UNIVERSITI PUTRA MALAYSIA

EXPRESSION PROFILES OF IMMUNE MEDIATORS IN FELINE INFECTIOUS PERITONITIS VIRUS INFECTED CELLS, WHOLE BLOOD AND PERITONEAL EFFUSION FLUIDS

SEYEDEH NIKOO SAFI

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SEYEDEH NIKOO SAFI

Thesis Submitted to School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for Degree of Master of Science

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I am honored to express my deepest gratefulness and warmest regards to my beloved parents and supportive husband, Amin. Without them, I would not pursue my dreams of being a researcher. I am dedicating this thesis to them.

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the degree of Master of Science

EXPRESSION PROFILES OF IMMUNE MEDIATORS IN FELINE INFECTIOUS PERITONITIS VIRUS INFECTED CELLS, WHOLE BLOOD AND PERITONEAL EFFUSION FLUIDS

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December 2015

Chairman: **Professor Abdul Rahman Omar, PhD**
Faculty: **Institute of Bioscience**

Feline infectious peritonitis virus (FIPV) is the causative agent of the one of the most lethal viral diseases of the wild and domestic cats. Despite of the research on the virus and the disease it causes, the molecular pathogenesis of feline infectious peritonitis (FIP) is poorly understood. In this study, *in vitro* samples from FIPV infected Crandell Ress Feline Kidney (CRFK) cells and *in vivo* samples obtained from FIP diagnosed cats were used in an attempt to identify the involvement of different immune mediators and their associations with viral replication. Viral load *in vitro* showed peak at 48 hours post infection (hpi), while the increased in viral load is associated with increased in the expression of immune mediators such as MX1, RSAD2 (viperin), MCP2 (CCL8) and CXCL10 (IP10). However, most of the FIP diagnosed cats did not express or expressed very low levels of MCP2 (CCL8) and CXCL10 (IP10) in the peripheral blood mononuclear cells (PBMC). Analysis based on MILIPLEX assay detected an increased in proinflammatory related cytokines namely RANTES (CCL5), KC (CXCL1), MCP1 (CCL2) and IL8 (CXCL8) in FIPV infected CRFK cells. The increased in these immune mediators were also detected in the clinical samples such as PBMC, serum, peritoneal effusion (PE) and the supernatant of PE (PES) of cats diagnosed with FIP. However, the PE samples tend to have higher viral load with distinct expression profiles of the different immune mediators compared to the blood samples of the FIP diagnosed cats. In addition, the detection of CCL17 expression in PE but not in PBMC. No obvious variations in the expression profiles of the different immune mediators were detected among the different forms of FIP, however, the wet and mixed forms of FIP tend to have generally higher immune mediator expressions compared to dry form. In addition, the differences in expression profiles of MX1 and RSAD2 in PBMC may serve as a good indicator in distinguishing wet and dry form of FIP. Hierarchical clustering analysis based on *in vivo* samples indicated that MX1, CCL17 and GM-CSF have the highest correlation with viral load. In addition, the different expression profiles of cytokines such as IL1β, IL6, IL18 and TNFα between blood and PE samples, and the down regulation of SCF and Flt3L expressions in the blood samples were also detected in some of the FIP diagnosed cats. In conclusion, this study has established some insight on the differential expressions of immune mediators in FIPV infected cells and in cats diagnosed with FIP.

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Keywords: Feline infectious peritonitis, immune mediators, RT-qPCR, Milliplex

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

PROFIL UNGKAPAN PENGANTARA IMUN DALAM SEL YANG DIJANGKITI VIRUS PERITONITIS BERJANGKIT FELIN, SAMPLE DARAH DAN CECAIR EFUSI PERITONEAL

