory cytokines and are elevated in TNFR1-associated periodic syndrome (TRAPS). *The Journal of Experimental Medicine*, *208*(3), 519–533. http://doi.org/10.1084/jem.20102049

Burger, G., Gray, M. W., & Lang, B. F. (2003). Mitochondrial genomes: Anything goes. *Trends in Genetics*, *19*(12), 709–716. http://doi.org/10.1016/j.tig.2003.10.012

Camus, G., Vogt, D. A., Kondratowicz, A. S., & Ott, M. (2013). Lipid droplets and viral infections. *Methods in Cell Biology*, *116*(1). http://doi.org/10.1016/B978-0-12-408051-5.00009-7

Cann, A. J. (2005). *Principles of Molecular Virology* (4th ed.). Elsevier Academic Press. http://doi.org/10.1016/0968-0004(94)90095-7

Capua, I., & Alexander, D. J. (2009). *Avian Influenza and Newcastle Disease*. http://doi.org/10.1007/978-88-470-0826-7

Cassel, S. L., Joly, S., & Sutterwala, F. S. (2009). The NLRP3 inflammasome: A sensor of immune danger signals. *Seminars in Immunology*, *21*(4), 194–198. http://doi.org/10.1016/j.smim.2009.05.002

Chambers, P., & Samson, A. C. R. (1982). Non-structural proteins in Newcastle disease virus-infected cells. *Journal of General Virology*, *58*(1982), 1–12.

Chen, G. Y., & Nunez, G. (2010). Sterile inflammation: sensing and reacting to damage. *Nature Reviews Immunology*, *10*(12), 826–37. http://doi.org/10.1038/nri2873

Chen, S., Cheng, A., & Wang, M. (2013). Innate sensing of viruses by pattern recognition receptors in birds. *Veterinary Research*, *44*(1), 1–12. http://doi.org/10.1186/1297-9716-44-82

Chen, W., Calvo, P. A. A., Malide, D., Gibbs, J., Schubert, U., Bacik, I., … Yewdell, J. W. W. (2001). A novel influenza A virus mitochondrial protein that induces cell death. *Nature Medicine*, *7*(12), 1306–1312. http://doi.org/10.1038/nm1201-1306

Childs, K., Stock, N., Ross, C., Andrejeva, J., Hilton, L., Skinner, M., … Goodbourn, S. (2007). mda-5, but not RIG-I, is a common target for paramyxovirus V proteins. *Virology*, *359*(1), 190–200. http://doi.org/10.1016/j.virol.2006.09.023

Cho, S.-H., Kwon, H.-J., Kim, T.-E., Kim, J.-H., Yoo, H.-S., Park, M.-H., … Kim, S.-J. (2008). Characterization of a recombinant Newcastle disease virus vaccine strain. *Clinical and Vaccine Immunology*, *15*(10), 1572–9. http://doi.org/10.1128/CVI.00156-08

Cloonan, S. M., & Choi, A. M. K. (2012). Mitochondria: commanders of innate immunity and disease? *Current Opinion in Immunology*, *24*(1), 32–40. http://doi.org/10.1016/j.coi.2011.11.001

Cohen, S., Bigazzi, P. E., & Yoshida, T. (1974). Similarities of T cell function in cell-mediated immunity and antibody production. *Cell Immunology*, *12*, 150–159.

Colombini, M. (2004). VDAC: The channel at the interface between mitochondria and the cytosol. *Molecular and Cellular Biochemistry*, *256–257*(1–2), 107–115. http://doi.org/10.1023/B:MCBI.0000009862.17396.8d

Cox, N., Webster, R. G., Krauss, S., Guan, Y., Hay, A., Yu, K., … Stöhr, K. (2005). WHO manual on animal influenza diagnosis and surveillance. In R. Webster, N. Cox, & K. Stohr (Eds.), *WHO/CDS/CSR/NCS/2002.5 Rev 1* (2nd ed.). World Health Organization. https://www.who.int/csr/resources/publications/influenza/whocdscsrncs20025rev.pdf

Creagh, E. M., & Martin, S. J. (2001). Caspases: cellular demolition experts. *Biochemical Society Transactions*, *29*(Pt 6), 696–702. http://doi.org/10.1042/BST0290696

Crompton, M. (1999). The mitochondrial permeability transition pore and its role in cell death. *The Biochemical Journal*, *341*, 233–249. http://doi.org/10.1007/s10495-007-0723-y

Cui, S., Eisenächer, K., Kirchhofer, A., Brzózka, K., Lammens, A., Lammens, K., … Hopfner, K.-P. (2008). The C-Terminal Regulatory Domain Is the RNA 5′-Triphosphate Sensor of RIG-I. *Molecular Cell*, *29*(2), 169–179. http://doi.org/10.1016/j.molcel.2007.10.032

Czeglédi, A., Ujvári, D., Somogyi, E., Wehmann, E., Werner, O., & Lomniczi, B. (2006). Third genome size category of avian paramyxovirus serotype 1 (Newcastle disease virus) and evolutionary implications. *Virus Research*, *120*(1–2), 36–48. http://doi.org/10.1016/j.virusres.2005.11.009

Davison, F. (2014). The Importance of the Avian Immune System and its Unique Features. In K. Schat, B. Kaspers, & P. Kaiser (Eds.), *Avian Immunology* (2nd ed.). Academic Press.

de Leeuw, O. S., Hartog, L., Koch, G., & Peeters, B. P. H. (2003). Effect of fusion protein cleavage site mutations on virulence of Newcastle disease virus: Non-virulent cleavage site mutants revert to virulence after one passage in chicken brain. *Journal of General Virology*, *84*(2), 475–484. http://doi.org/10.1099/vir.0.18714-0

Dedio, J., Jahnen-Dechent, W., Bachmann, M., & Müller-Esterl, W. (1998). The multiligand-binding protein gC1qR, putative C1q receptor, is a mitochondrial protein. *Journal of Immunology (Baltimore, Md. : 1950)*, *160*(7), 3534–3542.

Degen, W. G. J., Van Daal, N., Rothwell, L., Kaiser, P., & Schijns, V. E. J. C. (2005). Th1/Th2 polarization by viral and helminth infection in birds. *Veterinary Microbiology*, *105*(3–4), 163–167. http://doi.org/10.1016/j.vetmic.2004.12.001

Deretic, V. (2011). Autophagy in Immunity and Cell-Autonomous Defense Against Intracellular MIcrobes. *Immunology Review*, *240*(1), 92–104. http://doi.org/10.1111/j.1600-065X.2010.00995.x.Autophagy

Desagher, S., & Martinou, J.-C. (2000). Mitochondria as the central control of apoptosis. *Trends in Cell Biology*, *10*(September), 369–377. http://doi.org/http://dx.doi.org/10.1016/S0962-8924(00)01803-1

Deveraux, Q. L., & Reed, J. C. (1999). IAP family proteins – suppressors of apoptosis. *Genes and Development*, *13*, 239–252. http://doi.org/10.1101/gad.13.3.239

Dhanwani, R., Takahashi, M., & Sharma, S. (2018). Cytosolic sensing of immuno-stimulatory DNA, the enemy within. *Current Opinion in Immunology*, *50*, 82–87. http://doi.org/10.1016/j.coi.2017.11.004

Díaz-Guerra, M., Rivas, C., & Esteban, M. (1997). Activation of the IFN-inducible enzyme RNase L causes apoptosis of animal cells. *Virology*, *236*(2), 354–363. http://doi.org/10.1006/viro.1997.8719

Diel, D. G., Susta, L., Garcia, S. C., Killian, M. L., Brown, C. C., Miller, P. J., & Afonso, C. L. (2012). Complete genome and clinicopathological characterization of a virulent newcastle disease virus isolate from South America. *Journal of Clinical Microbiology*, *50*(2), 378–387. http://doi.org/10.1128/JCM.06018-11

Dixit, E., Boulant, S., Zhang, Y., Lee, A. S. Y., Odendall, C., Shum, B., … Kagan, J. C. (2010). Peroxisomes are signaling platforms for antiviral innate immunity. *Cell*, *141*(4), 668–681. http://doi.org/10.1016/j.cell.2010.04.018

Domingo, E., & Holland, J. J. (1997). RNA virus mutations and fitness for survival. *Annual Review of Microbiology*, *51*, 151–178.

Ebrahimi, M. M., Shahsavandi, S., Moazenijula, G., & Shamsara, M. (2012). Phylogeny and evolution of Newcastle disease virus genotypes isolated in Asia during 2008-2011. *Virus Genes*, *45*(1), 63–68. http://doi.org/10.1007/s11262-012-0738-5

Everett, H., & McFadden, G. (1999). Apoptosis: An innate immune response to virus infection. *Trends in Microbiology*, *7*(4), 160–165. http://doi.org/10.1016/S0966-842X(99)01487-0

Fang, C., Wei, X., & Wei, Y. (2016). Mitochondrial DNA in the regulation of innate immune responses. *Protein & Cell*, *7*(1), 11–16. http://doi.org/10.1007/s13238-015-0222-9

Fauquet, C. M., & Fargette, D. (2005). International Committee on Taxonomy of Viruses and the 3,142 unassigned species. *Virology Journal*, *2*, 64. http://doi.org/10.1186/1743-422X-2-64

Fearon, D. T., & Locksley, R. M. (1996). Elements of immunity - the instructive role of innate immunity in the acquired immune-response. *Science (New York, N.Y.)*, *272*(5258), 50–54. http://doi.org/10.1126/science.272.5258.50

Fellah, J. S., Jaffredo, T., Nagy, N., & Dunon, D. (2014). Development of the avian immune system. In K. A. Schat, B. Kaspers, & P. Kaiser (Eds.), *Avian Immunology* (2nd ed.). California, USA: Academic Press.

Freshney, R. I. (2011). *Culture of animal cells: A manual of basic technique and specialized applications* (6th ed.). John Wiley and Sons.

Galluzzi, L., Brenner, C., Morselli, E., Touat, Z., & Kroemer, G. (2008). Viral control of mitochondrial apoptosis. *PLoS Pathogens*, *4*(5). http://doi.org/10.1371/journal.ppat.1000018

Galluzzi, L., Kepp, O., & Kroemer, G. (2012). Mitochondria: master regulators of danger signalling. *Nature Reviews. Molecular Cell Biology*, *13*(12), 780–8. http://doi.org/10.1038/nrm3479

Ganar, K., Das, M., Sinha, S., & Kumar, S. (2014). Newcastle disease virus: Current status and our understanding. *Virus Research*, *184*, 71–81. http://doi.org/10.1016/j.virusres.2014.02.016

Gandre-Babbe, S., & van der Bliek, A. M. (2008). The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammlian cells. *Molecular Biology of the Cell*, *19*(1), 2402–2412. http://doi.org/10.1091/mbc.E07

Gitlin, L., Benoit, L., Song, C., Cella, M., Gilfillan, S., Holtzman, M. J., & Colonna, M. (2010). Melanoma differentiation-associated gene 5 (MDA5) is involved in the innate immune response to Paramyxoviridae infection in vivo. *PLoS Pathogens*, *6*(1). http://doi.org/10.1371/journal.ppat.1000734

Gobel, T. W., Schneider, K., Schaerer, B., Mejri, I., Puehler, F., Weigend, S., … Kaspers, B. (2003). IL-18 stimulates the proliferation and IFN-gamma release of CD4+ T cells in the chicken: Conservation of a Th1-like system in a nonmammalian species. *The Journal of Immunology*, *171*(4), 1809–1815. http://doi.org/10.4049/jimmunol.171.4.1809

Goldmacher, V. S. (2002). vMIA, a viral inhibitor of apoptosis targeting mitochondria. *Biochimie*, *84*(2–3), 177–185. http://doi.org/10.1016/S0300-9084(02)01367-6

Goldmacher, V. S., Bartle, L. M., Skaletskaya, A., Dionne, C. A., Kedersha, N. L., Vater, C. A., … Chittenden, T. (1999). A cytomegalovirus-encoded mitochondria-localized inhibitor of apoptosis structurally unrelated to Bcl-2. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(22), 12536–41. http://doi.org/10.1073/PNAS.96.22.12536

Goodman, J. M. (2008). The gregarious lipid droplet. *Journal of Biological Chemistry*, *283*(42), 28005–28009. http://doi.org/10.1074/jbc.R800042200

Green, D. R., & Reed, J. C. (1998). Mitochondria and Apoptosis. *Science*, *281*(1309), 1309–1312. http://doi.org/10.1126/science.281.5381.1309

Green, M. R., & Sambrook, J. (2012). *Cloning and transformation with plasmid vectors*. *Molecular Cloning - A Laboratory Manual* (4th ed., Vol. 1). Cold Spring Harbor Laboratory Press. http://doi.org/10.3724/SP.J.1141.2012.01075

Grimes, S. E. (2002). *A basic laboratory manual for the small scale production and testing of I-2 Newcastle Disease vaccine*. Food and Agricultural Organization (FAO).

Gunter, T. E., & Pfeiffer, D. R. (1990). Mechanisms by which mitochondria transport calcium. *The American Journal of Physiology*, *258*(5 Pt 1), C755–C786.

Gürtler, C., & Bowie, A. G. (2013). Innate immune detection of microbial nucleic acids. *Trends in Microbiology*, *21*(8), 413–420. http://doi.org/10.1016/j.tim.2013.04.004

Hakumäki, J. M., & Kauppinen, R. A. (2000). 1H NMR visible lipids in the life and death of cells. *Trends in Biochemical Sciences*, *25*(8), 357–362. http://doi.org/10.1016/S0968-0004(00)01614-5

Halestrap, A., McStay, G., & Clarke, S. (2002). The permeability transition pore complex: another view. *Biochimie*, *84*(2–3), 153–66. http://doi.org/10.1016/S0300-9084(02)01375-5

Hay, S., & Kannourakis, G. (2002). A time to kill: Viral manipulation of the cell death program. *Journal of General Virology*, *83*(7), 1547–1564. http://doi.org/10.1099/0022-1317-83-7-1547

Herczeg, J., Wehmann, E., Bragg, R. R., Travassos Dias, P. M., Hadjiev, G., Werner, O., & Lomniczi, B. (1999). Two novel genetic groups (VIIb and VIII) responsible for recent Newcastle disease outbreaks in Southern Africa, one (VIIb) of which reached Southern Europe. *Archives of Virology*, *144*, 2087–2099.

Herker, E., & Ott, M. (2012). Emerging role of lipid droplets in host/pathogen interactions. *Journal of Biological Chemistry*, *287*(4), 2280–2287. http://doi.org/10.1074/jbc.R111.300202

Holm, C. K., Rahbek, S. H., Gad, H. H., Bak, R. O., Jakobsen, M. R., Jiang, Z., … Paludan, S. R. (2016). Influenza A virus targets a cGAS-independent STING pathway that controls enveloped RNA viruses. *Nature Communications*, *7*, 1–9. http://doi.org/10.1038/ncomms10680

Hornung, V., Ellegast, J., Kim, S., Brzózka, K., Jung, A., Kato, H., … Hartmann, G. (2006). 5'-triphosphate RNA is the ligand for RIG-I. *Science*, *314*(2006), 994–997. http://doi.org/10.1126/science.1132505

Hou, F., Sun, L., Zheng, H., Skaug, B., Jiang, Q.-X., & Chen, Z. J. (2012). MAVS forms functional prion-like aggregates to activate and propagate antiviral innate immune response. *Cell*, *146*(3), 448–461. http://doi.org/10.1016/j.cell.2011.06.041.MAVS

Hsiung, G. D. (1984). Diagnostic virology: From animals to automation. *The Yale Journal of Biology and Medicine*, *57*(5), 727–733.

Hu, S., Ma, H., Wu, Y., Liu, W., Wang, X., Liu, Y., & Liu, X. (2009). A vaccine candidate of attenuated genotype VII Newcastle disease virus generated by reverse genetics. *Vaccine*, *27*(6), 904–910. http://doi.org/10.1016/j.vaccine.2008.11.091

Huang, Z., Panda, A., Elankumaran, S., Govindarajan, D., Rockemann, D. D., & Samal, S. K. (2004). The hemagglutinin-neuraminidase protein of Newcastle disease virus determines tropism and virulence. *Journal of Virology*, *78*(8), 4176–4184. http://doi.org/10.1128/JVI.78.8.4176

Hussain, I., & Rasool, M. H. (2005). Adaptation of an indigenous very virulent infectious bursal disease virus on vero cell line. *Pakistan Veterinary Journal*, *25*(3), 103–106.

Ijzermans, J. N. M., & Marquet, R. L. (1989). Interferon-gamma: A Review. *Immunobiology*, *179*(4–5), 456–473. http://doi.org/10.1016/S0171-2985(89)80049-X

Ikegame, S., Takeda, M., Ohno, S., Nakatsu, Y., Nakanishi, Y., & Yanagi, Y. (2010). Both RIG-I and MDA5 RNA helicases contribute to the induction of alpha/beta interferon in measles virus-Infected human cells. *Journal of Virology*, *84*(1), 372–379. http://doi.org/10.1128/JVI.01690-09

Iqbal, M., Cawthon, D., Wideman, R. F., & Bottje, W. G. (2001). Lung mitochondrial dysfunction in pulmonary hypertension syndrome. I. Site-specific defects in the electron transport chain. *Poultry Science*, *80*(4), 485–95. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/11297288

Ishikawa, H., & Barber, G. N. (2008). STING is an endoplasmic reticulum adaptor that facilitates innate immune signalling. *Nature*, *455*(7213), 674–678. http://doi.org/10.1038/nature07317

Iwasaki, A., & Medzhitov, R. (2010). Regulation of adaptive immunity by the innate immune system. *Science*, *327*(5963), 291–295. http://doi.org/10.1126/science.1183021

Janeway, C. A. (1989). Approaching the asymptote? Evolution and revolution in immunology. In *Cold Spring Harbor Symposia on Quantitative Biology* (Vol. 54, pp. 1–13). http://doi.org/10.1101/SQB.1989.054.01.003

Janeway, C. A. (1992). The immune system evolved to discriminate infectious nonself from noninfectious self. *Immunology Today*, *13*(1), 11–16. http://doi.org/10.1016/0167-5699(92)90198-G

Janeway, C. A., & Medzhitov, R. (2002). Innate immune recognition. *Annual Review of Immunology*, *20*(2), 197–216. http://doi.org/10.1146/annurev.immunol.20.083001.084359

Jouaville, L. S., Pinton, P., Bastianutto, C., Rutter, G. a, & Rizzuto, R. (1999). Regulation of mitochondrial ATP synthesis by calcium: Evidence for a long-term metabolic priming. *Proceedings of the National Academy of Sciences of the United States of America*, *96*(24), 13807–13812. http://doi.org/10.1073/pnas.96.24.13807

Juul-Madsen, H. R., Viertlboeck, B., Hartle, S., Smith, A. L., & Gobel, T. W. (2014). Innate immune responses. In K. A. Schat, B. Kaspers, & P. Kaiser (Eds.), *Avian Immunology* (2nd ed.). Academic Press.