Oleh

SEYEDEH NIKOO SAFI

December 2015

Pengerusi: **Professor Abdul Rahman Omar, PhD**
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Virus peritonitis berjangkit felin (FIPV) merupakan salah satu agen penyebab kepada penyakit virus maut kepada kucing liar dan domestik. Walaupun pelbagai kajian telah dilakukan ke atas virus dan penyakit yang disebabkannya, namun patogenesis molekul peritonitis berjangkit felin (FIP) masih kurang jelas. Dalam kajian ini, sampel *in vitro* daripada sel Crandell Ress Feline Kidney (CRFK) yang dijangkiti dengan FIPV dan sampel *in vivo* daripada kucing yang menghidap FIP telah digunakan dalam usaha untuk mengenalpasti penglibatan pengantara imun yang berbeza dan kaitannya dengan replikasi virus. Seperti yang dijangkakan, sel CRFK yang dijangkiti dengan FIPV tip II strain 79-1146 menyokong replikasi virus pada tempoh kemuncak 48 jam jangkitan. Berdasarkan kajian *in vitro*, peningkatan pada bebanan virus adalah berkait dengan peningkatan perungkapan pengantara imun seperti MX1, RSAD2 (viperin), MCP2 (CCL8) dan CXCL10 (IP10) yang menunjukkan pengaktifan tindak balas imun inat serta tindak balas inflamasi berikutan jangkitan virus. Walau bagaimanapun, kebanyakan kucing yang menghidap FIP tidak menyatakan atau menyatakan pada tahap sangat rendah MCP2 (CCL8) dan CXCL10 (IP10) dalam *sel mononuklear darah* perifer. Berdasarkan analisis asai MILIPLEX, peningkatan pada sitokin berkait proinflamasi seperti RANTES (CCL5), KC (CXCL1), MCP1 (CCL2) dan IL8 (CXCL8) telah dikesan peningkatannya dalam sel CRFK jangkitan FIPV. Peningkatan pengantara imun juga dikesan dalam sampel klinikal seperti PBMC, serum, efusi peritoneal (PE) dan supernatant PE pada kucing yang menghidap FIP. Walau bagaimanapun, sampel PE cenderung untuk mempunyai beban virus yang lebih tinggi dengan profil ungkapan pengantara imun yang berbeza berbanding dengan sampel darah daripada kucing yang menghidap FIP. Disamping itu, ungkapan CCL17 hanya dikesan dalam PE tetapi tidak terdapat dalam PBMC telah mencadangkan ketiadaan tindak balas sel Th2 dalam darah kucing yang menghidap FIP, bagaimanapun, pengesahan perlu dilakukan dalam kajian lanjutan. Tiada variasi yang jelas dalam ungkapan pengantara imun termasuk ketidakseimbangan antara sitokin Th1 dan Th2 dikalangan kucing yang menghidap bentuk FIP yang berlainan. Walau bagaimanapun, FIP berbentuk campuran dan lembap cenderung untuk memperolehi ungkapan pengantara imun lebih tinggi berbanding dengan FIP bentuk kering. Disamping itu, perbezaan dalam profil ungkapan MX1 dan

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RSAD2 dalam PBMC mungkin boleh digunakan sebagai penunjuk yang baik bagi membezakan FIP berbentuk lembap dan kering. Analisis pengelompokkan hierarki berdasarkan sampel *in vivo* menunjukkan MX1, CCL17 dan GM-CSF mempunyai hubungkait tertinggi dengan beban virus. Disamping itu juga, terdapat perbezaan profil ungkapan sitokin seperti IL1β, IL6, IL18 dan TNFα antara sampel PE dan darah, serta pengawalaturan menurun ungkapan SCF dan Flt3L dalam sampel darah juga turut dikesan dalam beberapa ekor kucing yang menghidap FIP. Kesimpulan, kajian ini telah mengemukakan beberapa sudut pandangan terhadap ungkapan pengantara imun yang berbeza pada sel jangkitan FIPV dan pada kucing yang menghidap FIP. Kajian lanjutan dengan menggunakan sampel daripada jangkitan eksperimen FIPV dalam kucing bebas-patogen-khusus dapat mengesahkan kepentingan fungsi kepelbagaian pengantara imun dalam pemodulasian jangkitan FIPV dan perkembangan FIP.

Kata Kunci: Peritonitis berjangkit felin, pengantara imun, RT-qPCR, Milliplex

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

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This is to confirm that:

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LIST OF ABBREVIATIONS

A:G	Albumin:Globulin
ADE	Antibody Dependent Enhancement
AGP	Alpha 1-Acid Glycoprotein
AIBV	Avian Infectious Bronchitis Virus
APN	Amino Peptidase-N
ATCC	American Tissue Culture Collection
BCoV	Bovine Coronavirus
BLAST	Basic Local Alignment Search Tool
Blimp-1	B-Lymphocyte-Induced Maturation Protein 1
BSL-2	Biosafety Level 2
CBC	Complete Blood Count
CCL17	Chemokine (C-C Motif) Ligand 17 [Source:HGNC Symbol;Acc:10615]
CCL2 (MCP-1)	Chemokine (C-C Motif) Ligand 2 [Source:HGNC Symbol;Acc:10618]
CCL5 (RANTES)	Chemokine (C-C Motif) Ligand 5 [Source:HGNC Symbol;Acc:10632]
CCL8	Chemokine (C-C Motif) Ligand 8 [Source:HGNC Symbol;Acc:10635]
CCoV	Canine Coronavirus
CMI	Cell Mediated Immunity
CNS	Central Nervous System
CPE	Cytopathic Effect
CRFK	Crandell Ress Feline Kidney
CRIP1 (CRIP)	Cysteine-Rich Protein 1 (Intestinal) [Source:HGNC Symbol;Acc:2360]
CSF	Cerebrospinal Fluids
CSF2 (GM-CSF)	Colony Stimulating Factor 2 (Granulocyte-Macrophage) [Source:HGNC Symbol;Acc:2434]
CXCL1 (KC)	Chemokine (C-X-C Motif) Ligand 1 (Melanoma Growth Stimulating Activity, Alpha) [Source:HGNC Symbol;Acc:4602]
CXCL10	Chemokine (C-X-C Motif) Ligand 10 [Source:HGNC Symbol;Acc:10637]
CXCL12 (SDF1)	Chemokine (C-X-C Motif) Ligand 12 [Source:HGNC Symbol;Acc:10672]
DENV	Dengue Virus
DIC	Disseminated Intravascular Coagulopathy
DMSO	Dimethyl Sulfoxide
DPBS	Dulbecco's Phosphate-Buffered Saline
E	Envelope
EBV	Epstein Barr Virus
ECoV	Equine Coronavirus
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Fas Cell Surface Death Receptor [Source:HGNC Symbol;Acc:11920]
FBS	Fetal Bovine Serum
FCoV	Feline Coronavirus

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Fcwf-4	*Felis catus* Whole Fetus
FECV	Feline Enteric Coronavirus
FELV	Feline Leukemia Virus
FIP	Feline Infectious Peritonitis
FIPV	Feline Infectious Peritonitis Virus
Flt-3l	FMS-related Tyrosine Kinase 3 Ligand
FIV	Feline Immunodeficiency Virus
G-CSF	Granulocyte-Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
GO	Gene Ontology
HCoV-229E	Human Respiratory Coronavirus-229E
HCoV-OC43	Human Coronavirus
HEL	RNA Helicase
HEV	Porcine Hemagglutination Encephalomyelitis Virus
HIV	Human Immunodeficiency Virus
hpi	Hours Post Infection
HSV	Herpes Simplex Virus
IACUC	Institutional Animal Care And Use Committee
IBS	Institute Of Bioscience
ID1	Inhibitor Of DNA Binding 1, Dominant Negative Helix-Loop-Helix Protein [Source:HGNC Symbol;Acc:5360]
IFA	Immunofluorescent Antibody
IFN	Interferon
IFNγ	Interferon, Gamma [Source:HGNC Symbol;Acc:5438]
IL	Interleukin
IL12β	Interleukin 12B (Natural Killer Cell Stimulatory Factor 2, Cytotoxic Lymphocyte Maturation Factor 2, P40) [Source:HGNC Symbol;Acc:5970]
IL13	Interleukin 13 [Source:Hgnc Symbol;Acc:5973]
IL18	Interleukin 18 (Interferon-Gamma-Inducing Factor) [Source:HGNC Symbol;Acc:5986]
IL1β	Interleukin 1, Beta [Source:HGNC Symbol;Acc:5992]
IL2	Interleukin 2 [Source:Hgnc Symbol;Acc:6001]
IL4	Interleukin 4 [Source:Hgnc Symbol;Acc:6014]
IL6	Interleukin 6 (Interferon, Beta 2) [Source:HGNC Symbol;Acc:6018]
IL8	Interleukin 8 [Source:Hgnc Symbol;Acc:6025]
JEV	Japanese Encephalitis Virus
KITLG (SCF)	KIT Ligand [Source:HGNC Symbol;Acc:6343]
LTB4	Leukotriene B4
M	Membrane
MCoV	Murine Coronavirus
MEM	Minimum Essential Media
MHV	Murine Hepatitis Virus
MILLIPLEX	Multiplex Bead-Based Immunoassay
MIP	Macrophage Inhibitory Protein
MX1	MX Dynamin-Like Gtpase 1 [Source:HGNC Symbol;Acc:HGNC:7532]
N	Nucleocapsid
NEAA	Non Essential Amino Acids
NGS	Next-Generation Sequencing