Kaiser, M. G., Cheeseman, J. H., Kaiser, P., & Lamont, S. J. (2006). Cytokine expression in chicken peripheral blood mononuclear cells after In vitro exposure to Salmonella enterica serovar Enteritidis. *Poultry Science*, *85*, 1907–1911.

Kaiser, P. (n.d.). *Chikenology – Importance of chicken immunology research and studying host-pathogen interactions*. Retrieved February 10, 2016, from https://www.abdserotec.com/avian-immunology-importance-of-chicken-immunology-research.html

Kaiser, P., Poh, T. Y., Rothwell, L., Avery, S., Balu, S., Pathania, U. S., … Young, J. R. (2005). A genomic analysis of chicken cytokines and chemokines. *Journal of*

Interferon & Cytokine Research, *25*(8), 467–484. http://doi.org/10.1089/jir.2005.25.467

Kaiser, P., Rothwell, L., Galyov, E. E., Barrow, P. a, Burnside, J., & Wigley, P. (2000). Differential cytokine expression in avian cells in response to invasion by *Salmonella typhimurium*, *Salmonella enteritidis* and *Salmonella gallinarum*. *Microbiology*, *146*(12), 3217–3226. http://doi.org/10.1099/00221287-146-12-3217

Kaiser, P., & Staeheli, P. (2014). Avian cytokines and chemokines. In K. A. Schat, B. Kaspers, & P. Kaiser (Eds.), *Avian Immunology* (2nd ed.). California, USA.

Kapczynski, D. R., Afonso, C. L., & Miller, P. J. (2013). Immune responses of poultry to Newcastle disease virus. *Developmental and Comparative Immunology*, *41*, 447–453.

Karber, G. (1931). 50% end-point calculation. *Archive of Experimental Pathology and Pharmakology*, *162*, 480–83.

Karpala, A. J., Stewart, C., Mckay, J., John, W., Bean, A. G. D., Karpala, A. J., … Bean, A. G. D. (2011). Characterization of chicken MDA5 activity: Regulation of IFN- β in the absence of RIG-I functionality. *Journal of Immunology*, *186*, 5397–5405. http://doi.org/10.4049/jimmunol.1003712

Kasashima, K., Sumitani, M., & Endo, H. (2011). Human mitochondrial transcription factor A is required for the segregation of mitochondrial DNA in cultured cells. *Experimental Cell Research*, *317*(2), 210–220. http://doi.org/10.1016/j.yexcr.2010.10.008

Kato, H., Takeuchi, O., Mikamo-Satoh, E., Hirai, R., Kawai, T., Matsushita, K., … Akira, S. (2008). Length-dependent recognition of double-stranded ribonucleic acids by retinoic acid-inducible gene-I and melanoma differentiation-associated gene 5. *The Journal of Experimental Medicine*, *205*(7), 1601–1610. http://doi.org/10.1084/jem.20080091

Kattenbelt, J. A., Stevens, M. P., Selleck, P. W., & Gould, A. R. (2010). Analysis of Newcastle disease virus quasispecies and factors affecting the emergence of virulent virus. *Archives of Virology*, *155*(10), 1607–1615. http://doi.org/10.1007/s00705-010-0739-4

Kawai, T., & Akira, S. (2006). Innate immune recognition of viral infection. *Nature Immunology*, *7*(2), 131–137. http://doi.org/10.1038/ni1303

Kawai, T., Takahashi, K., Sato, S., Coban, C., Kumar, H., Kato, H., … Akira, S. (2005). IPS-1, an adaptor triggering RIG-I- and MDA5-mediated type I interferon induction. *Nature Immunology*, *6*(10), 981–988. http://doi.org/10.1038/ni1243

Kerr, J. F. R., Wyllie, A. H., & Currie, A. R. (1972). Apoptosis : A basic biological phenomenon with wide-ranging implications in tissue kinetics. *British Journal of Cancer*, *26*, 239–257.

Khan, M., Syed, G. H., Kim, S. J., & Siddiqui, A. (2015). Mitochondrial dynamics and viral infections: A close nexus. *Biochimica et Biophysica Acta*, *1853*(10), 2822–2833. http://doi.org/10.1016/j.bbamcr.2014.12.040

Khan, T. A., Rue, C. A., Rehmani, S. F., Ahmed, A., Wasilenko, J. L., Miller, P. J., & Afonso, C. L. (2010). Phylogenetic and biological characterization of Newcastle disease virus isolates from Pakistan. *Journal of Clinical Microbiology*, *48*(5), 1892–1894. http://doi.org/10.1128/JCM.00148-10

Khoo, J., Nagley, P., & Mansell, A. (2013). Mitochondria : an Unexpected Force in Innate Immunity. *Australian Biochemist*, *44*(1), 17–20.

Killian, M. L. (2008). Hemagglutination assay for the avian influenza virus. In E. Speckman (Ed.), *Methods in Molecular Biology* (Vol. 436, pp. 47–52). Humana Press. http://doi.org/doi.org/10.1007/978-1-59745-279-3_7

Kobayashi, K. S., & Flavell, R. A. (2004). Shielding the double-edged sword: negative regulation of the innate immune system. *Journal of Leukocyte Biology*, *75*(3), 428–433. http://doi.org/10.1189/jlb.0703321

Koch, A., Yoon, Y., Bonekamp, N. A., McNiven, M. A., & Schrader, M. (2005). A role for Fis1 in both mitochondrial and peroxisomal fission in mammalian cells. *Molecular Biology of the Cell*, *16*, 5077–5086. http://doi.org/10.1091/mbc.E05

Kogut, M. H. (2002). Dynamics of a protective avian inflammatory response: The role of an IL-8-like cytokine in the recruitment of heterophils to the site of organ invasion by Salmonella enteritidis. *Comparative Immunology, Microbiology and Infectious Diseases*, *25*(3), 159–172. http://doi.org/10.1016/S0147-9571(01)00035-2

Kogut, M. H., Rothwell, L., & Kaiser, P. (2003). Differential regulation of cytokine gene expression by avian opsonized and nonopsonized *Salmonella enteritidis*. *Journal of Interferon & Cytokine Research*, *23*, 319–327.

Komuro, A., & Horvath, C. M. (2006). RNA- and virus-independent inhibition of antiviral signaling by RNA helicase LGP2. *Journal of Virology*, *80*(24), 12332–12342. http://doi.org/10.1128/JVI.01325-06

Koshiba, T. (2013). Mitochondrial-mediated antiviral immunity. *Biochimica et Biophysica Acta*, *1833*(1), 225–232. http://doi.org/10.1016/j.bbamcr.2012.03.005

Koshiba, T., Bashiruddin, N., & Kawabata, S. (2011). Mitochondria and antiviral innate immunity. *International Journal of Biochemistry and Molecular Biology*, *2*(3), 257–62.

Krishnamurthy, S., & Samal, S. K. (1998). Nucleotide sequences of the trailer, nucleocapsid protein gene and intergenic regions of Newcastle disease virus strain Beaudette C and completion of the entire genome sequence. *Journal of General Virology*, *79*(10), 2419–2424. http://doi.org/10.1099/0022-1317-79-10-2419

Kristeen-Teo, Y. W., Yeap, S. K., Tan, S. W., Omar, A. R., Ideris, A., Tan, S. G., & Alitheen, N. B. (2017). The effects of different velogenic NDV infections on the chicken bursa of Fabricius. *BMC Veterinary Research*, *13*(1), 151. http://doi.org/10.1186/s12917-017-1071-y

Kroemer, G., & Reed, J. C. (2000). Mitochondrial control of cell death. *Nature America*, *6*(5), 513–519. http://doi.org/10.1038/74994

Kugelberg, E. (2015). Innate immunity: Stressed mitochondria provide protection. *Nature Reviews Immunology*, *15*(3), 134–134. http://doi.org/10.1038/nri3828

Kumar, H., Kawai, T., Kato, H., Sato, S., Takahashi, K., Coban, C., … Akira, S. (2006). Essential role of IPS-1 in innate immune responses against RNA viruses. *The Journal of Experimental Medicine*, *203*(7), 1795–803. http://doi.org/10.1084/jem.20060792

Lai, M. M. (1992). RNA recombination in animal and plant viruses. *Microbiological Reviews*, *56*(1), 61–79.

Lamb, R., & Parks, G. (2007). Paramyxoviridae: The viruses and their replication. In S. E. Knipe, D. M., Howley, P. M., Griffin, D. E., Lamb, R. A., Martin, M. A., Roizman, & B., Straus (Eds.), *Fields Virology* (5th ed.). Lippincott Williams & Wilkins.

Lambrecht, B., Gonze, M., Morales, D., Meulemans, G., & van den Berg, T. P. (1999). Comparison of biological activities of natural and recombinant chicken interferon-gamma. *Veterinary Immunology and Immunopathology*, *70*(3–4), 257–267. http://doi.org/10.1016/S0165-2427(99)00080-X

Lee, C., Wu, C. C., & Lin, T. L. (2012). Characterization of chicken melanoma differentiation-associated gene 5 (MDA5) from alternative translation initiation. *Comparative Immunology, Microbiology and Infectious Diseases*, *35*(4), 335–343. http://doi.org/10.1016/j.cimid.2012.02.004

Lei, Y., Moore, C. B., Liesman, R. M., O'Connor, B. P., Bergstralh, D. T., Chen, Z. J., … Ting, J. P.-Y. (2009). MAVS-mediated apoptosis and its inhibition by viral proteins. *PloS One*, *4*(5), e5466. http://doi.org/10.1371/journal.pone.0005466

Leland, D. S., & Ginocchio, C. C. (2007). Role of cell culture for virus detection in the age of technology. *Clinical Microbiology Reviews*, *20*(1), 49–78. http://doi.org/10.1128/CMR.00002-06

Li, L. Y., Luo, X., & Wang, X. (2001). Endonuclease G is an apoptotic DNase when released from mitochondria. *Nature*, *412*(6842), 95–99. http://doi.org/10.1038/35083620

Liniger, M., Moulin, H. R., Sakoda, Y., Ruggli, N., & Summerfield, A. (2012a). Highly pathogenic avian influenza virus H5N1 controls type I IFN induction in chicken macrophage HD-11 cells: a polygenic trait that involves NS1 and the

polymerase complex. *Virology Journal*, *9*(1), 7. http://doi.org/10.1186/1743-422X-9-7

Liniger, M., Summerfield, A., & Ruggli, N. (2012b). MDA5 can be exploited as efficacious genetic adjuvant for DNA vaccination against lethal H5N1 influenza virus infection in chickens. *PloS One*, *7*(12), e49952. http://doi.org/10.1371/journal.pone.0049952

Liniger, M., Summerfield, A., Zimmer, G., McCullough, K. C., & Ruggli, N. (2012c). Chicken cells sense influenza A virus infection through MDA5 and CARDIF signaling involving LGP2. *Journal of Virology*, *86*(2), 705–717. http://doi.org/10.1128/JVI.00742-11

Lipford, G. B., Heeg, K., & Wagner, H. (1998). Bacterial DNA as immune cell activator. *Trends in Microbiology*, *6*(12), 496–500. http://doi.org/10.1016/S0966-842X(98)01408-5

Liu, W. Q., Tian, M. X., Wang, Y. P., Zhao, Y., Zou, N. L., Zhao, F. F., … Huang, Y. (2012). The different expression of immune-related cytokine genes in response to velogenic and lentogenic Newcastle disease viruses infection in chicken peripheral blood. *Molecular Biology Reports*, *39*(4), 3611–3618. http://doi.org/10.1007/s11033-011-1135-1

Liu, X. F., Wan, H. Q., Ni, X. X., Wu, Y. T., & Liu, W. B. (2003). Pathotypical and genotypical characterization of strains of Newcastle disease virus isolated from outbreaks in chicken and goose flocks in some regions of China during 1985-2001. *Archives of Virology*, *148*, 1387–1403. http://doi.org/10.1007/s00705-003-0014-z

Liu, X., Kim, C. N., Yang, J., Jemmerson, R., & Wang, X. (1996). Induction of apoptotic program in cell-free extracts: Requirement for dATP and cytochrome c. *Cell*, *86*(1), 147–157. http://doi.org/10.1016/S0092-8674(00)80085-9

Liu, Y.-J. (2001). Dendritic cell subsets and lineages, and their functions in innate and adaptive immunity. *Cell*, *106*(3), 259–262. http://doi.org/S0092-8674(01)00456-1 [pii]

Loo, Y. M., & Gale, M. (2011). Immune signaling by RIG-I-like receptors. *Immunity*, *34*(5), 680–692. http://doi.org/10.1016/j.immuni.2011.05.003

Lowenthal, J. W., Digby, M. R., & York, J. J. (1995). Production of interferon-gamma by chicken T cells. *Journal of Interferon & Cytokine Research*, *15*, 933–938.

Lowenthal, J. W., York, J. J., O'Neil, T. E., Rhodes, S., Prowse, S. J., Strom, D. G., & Digby, M. R. (1997). In vivo effects of chicken interferon-gamma during infection with Eimeria. *Journal of Interferon & Cytokine Researchterferon*, *17*(9), 551–8. http://doi.org/10.1089/jir.1997.17.551

Ly, J. D., Grubb, D. R., & Lawen, A. (2003). The mitochondrial membrane potential (deltapsi(m)) in apoptosis; an update. *Apoptosis*, *8*(2), 115–128. http://doi.org/5119089 [pii]

Machida, K., McNamara, G., Cheng, K. T.-H., Huang, J., Wang, C.-H., Comai, L., … Lai, M. M. C. (2010). Hepatitis C Virus Inhibits DNA Damage Repair through Reactive Oxygen and Nitrogen Species and by Interfering with the ATM-NBS1/Mre11/Rad50 DNA Repair Pathway in Monocytes and Hepatocytes. *The Journal of Immunology*, *185*(11), 6985–6998. http://doi.org/10.4049/jimmunol.1000618

Mahon, P. J., Mirza, A. M., & Iorio, R. M. (2011). Role of the two sialic acid binding sites on the Newcastle disease virus HN protein in triggering the interaction with the F protein required for the promotion of fusion. *Journal of Virology*, *85*(22), 12079–12082. http://doi.org/Doi 10.1128/Jvi.05679-11

Mase, M., Imai, K., Sanada, Y., Sanada, N., Yuasa, N., Imada, T., … Yamaguchi, S. (2002). Phylogenetic analysis of Newcastle disease virus genotypes isolated in Japan. *Journal of Clinical Microbiology*, *40*(10), 3826–3830. http://doi.org/10.1128/JCM.40.10.3826

Mayo, M. (2002). Virus taxonomy-Houston 2002. *Archives of Virology*, *5*. http://doi.org/10.1007/s007050200036

McBride, H. M., Neuspiel, M., & Wasiak, S. (2006). Mitochondria: More Than Just a Powerhouse. *Current Biology*. http://doi.org/10.1016/j.cub.2006.06.054

McCormick, A. L., Smith, V. L., Chow, D., & Mocarski, E. S. (2003). Disruption of mitochondrial networks by the human cytomegalovirus UL37 gene product viral mitochondrion-localized inhibitor of apoptosis. *Journal of Virology*, *77*(1), 631–41. http://doi.org/10.1128/JVI.77.1.631

Medzhitov, R., & Janeway, C. A. (1997). Innate immunity: the virtues of a nonclonal system of recognition. *Cell*, *91*(3), 295–8. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/9363937

Meylan, E., Curran, J., Hofmann, K., Moradpour, D., Binder, M., Bartenschlager, R., & Tschopp, J. (2005). Cardif is an adaptor protein in the RIG-I antiviral pathway and is targeted by hepatitis C virus. *Nature*, *437*(7062), 1167–72. http://doi.org/10.1038/nature04193

Meylan, E., & Tschopp, J. (2008). NLRX1: friend or foe? *EMBO Reports*, *9*(3), 10–12. http://doi.org/10.1038/ncb1722

Miller, P. J., Decanini, E. L., & Afonso, C. L. (2010). Newcastle disease : Evolution of genotypes and the related diagnostic challenges. *Infection, Genetics and Evolution*, *10*, 26–35. http://doi.org/10.1016/j.meegid.2009.09.012

Miller, P. J., Kim, L. M., Ip, H. S., & Afonso, C. L. (2009). Evolutionary dynamics of Newcastle disease virus. *Virology*, *391*(1), 64–72. http://doi.org/10.1016/j.virol.2009.05.033

Monson, E. A., Crosse, K. M., Das, M., & Helbig, K. J. (2018). Lipid droplet density alters the early innate immune response to viral infection. *PLoS ONE*, 1–18. http://doi.org/10.1371/journal.pone.0190597

Moore, C. B., & Ting, J. P.-Y. Y. (2008). Regulation of Mitochondrial Antiviral Signaling Pathways. *Immunity*, *28*(6), 735–9. http://doi.org/10.1016/j.immuni.2008.05.005

Moser, B., Wolf, M., Walz, A., & Loetscher, P. (2004). Chemokines: Multiple levels of leukocyte migration control. *Trends in Immunology*, *25*(2), 75–84. http://doi.org/10.1016/j.it.2003.12.005

Mosmann, T. (1983). Rapid colorimetric assay for cellular growth and survival: Application to proliferation and cytotoxicity assays. *Journal of Immunological Methods*, *65*(1–2), 55–63. http://doi.org/10.1016/0022-1759(83)90303-4

Mujahid, A., Pumford, N. R., Bottje, W., Nakagawa, K., Miyazawa, T., Akiba, Y., & Toyomizu, M. (2007). Mitochondrial Oxidative Damage in Chicken Skeletal Muscle Induced by Acute Heat Stress. *The Journal of Poultry Science*, *44*, 39–445. http://doi.org/10.2141/jpsa.44.439