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NK	Natural Killer
NSP	Non-Structural Protein
NTC	Non-Template Control
ORF	Open Reading Frame
PBMC	Peripheral Blood Mononuclear Cells
PCR	Polymerase Chain Reaction
PDGF-BB	Platelet-Derived Growth Factor Beta Polypeptide [Source:HGNC Symbol;Acc:8800]
PE	Peritoneal Effusion
PEDV	Porcine Epidemic Diarrhea Virus
PES	Peritoneal Effusions Supernatant
PGE2	Prostaglandin E2
PhCoV	Pheasant Coronavirus
PMN	Polymorphonuclear
RdRp	RNA-Dependent RNA Polymerase
Reg	Regulatory
RNF7	Ring Finger Protein 7 [Source:HGNC Symbol;Acc:10070]
RSAD2 (viperin)	Radical S-Adenosyl Methionine Domain Containing 2 [Source:HGNC Symbol;Acc:30908]
RT-PCR	Reverse Transcriptase Polymerase Chain Reaction
RT-qPCR	Real-Time Quantitative Polymerase Chain Reaction
RtCoV	Rat Coronavirus
S	Spike
SARS	Severe Acute Respiratory Syndrome
SD	Standard Deviation
SEM	Standard Of Error Of The Mean
SPSS	Statistical Package For The Social Sciences
TCID	Tissue Culture Infective Dose
TCoV	Turkey Coronavirus
TGEV	Transmissible Gasteroenteritis Virus Of Swine
TNF	Tumor Necrosis Factor [Source:HGNC Symbol;Acc:11892]
TNFα	Tumor Necrosis Factor Alpha
UNG	Uracil-N Glycosylase
UPM	Universiti Putra Malaysia
UTR	Untranslated Region
UVH	University Veterinary Hospital
VEGF	Vascular Endothelial Growth Factor
VLSU	Veterinary Laboratory Service Unit
VNT	Virus Neutralization Test

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CHAPTER 1

INTRODUCTION

Feline Infectious Peritonitis (FIP) is a viral, immune-mediated, fatal disease cause by a virulent mutant of feline coronavirus (FCoV). Although the disease has been studied for over 50 years, the molecular pathogenesis and the ability of the virus to mutate and become pathogenic in cats are poorly understood. Nevertheless, it has been shown that spike (S) gene of the virus encode for the protein that is crucial for infection and immunity, the involvement of other genes in modulating the host immune responses are not fully studied. Currently, there is no diagnostic test for early detection of the disease and effective vaccine or therapeutic approach to control and/or prevent the disease (Pedersen, 2014a).

Feline coronavirus (FCoV) can be classified into 2 types based on virus virulence, ability to grow *in vitro* and similarity to other coronaviruses (Hohdatsu et al., 1991). More than 90% of cats worldwide are seropositive for type I FCoV, an ubiquitous virus that does not cause any specific symptoms except for very mild diarrhea in cats (Addie and Jarrett, 1992). However, 1-5% of these cats may succumb to a pathogenic FCoV infection due to mutation of type I FCoV into a virulent virus know as feline infectious peritonitis (FIPV), which is also known as type II FCoV (Addie et al., 1995). Subsequent studies have shown that most of the mutations are at 3c, 7b and S genes of the virus (Lin et al., 2009; Rottier et al., 2005; Vennema et al., 1998). In addition, these mutations would also change the virus tissue tropism from enterocytes to monocytes/macrophages that prompt disease development (Rottier et al., 2005).

Generally, FIP is a result of host immune responses to the infected macrophages. The severity of this disease is correlated with the type of the immune responses, where the strength between the humoral and cell-mediated immune (CMI) responses will determine the outcome of FIP (Foley et al., 1998). Clinical manifestation of FIP can be divided into three forms namely, wet form (non-parenchymatous), dry form (parenchymatous) and a mixed transient form of both wet and dry symptoms (Pedersen, 2014a). The wet form is more frequently reported from clinicians due to obvious symptoms of painless, splashy and enlarged abdomen (Pedersen, 2009). However, generally FIP is recognized as a disease with dissemination of granulomatous lesions mainly localized at vessels, liver, intestines, kidney and central nervous system (CNS) with the presence of effusive pleuritic and/or peritonitis (Pedersen, 2009).