Mukundan, L., Odegaard, J. I., Morel, C. R., Heredia, J. E., Mwangi, W., Ricardo-gonzalez, R. R., … Chawla, A. (2010). PPAR-δ senses and orchestrates clearance of apoptotic cells to promote tolerance. *Nature Medicine*, *15*(11), 1266–1272. http://doi.org/10.1038/nm.2048.PPAR-

Munir, M., Abbas, M., Khan, M. T., Zohari, S., & Berg, M. (2012). Genomic and biological characterization of a velogenic Newcastle disease virus isolated from a healthy backyard poultry flock in 2010. *Virology Journal*, *9*(August 2016), 46. http://doi.org/10.1186/1743-422X-9-46

Muñoz-Planillo, R., Kuffa, P., Martínez-Colón, G., Smith, B., Rajendiran, T., & Núñez, G. (2013). K+ Efflux Is the Common Trigger of NLRP3 Inflammasome Activation by Bacterial Toxins and Particulate Matter. *Immunity*, *38*(6), 1142–1153. http://doi.org/10.1016/j.immuni.2013.05.016

Muta, T., Kang, D., Kitajima, S., Fujiwara, T., & Hamasaki, N. (1997). P32 Protein, a Splicing Factor 2-Associated Protein, Is Localized in Mitochondrial Matrix and Is Functionally Important in Maintaining Oxidative Phosphorylation. *Journal of Biological Chemistry*, *272*(39), 24363–24370. http://doi.org/10.1074/jbc.272.39.24363

Nakahira, K., Haspel, J. A., Rathinam, V. A. K., Lee, S.-J., Dolinay, T., Lam, H. C., … Choi, A. M. K. (2011). Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nature Immunology*, *8*(3), 222–30. http://doi.org/10.1038/ni.1980

Nakanishi, K., Yoshimoto, T., Tsutsui, H., & Okamura, H. (2001). Interleukin-18 regulates both Th1 and Th2 responses. *Annual Review of Immunology*, *19*, 423–74.

Newman, T. (2016). Inflammation turns mitochondria into toxic factories. *Medical News Today*.

Nicholls, J. M., Lai, J., & Garcia, J.-M. (2012). Investigating the interaction between influenza and sialic acid: Making and breaking the link. In M. von Itzstein (Ed.), *Milestones in Drug Therapy* (Vol. 36, pp. 31–46). Springer. http://doi.org/10.1007/978-3-7643-8927-7

Office of International Epizootes (OIE). (2009). Manual of diagnostic tests and vaccines for terrestrial animals: Mammals, birds and bees. In *Biological Standards Commission, World Organization for Animal Health* (pp. 576–589). Paris.

Office of International Epizootes (OIE). (2012). Newcastle disease. In *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (Vol. 1, pp. 1–19). World Organization for Animal Health. http://doi.org/10.1080/713655022

Ohta, A., & Nishiyama, Y. (2011). Mitochondria and viruses. *Mitochondrion*, *11*(1), 1–12. http://doi.org/10.1016/j.mito.2010.08.006

Okamura, H., Tsutsui, H., Komatsu, T., Yutsudo, M., Hakura, A., Tanimoto, T., … Kurimoto, M. (1995). Cloning of a new cytokine that induces IFN-γ production by T cells. *Letters to Nature*, *378*(6555), 88–91. http://doi.org/10.1038/378088a0

Panda, A., Huang, Z., Elankumaran, S., Rockemann, D. D., & Samal, S. K. (2004). Role of fusion protein cleavage site in the virulence of Newcastle disease virus. *Microbial Pathogenesis*, *36*(1), 1–10. http://doi.org/10.1016/j.micpath.2003.07.003

Pantua, H. D., McGinnes, L. W., Peeples, M. E., & Morrison, T. G. (2006). Requirements for the assembly and release of Newcastle disease virus-like particles. *Journal of Virology*, *80*(22), 11062–11073. http://doi.org/10.1128/JVI.00726-06

Pedersen, J. C., Senne, D. A., Woolcock, P. R., Kinde, H., King, D. J., Wise, M. G., … Seal, B. S. (2004). Phylogenetic relationships among virulent Newcastle disease virus isolates from the 2002-2003 outbreak in California and other recent outbreaks in North America. *Journal of Clinical Microbiology*, *42*(5), 2329–2334. http://doi.org/10.1128/JCM.42.5.2329-2334.2004

Peeters, B. P. H., de Leeuw, O. S., Koch, G., & Gielkens, A. L. J. (1999). Rescue of Newcastle disease virus from cloned cDNA: Evidence that cleavability of the fusion protein is a major determinant for virulence. *Journal of Virology*, *73*(6), 5001–5009.

Perozo, F., Marcano, R., & Afonso, C. L. (2012). Biological and phylogenetic characterization of a genotype VII Newcastle disease virus from Venezuela: Efficacy of field vaccination. *Journal of Clinical Microbiology*, *50*(4), 1204–1208. http://doi.org/10.1128/JCM.06506-11

Pichlmair, A., & Reis e Sousa, C. (2007). Innate recognition of viruses. *Immunity*, *27*(3), 370–383. http://doi.org/10.1016/j.immuni.2007.08.012

Pichlmair, A., Schulz, O., Tan, C. P., Naslund, T. I., Liljestrom, P., Weber, F., & Reis e Sousa, C. (2006). RIG-I–mediated antiviral responses to single-stranded RNA bearing 5'-phosphates. *Science*, *314*(2006), 997–1001. http://doi.org/10.1126/science.1132998

Rahman, M. M., & Eo, S. K. (2012). Prospects and challenges of using chicken cytokines in disease prevention. *Vaccine*, *30*(50), 7165–7173. http://doi.org/10.1016/j.vaccine.2012.10.011

Rapaport, D. (2003). Finding the right organelle. Targeting signals in mitochondrial outer-membrane proteins. *EMBO Reports*, *4*(10), 948–52. http://doi.org/10.1038/sj.embor.embor937

Rasoli, M., Yeap, S. K., Tan, S. W., Moeini, H., Ideris, A., Bejo, M. H., … Omar, A. R. (2014). Alteration in lymphocyte responses, cytokine and chemokine profiles in chickens infected with genotype VII and VIII velogenic Newcastle disease virus. *Comparative Immunology, Microbiology and Infectious Diseases*, *37*(1), 11–21. http://doi.org/10.1016/j.cimid.2013.10.003

Raturi, A., & Simmen, T. (2013). Where the endoplasmic reticulum and the mitochondrion tie the knot: The mitochondria-associated membrane (MAM). *Biochimica et Biophysica Acta*, *1833*(1), 213–224. http://doi.org/10.1016/j.bbamcr.2012.04.013

Read, A. F., Baigent, S. J., Powers, C., Kgosana, L. B., Blackwell, L., Smith, L. P., … Nair, V. K. (2015). Imperfect vaccination can enhance the transmission of highly virulent pathogens. *PLoS Biology*, *13*(7), 1–18. http://doi.org/10.1371/journal.pbio.1002198

Reed, L. J., & Muench, H. (1938). A simple method of estimating fifty per cent endpoints. *The American Jounal of Hygiene*, *27*(3), 493–497. http://doi.org/10.1016/j.jvs.2011.05.096

Reshi, L., & Hong, J. R. (2017). Mitochondria as a favourite organelle for invading viruses. *Molecular Biology*, *6*(1), 1–12. http://doi.org/10.4172/2168-9547.1000181

Riemer, J., Bulleid, N., & Herrmann, J. M. (2009). Disulfide formation in the ER and mitochondria: Two solutions to a common process. *Science*, *324*(5932), 1284–1287. http://doi.org/10.1126/science.1170653

Riss, T. L., Moravec, R. A., Niles, A. L., Benink, H. A., Worzella, T. J., & Minor, L. (2015). Cell viability assays. *Assay Guidance Manual*, 1–23. http://doi.org/10.1016/j.acthis.2012.01.006

Rock, K. L., Latz, E., Ontiveros, F., & Kono, H. (2010). The sterile inflammatory response. *Annual Review of Immunology*, *28*, 321–42. http://doi.org/10.1146/annurev-immunol-030409-101311

Römer-Oberdörfer, A., Mundt, E., Mebatsion, T., Buchholz, U. J., & Mettenleiter, T. C. (1999). Generation of recombinant lentogenic Newcastle disease virus from cDNA. *Journal of General Virology*, *80*(11), 2987–2995. http://doi.org/10.1099/0022-1317-80-11-2987

Rongvaux, A., Jackson, R., Harman, C. C. D., Li, T., West, A. P., De Zoete, M. R., … Flavell, R. A. (2014). Apoptotic caspases prevent the induction of Type I interferons by mitochondrial DNA. *Cell*, *159*(7), 1563–1577. http://doi.org/10.1016/j.cell.2014.11.037

Roohani, K., Tan, S. W., Yeap, S. K., Ideris, A., Bejo, M. H., & Omar, A. R. (2015). Characterisation of genotype VII Newcastle disease virus (NDV) isolated from NDV vaccinated chickens, and the efficacy of LaSota and recombinant genotype VII vaccines against challenge with velogenic NDV. *Journal of Veterinary Science*, *16*(4), 447–457. http://doi.org/10.4142/jvs.2015.16.4.447 JVS