Although the exact mechanisms of FIP are unclear, various studies have proposed that the formation of this disease is mainly related to the ability of FIPV to replicate in monocytes and macrophages (Dewerchin et al., 2008). Infection of these cells is known to be the first step of FIP induction and spread of the virus to other organs such as intestine, omentum, mesenteric lymph node and CNS (Pedersen, 2014b). In addition, the induction of overwhelming humoral responses instead of CMI responses led to

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formation of extensive antigen-antibody immune complexes, which attract macrophages to the site of the infection to engulf the complexes, further cause tissue destructions and promote the internalization of the virus via the infected macrophages. In the effort of the humoral immune response to eliminate the infected cells, severity of the disease may be worsen due to antibody-dependent enhancement (ADE) and the development of disseminated intravascular coagulopathy (DIC) (Weiss et al., 1980), which further cause tissue damages, hypersensitivity responses (type III and IV) and probably death (Jacobse-Geels et al., 1982; Jutel and Akdis, 2011). In addition to this, other complications such as T cells depletion from peripheral blood, mesenteric lymph node and spleen of FIP cats would also deteriorate CMI responses (Takano et al., 2007a; Vermeulen et al., 2013). Meanwhile, over stimulation of humoral immunity can be interpreted as the end stage FIP, suggesting that if CMI were strong enough to clear the virus, the disease would be mild and the cat might survive from FIP.

All the aforementioned inflammatory and immune responses and their interactions during FIP are highly regulated by various mediators such as cytokines, chemokines, interferons and interleukins to name but a few. Previous studies have showed increased proinflammatory cytokines such as IL1β, IL6, TNFα, MIP1α, RANTES, and IFNγ in peritoneal effusions and serum samples of FIP clinical cases (Foley et al., 2003; Goitsuka et al., 1991; Goitsuka et al., 1990). Subsequent study based on FIPV experimental infection showed that the increased in cytokines such as IL10, IL12/p40 and IFNγ was associated with decreased of cytokine IL4 in the lymphoid tissue of FIP infected cats (Dean et al., 2003). Both studies indicated that cats succumbed to FIP develop intense inflammatory responses. However, the importance of these cytokines in context of viral replication and progression of FIP are largely not known.

Recently, we have used transcriptome approach by next-generation sequencing of RNA (RNA Seq) of Crandell Ress Feline Kidney (CRFK) cells infected with type II FIPV strain 79-1146 in an effort to elucidate the complex interaction of FIPV and the host immune responses (Harun et al., 2013). The results revealed that during the first 3 hours of FIPV infection, at least 96 transcripts that associated with immune responses (e.g. ISGs, MX1, RSAD2, A3C, ID1, CRIP1, TRIM25 and MDA5), apoptosis (ID1, ATF3, TNFα, and RNF7) and pro-inflammatory responses (e.g. PD-L1, CCL8, CXCL10 and CCL17) were highly deregulated. Only a few of the genes, namely PD-1, PD-L1 and A3H, were further characterized based on a time course study of FIPV infected CFFK cells and expression profiles in peripheral blood mononuclear cells (PBMC) of FIP diagnosed cats (Harun et al., 2013). Functional characterizations of additional mediators that modulate innate and acquired immune responses will increase our understanding on their roles and involvement during FIPV infection.

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The long-term objective of this study is to identify the key mediators that can be used as biomarkers in determining the progression and outcome of FIPV infection in cats. In order to elucidate the specific involvement of some of the immune mediators, the specific objectives of this study are:

1. To determine the viral load in FIPV infected CRFK cells as well as in peripheral blood mononuclear cells (PBMC) and peritoneal effusions of cats diagnosed with FIP.
2. To characterize the RNA transcript expression profiles of selected immune-related genes namely CCL8, CCL17, CXCL10, CRIP1, ID1, RNF7 and RSAD2 in FIPV infected CRFK cells as well as in peripheral blood mononuclear cells (PBMC) and peritoneal effusions of cats diagnosed with FIP.
3. To characterize the protein expression profiles of 19 different immune-related mediators in FIPV infected CRFK cells as well as in serum and supernatant of peritoneal effusions of cats diagnosed with FIP.
4. To understand the correlation between viral load and expression profiles of different immune mediators in FIPV infected CRFK cells as well as in peripheral blood mononuclear cells (PBMC) and peritoneal effusions of cats diagnosed with FIP.

Hence, the results of this study will provide some new insights into FIPV pathogenesis and immune mechanism, which can facilitate future researches on different aspects of this disease including immunology of the disease and development of new diagnostic, vaccine and therapeutics approaches.

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