Rothenfusser, S., Goutagny, N., DiPerna, G., Gong, M., Monks, B. G., Schoenemeyer, A., … Fitzgerald, K. A. (2005). The RNA helicase LGP2 inhibits TLR-independent sensing of viral replication by retinoic acid-inducible gene-I. *Journal of Immunology*, *175*(8), 5260–5268. http://doi.org/10.4049/jimmunol.175.8.5260

Rubin, B. Y., & Gupta, S. L. (1980). Differential efficacies of human type I and type II interferons as antiviral and antiproliferative agents. *Proceedings of the National Academy of Sciences of the United States of America*, *77*(10), 5928–5932. Retrieved from http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=6160587&retmode=ref&cmd=prlinks%5Cnpapers2://publication/uuid/913A3E4A-465F-4B7C-968B-3DB2316CDE78

Rue, C. A., Susta, L., Cornax, I., Brown, C. C., Kapczynski, D. R., Suarez, D. L., … Afonso, C. L. (2011). Virulent Newcastle disease virus elicits a strong innate immune response in chickens. *Journal of General Virology*, *92*(4), 931–939. http://doi.org/10.1099/vir.0.025486-0

Ryan, M. T., & Hoogenraad, N. J. (2007). Mitochondrial-nuclear communications. *Annual Review of Biochemistry*, *76*(1), 701–722. http://doi.org/10.1146/annurev.biochem.76.052305.091720

Saitoh, T., Satoh, T., Yamamoto, N., Uematsu, S., Takeuchi, O., Kawai, T., & Akira, S. (2011). Antiviral protein viperin promotes toll-like receptor 7- and toll-like receptor 9-mediated type i interferon production in plasmacytoid dendritic cells. *Immunity*, *34*(3), 352–363. http://doi.org/10.1016/j.immuni.2011.03.010

Saka, H. A., & Valdivia, R. (2012). Emerging roles for lipid droplets in immunity and host-pathogen interactions. *Annual Review of Cell and Developmental Biology*, *28*(1), 411–437. http://doi.org/10.1146/annurev-cellbio-092910-153958

Samal, S., Kumar, S., Khattar, S. K., & Samal, S. K. (2011). A single amino acid change, Q114R, in the cleavage-site sequence of Newcastle disease virus fusion protein attenuates viral replication and pathogenicity. *Journal of General Virology*, *92*(10), 2333–2338. http://doi.org/10.1099/vir.0.033399-0

Samuel, A., Nayak, B., Paldurai, A., Xiao, S., Aplogan, G. L., Awoume, K. A., … Samal, S. K. (2013). Phylogenetic and pathotypic characterization of Newcastle disease viruses circulating in West Africa and efficacy of a current vaccine. *Journal of Clinical Microbiology*, *51*(3), 771–781. http://doi.org/10.1128/JCM.02750-12

Santhakumar, D., Rubbenstroth, D., Martinez-Sobrido, L., & Munir, M. (2017). Avian interferons and their antiviral effectors. *Frontiers in Immunology*, *8*, 49. http://doi.org/10.3389/fimmu.2017.00049

Saraste, A., & Pulkki, K. (2000). Morphologic and biochemical hallmarks of apoptosis. *Cardiovascular Research*, *45*(3), 528–537. http://doi.org/10.1016/S0008-6363(99)00384-3

Satharasinghe, D. A., Murulitharan, K., Tan, S. W., Yeap, S. K., Munir, M., Ideris, A., & Omar, A. R. (2016). Detection of inter-lineage natural recombination in avian paramyxovirus serotype 1 using simplified deep sequencing platform. *Frontiers in Microbiology*, *7*(November), 1–14. http://doi.org/10.3389/fmicb.2016.01907

Satoh, T., Kato, H., Kumagai, Y., Yoneyama, M., Sato, S., Matsushita, K., … Takeuchi, O. (2010). LGP2 is a positive regulator of RIG-I- and MDA5-mediated antiviral responses. *Proceedings of the National Academy of Sciences of the United States of America*, *107*(4), 1512–1517. http://doi.org/10.1073/pnas.0912986107

Savill, J., & Fadok, V. (2000). Corpse clearance defines the meaning of cell death. *Nature*, *407*(6805), 784–8. http://doi.org/10.1038/35037722

Schlee, M., Roth, A., Hornung, V., Hagmann, C. A., Wimmenauer, V., Barchet, W., … Hartmann, G. (2009). Recognition of 5' triphosphate by RIG-I helicase requires short blunt double-stranded RNA as contained in panhandle of negative-strand virus. *Immunity*, *31*(1), 25–34. http://doi.org/10.1016/j.immuni.2009.05.008

Schmidt, A., Rothenfusser, S., & Hopfner, K. P. (2012). Sensing of viral nucleic acids by RIG-I: From translocation to translation. *European Journal of Cell Biology*, *91*(1), 78–85. http://doi.org/10.1016/j.ejcb.2011.01.015

Schoggins, J. W., MacDuff, D. A., Imanaka, N., Gainey, M. D., Shrestha, B., Eitson, J. L., … Rice, C. M. (2014). Pan-viral specificity of IFN-induced genes reveals new roles for cGAS in innate immunity. *Nature*, *505*(7485), 691–695. http://doi.org/10.1038/nature12862

Scott, I. (2010). The role of mitochondria in the mammalian antiviral defense system. *Mitochondrion*, *10*(4), 316–20. http://doi.org/10.1016/j.mito.2010.02.005

Scott, I., & Norris, K. L. (2008). The mitochondrial antiviral signaling protein, MAVS, is cleaved during apoptosis. *Biochemical and Biophysical Research Communications*, *375*, 101–106. http://doi.org/10.1016/j.bbrc.2008.07.147

Seal, B. S., King, D. J., & Sellers, H. S. (2000). The avian response to Newcastle disease virus. *Developmental and Comparative Immunology*, *24*(2–3), 257–268. http://doi.org/10.1016/S0145-305X(99)00077-4

Seth, R. B., Sun, L., & Chen, Z. J. (2006). Antiviral innate immunity pathways. *Cell Research*, *16*(2), 141–7. http://doi.org/10.1038/sj.cr.7310019

Seth, R. B., Sun, L., Ea, C.-K., & Chen, Z. J. (2005). Identification and characterization of MAVS, a mitochondrial antiviral signaling protein that activates NF-kappaB and IRF 3. *Cell*, *122*(5), 669–82. http://doi.org/10.1016/j.cell.2005.08.012

Sharma, S., & Fitzgerald, K. A. (2010). Viral defense: it takes two MAVS to Tango. *Cell*, *141*(4), 570–2. http://doi.org/10.1016/j.cell.2010.04.043

Shimada, K., Crother, T. R., Karlin, J., Dagvadorj, J., Chiba, N., Chen, S., … Arditi, M. (2012). Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis. *Immunity*, *36*(3), 401–414. http://doi.org/10.1016/j.immuni.2012.01.009

Shini, S., & Kaiser, P. (2009). Effects of stress, mimicked by administration of corticosterone in drinking water, on the expression of chicken cytokine and chemokine genes in lymphocytes. *Stress*, *12*(5), 388–399. http://doi.org/10.1080/10253890802526894

Shini, S., Shini, A., & Kaiser, P. (2010). Cytokine and chemokine gene expression profiles in heterophils from chickens treated with corticosterone. *Stress*, *13*(3), 185–194. http://doi.org/10.3109/10253890903144639

Sick, C., Schneider, K., Staeheli, P., & Weining, K. C. (2000). Novel chicken CXC and CC chemokines. *Cytokine*, *12*(3), 181–186. http://doi.org/10.1006/cyto.1999.0543

Sick, C., Schultz, U., Münster, U., Meier, J., Kaspers, B., & Staeheli, P. (1998). Promoter structures and differential responses to viral and nonviral inducers of chicken type I interferon genes. *Journal of Biological Chemistry*, *273*(16), 9749–9754. http://doi.org/10.1074/jbc.273.16.9749

Snoeck, C. J., Owoade, A. A., Couacy-Hymann, E., Alkali, B. R., Okwen, M. P., Adeyanju, A. T., … Muller, C. P. (2013). High genetic diversity of Newcastle disease virus in poultry in west and central Africa: Cocirculation of genotype XIV and newly defined genotypes XVII and XVIII. *Journal of Clinical Microbiology*, *51*(7), 2250–2260. http://doi.org/10.1128/JCM.00684-13

Solaini, G., Sgarbi, G., Lenaz, G., & Baracca, A. (2007). Evaluating mitochondrial membrane potential in cells. *Bioscience Reports*, *27*(1–3), 11–21. http://doi.org/10.1007/s10540-007-9033-4

Spelbrink, J. N. (2010). Functional organization of mammalian mitochondrial DNA in nucleoids: History, recent developments, and future challenges. *IUBMB Life*, *62*(1), 19–32. http://doi.org/10.1002/iub.282

Strowig, T., Henao-Mejia, J., Elinav, E., & Flavell, R. (2012). Inflammasomes in health and disease. *Nature*, *481*(7381), 278–286. http://doi.org/10.1038/nature10759

Sun, Q., Sun, L., Liu, H. H., Chen, X., Seth, R. B., Forman, J., & Chen, Z. J. (2006). The Specific and Essential Role of MAVS in Antiviral Innate Immune Responses. *Immunity*, *24*(5), 633–642. http://doi.org/10.1016/j.immuni.2006.04.004

Susin, S. A., Lorenzo, H. K., Zamzami, N., Marzo, I., Snow, B. E., Brothers, G. M., … Loeffler, M. (1999). Molecular characterization of mitochondrial apoptosis-inducing factor. *Nature*, *397*, 441–446.

Susta, L., Cornax, I., Diel, D. G., Garcia, S. C., Miller, P. J., Liu, X., … Afonso, C. L. (2013). Expression of interferon gamma by a highly virulent strain of Newcastle disease virus decreases its pathogenicity in chickens. *Microbial Pathogenesis*, *61–62*, 73–83. http://doi.org/10.1016/j.micpath.2013.05.009

Susta, L., Hamal, K. R., Miller, P. J., Cardenas-Garcia, S., Brown, C. C., Pedersen, J. C., … Afonso, C. L. (2014). Separate evolution of virulent Newcastle disease viruses from Mexico and Central America. *Journal of Clinical Microbiology*, *52*(5), 1382–1390. http://doi.org/10.1128/JCM.00066-14

Takeuchi, O., & Akira, S. (2007). Recognition of viruses by innate immunity. *Immunological Reviews*, *220*(1), 214–224. http://doi.org/10.1111/j.1600-065X.2007.00562.x

Takeuchi, O., & Akira, S. (2009). Innate immunity to virus infection. *Immunological Reviews*, *227*(1), 75–86. http://doi.org/10.1111/j.1600-065X.2008.00737.x

Takeuchi, O., & Akira, S. (2010). Pattern recognition receptors and inflammation. *Cell*, *140*(6), 805–20. http://doi.org/10.1016/j.cell.2010.01.022

Tan, S. W., Ideris, A., Omar, A. R., Yusoff, K., & Hair-Bejo, M. (2010). Sequence and phylogenetic analysis of Newcastle disease virus genotypes isolated in Malaysia between 2004 and 2005. *Archives of Virology*, *155*(1), 63–70. http://doi.org/10.1007/s00705-009-0540-4

Tang, D., Kang, R., Coyne, C. B., Zeh, H. J., & Lotze, M. T. (2012). PAMPs and DAMPs: Signal 0s that spur autophagy and immunity. *Immunological Reviews*, *249*(1), 158–175. http://doi.org/10.1111/j.1600-065X.2012.01146.x

Tattoli, I., Carneiro, L. a, Jéhanno, M., Magalhaes, J. G., Shu, Y., Philpott, D. J., … Girardin, S. E. (2008). NLRX1 is a mitochondrial NOD-like receptor that amplifies NF-kappaB and JNK pathways by inducing reactive oxygen species production. *EMBO Reports*, *9*(3), 293–300. http://doi.org/10.1038/sj.embor.7401161

Tschopp, J. (2011). Mitochondria: Sovereign of inflammation? *European Journal of Immunology*, *41*(5), 1196–1202. http://doi.org/10.1002/eji.201141436

Unterholzner, L. (2013). The interferon response to intracellular DNA: Why so many receptors? *Immunobiology*, *218*(11), 1312–1321. http://doi.org/10.1016/j.imbio.2013.07.007

van der Burgh, R., & Boes, M. (2015). Mitochondria in autoinflammation: Cause, mediator or bystander? *Trends in Endocrinology and Metabolism*, *26*(5), 263–271. http://doi.org/10.1016/j.tem.2015.03.004

Venkataraman, T., Valdes, M., Elsby, R., Kakuta, S., Caceres, G., Saijo, S., … Barber, G. N. (2007). Loss of DExD/H box RNA helicase LGP2 manifests disparate antiviral responses. *Journal of Immunology*, *178*(10), 6444–6455. http://doi.org/178/10/6444 [pii]

Wagner, H. (2002). Interactions between bacterial CpG-DNA and TLR9 bridge innate and adaptive immunity. *Current Opinion in Microbiology*, *5*(1), 62–69. http://doi.org/10.1016/S1369-5274(02)00287-4

Walker, M. A., Volpi, S., Sims, K. B., Walter, J. E., & Traggiai, E. (2014). Powering the immune system : Mitochondria in immune function and deficiency. *Journal of Immunology Research*, *2014*(Article ID 164309). http://doi.org/http://dx.doi.org/10.1155/2014/164309

Wallace, D. C. (2005). A mitochondrial paradigm of metabolic and degenerative diseases, aging, and cancer: a dawn for evolutionary medicine. *Annual Review of Genetics*, *39*, 359–407. http://doi.org/10.1146/annurev.genet.39.110304.095751

Walther, T. C., & Farese Jr., R. V. (2009). The life of lipid droplets. *Biochimica et Biophysica Acta*, *1791*(6), 459–466. http://doi.org/10.1016/j.bbalip.2008.10.009.The

Wang, B. X., & Fish, E. N. (2012). The yin and yang of viruses and interferons. *Trends in Immunology*, *33*(4), 190–7. http://doi.org/10.1016/j.it.2012.01.004

Wang, J. P., Cerny, A., Asher, D. R., Kurt-Jones, E. A., Bronson, R. T., & Finberg, R. W. (2010). MDA5 and MAVS mediate type I interferon responses to Coxsackie B virus. *Journal of Virology*, *84*(1), 254–260. http://doi.org/10.1128/JVI.00631-09

Wang, X. (2001). The expanding role of mitochondria in apoptosis. *Genes & Development*, *15*(22), 2922–2933.

Wang, X. (2001). The expanding role of mitochondria in apoptosis The expanding role of mitochondria in apoptosis, 2922–2933.

Wang, Z., Liu, H., Xu, J., Bao, J., Zheng, D., Sun, C., … Chen, J. (2006). Genotyping of Newcastle disease viruses isolated from 2002 to 2004 in China. *Annals of the New York Academy of Sciences*, *1081*, 228–239. http://doi.org/10.1196/annals.1373.027

Weining, K. C., Schultz, U., Münster, U., Kaspers, B., & Staeheli, P. (1996). Biological properties of recombinant chicken interferon-gamma. *European Journal of Immunology*, *26*(10), 2440–2447. http://doi.org/10.1002/eji.1830261026

Welte, M. A. (2015). Expanding roles for lipid droplets. *Current Biology*, *25*(11), R470–R481. http://doi.org/10.1016/j.cub.2015.04.004

West, A. P., Khoury-Hanold, W., Staron, M., Tal, M. C., Pineda, C. M., Lang, S. M., … Shadel, G. S. (2015). Mitochondrial DNA stress primes the antiviral innate immune response. *Nature*, *520*(7548), 553–7. http://doi.org/10.1038/nature14156

West, A. P., Koblansky, A. A., & Ghosh, S. (2006). Recognition and Signaling by Toll-Like Receptors. *Annual Review of Cell and Developmental Biology*, *22*(1), 409–437. http://doi.org/doi:10.1146/annurev.cellbio.21.122303.115827

West, A. P., & Shadel, G. S. (2017). Mitochondrial DNA in innate immune responses and inflammatory pathology. *Nature Reviews Immunology*, *17*(6), 363–375. http://doi.org/10.1038/nri.2017.21

West, A. P., Shadel, G. S., & Ghosh, S. (2011). Mitochondria in innate immune responses. *Nature Reviews. Immunology*, *11*(6), 389–402. http://doi.org/10.1038/nri2975

White, M. J., McArthur, K., Metcalf, D., Lane, R. M., Cambier, J. C., Herold, M. J., … Kile, B. T. (2014). Apoptotic caspases suppress mtDNA-induced STING-mediated Type I IFN production. *Cell*, *159*(7), 1549–1562. http://doi.org/10.1016/j.cell.2014.11.036

Worobey, M., & Holmes, E. C. (1999). Evolutionary aspects of recombination in RNS viruses. *Journal of General Virology*, *80*(May), 2535–2543.

Xiao, S., Nayak, B., Samuel, A., Paldurai, A., Kanabagattebasavarajappa, M., Prajitno, T. Y., … Samal, S. K. (2012). Generation by reverse genetics of an effective, stable, live-attenuated Newcastle disease virus vaccine based on a currently circulating, highly virulent Indonesian strain. *PLoS ONE*, *7*(12). http://doi.org/10.1371/journal.pone.0052751

Xing, Z., Harper, R., Anunciacion, J., Yang, Z., Gao, W., Qu, B., … Cardona, C. J. (2010). Host immune and apoptotic responses to avian influenza virus H9N2 in human tracheobronchial epithelial cells. *American Journal of Respiratory Cell and Molecular Biology*, *44*(1), 24–33. http://doi.org/10.1165/rcmb.2009-0120OC

Xu, L.-G., Wang, Y.-Y., Han, K.-J., Li, L.-Y., Zhai, Z., & Shu, H.-B. (2005). VISA is an adapter protein required for virus-triggered IFN-beta signaling. *Molecular Cell*, *19*(6), 727–40. http://doi.org/10.1016/j.molcel.2005.08.014

Yasukawa, K., Oshiumi, H., Takeda, M., Ishihara, N., Yanagi, Y., Seya, T., … Ohno, S. (2009). Mitofusin 2 inhibits mitochondrial antiviral signaling. *Science Signaling*, *2*(84), ra47. http://doi.org/10.1126/scisignal.2000287

Yi, J., & Liu, C. (2011). Detecting Newcastle disease virus in combination of RT-PCR with red blood cell absorption. *Virology Journal*, *8*(1), 202. http://doi.org/10.1186/1743-422X-8-202

Yoneyama, M., & Fujita, T. (2008). Structural mechanism of RNA recognition by the RIG-I-like receptors. *Immunity*, *29*(2), 178–181. http://doi.org/10.1016/j.immuni.2008.07.009

Yoneyama, M., & Fujita, T. (2009). RNA recognition and signal transduction by RIG-I-like receptors. *Immunological Reviews*, *227*, 54–65. http://doi.org/10.1111/j.1600-065X.2008.00727.x

Yoneyama, M., Kikuchi, M., Matsumoto, K., Imaizumi, T., Miyagishi, M., Taira, K., … Fujita, T. (2005). Shared and unique functions of the DExD/H-box helicases RIG-I, MDA5, and LGP2 in antiviral innate immunity. *Journal of Immunology*, *175*(5), 2851–2858. http://doi.org/175/5/2851 [pii]

Yoneyama, M., Kikuchi, M., Natsukawa, T., Shinobu, N., Imaizumi, T., Miyagishi, M., … Fujita, T. (2004). The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. *Nature Immunology*, *5*(7), 730–737. http://doi.org/10.1038/ni1087

Yu, D., Xu, L., Peng, L., Chen, S.-Y. Y., Liu, Y.-P. P., & Yao, Y.-G. G. (2014). Genetic variations of mitochondrial antiviral signaling gene (MAVS) in domestic chickens. *Gene*, *545*(2), 226–32. http://doi.org/10.1016/j.gene.2014.05.029

Yu, L. I., Wang, Z., Jiang, Y., Chang, L. E. O., & Kwang, J. (2001). Characterization of Newly Emerging Newcastle Disease Virus Isolates from the People ' s Republic of China and Taiwan. *Society*, *39*(10), 3512–3519. http://doi.org/10.1128/JCM.39.10.3512

Yusoff, K., & Tan, W. S. (2001). Newcastle disease virus: macromolecules and opportunities. *Avian Pathology*, *30*(5), 439–455. http://doi.org/10.1080/03079450120078626

Zemirli, N., Morel, E., & Molino, D. (2018). Mitochondrial dynamics in basal and stressful conditions. *International Journal of Molecular Sciences*, *19*(2), 1–19. http://doi.org/10.3390/ijms19020564

Zhang, Q.-M., Song, W.-Q., Li, Y.-J., Qian, J., Zhai, A.-X., Wu, J., … Zhang, F.-M. (2012). Over-expression of mitochondrial antiviral signaling protein inhibits coxsackievirus B3 infection by enhancing type-I interferons production. *Virology Journal*, *9*, 312. http://doi.org/10.1186/1743-422X-9-312

Zhang, Q., Itagaki, K., & Hauser, C. J. (2010a). Mitochondrial DNA is released by shock and activates neutrophils via p38 map kinase. *Shock*, *34*(1), 55–9. http://doi.org/10.1097/SHK.0b013e3181cd8c08

Zhang, Q., Raoof, M., Chen, Y., Sumi, Y., Sursal, T., Junger, W., … Hauser, C. J. (2010b). Circulating mitochondrial DAMPs cause inflammatory responses to injury. *Nature*, *464*(7285), 104–7. http://doi.org/10.1038/nature08780

Zhong, B., Yang, Y., Li, S., Wang, Y. Y., Li, Y., Diao, F., … Shu, H. B. (2008). The Adaptor Protein MITA Links Virus-Sensing Receptors to IRF3 Transcription Factor Activation. *Immunity*, *29*(4), 538–550. http://doi.org/10.1016/j.immuni.2008.09.003

Zhou, R., Yazdi, A. S., Menu, P., & Tschopp, J. (2010). A role for mitochondria in NLRP3 inflammasome activation. *Nature*, *469*, 221–5. http://doi.org/10.1038/nature09663

Zhou, X., Jiang, W., Liu, Z., Liu, S., & Liang, X. (2017). Virus infection and death receptor-mediated apoptosis. *Viruses*, *9*(11). http://doi.org/10.3390/v9110316

Zoratti, M., & Szabo, I. (1995). The mitochondrial permeability transition. *Biochimica et Biophysica Acta*, *1241*(2), 139–176.

Zou, J., Chang, M., Nie, P., & Secombes, C. J. (2009). Origin and evolution of the RIG-I like RNA helicase gene family. *BMC Evolutionary Biology*, *9*(1), 85. http://doi.org/10.1186/1471-2148-9-85

BIODATA OF STUDENT

Haryati Shila Mohamad Wali was born on October 24, 1974, in Kuala Lumpur. She enrolled at Universiti Putra Malaysia in 1994 in the Bachelor of Science (Biotechnology) degree program. Upon her graduation in 1998, she secured her first teaching job in a private college in Langkawi, Kedah. Intending to pursue her passion in teaching and research, she enlisted herself in the Master of Science program majoring in Virology at the Faculty of Veterinary Medicines, UPM in the year 2000. Her MSc. research study revolved around the effects of local Newcastle disease virus (NDV) strain on breast cancer cell lines. She completed her Masters study in the year 2003 and was offered a job as a Research Assistant in the Faculty of Medicine and Health Sciences, UPM. Later on, she became a part-time lecturer in the Faculty of Biotechnology, Universiti Industri Selangor from the year 2005 until 2007 teaching the subject Animal Cell Culture to diploma and degree level courses. Eventually she was tendered a full-time teaching job in the same faculty in the year 2008. She was the Head of Program for the Bac. of Science in Biotechnolgy course, and was involved in teaching Animal Cell Culture as well as Immunology subjects to degree students. She persisted as a lecturer in Universiti Selangor until the year 2011. She went on to pursue her higher degree as a PhD candidate in the Institute of Bioscience, UPM since then to date. She assumed her study in the field of Vaccine Technology under the main supervision of Prof. Datin Paduka Dato' Dr. Aini Ideris**.**

LIST OF PUBLICATIONS

Conferences and Proceedings

Haryati, S.M.W., Aini, I., Abdul Rahman, O. & Hair Bejo, M. (2013). Construction of a plasmid encoding chicken mitochondrial antiviral signaling (MAVS) gene. *Proceedings of the Scientific Conference 2013 of World's Poultry Science Association (Malaysia) & World Veterinary Poultry Association (Malaysia)*. Serdang, Selangor.

Haryati, S.M.W., Aini, I., Abdul Rahman, O. & Hair Bejo, M. (2014). Subcloning of chicken mitochondrial antiviral signaling (MAVS) gene into an expression vector. *Proceedings of the 32nd Symposium of the Malaysian Society for Microbiology ~ Sustainable Microbiology for Global Solutions*. Kuala Terengganu, Terengganu.

Haryati, S.M.W., Aini, I., Abdul Rahman, O. & Hair Bejo, M. (2015). Determination of Newcastle disease virus (NDV) strain UPM-IBS/002/2011 titer ($TCID_{50}$) in transformed chicken embryo fibroblast cell line. *Proceedings of the 2nd WVPA-WPSA Scientific Conference*. Kuala Lumpur Convention Centre.

Haryati, S.M.W., Aini, I., Abdul Rahman, O. & Hair Bejo, M. (2016). Induction of apoptosis in CARDIF-protected chicken cell lines following Newcastle Disease Virus (NDV) infection (oral presentation). *UK-Malaysia Vaccinology Workshop 2016 ~ Emerging and Next Generation Vaccine Technologies against Veterinary Pathogens*. Institute of Bioscience, UPM.

UNIVERSITI PUTRA MALAYSIA

STATUS CONFIRMATION FOR THESIS / PROJECT REPORT AND COPYRIGHT

ACADEMIC SESSION : _____

TITLE OF THESIS / PROJECT REPORT :

_____

_____

_____

NAME OF STUDENT : _____

I acknowledge that the copyright and other intellectual property in the thesis/project report belonged to Universiti Putra Malaysia and I agree to allow this thesis/project report to be placed at the library under the following terms:

1. This thesis/project report is the property of Universiti Putra Malaysia.
2. The library of Universiti Putra Malaysia has the right to make copies for educational purposes only.
3. The library of Universiti Putra Malaysia is allowed to make copies of this thesis for academic exchange.

I declare that this thesis is classified as :

*Please tick (√)

☐	**CONFIDENTIAL**	(Contain confidential information under Official Secret Act 1972).
☐	**RESTRICTED**	(Contains restricted information as specified by the organization/institution where research was done).
☑	**OPEN ACCESS**	I agree that my thesis/project report to be published as hard copy or online open access.

This thesis is submitted for :

☐	**PATENT**	Embargo from_____ until _____ (date) (date)

Approved by:

_____ _____

(Signature of Student) (Signature of Chairman of Supervisory Committee)

New IC No/ Passport No.: Name:

Date : Date :

[Note : If the thesis is CONFIDENTIAL or RESTRICTED, please attach with the letter from the organization/institution with period and reasons for confidentially or restricted.]