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Felis catus Papillomavirus Type 2
Infection and Skin Cancer in
Domestic Cats

A thesis presented in partial fulfilment of the requirements for the
degree of

Doctor of Philosophy

in

Veterinary Science

at Massey University, Manawatū,
New Zealand

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2017

Abstract

Felis catus papillomavirus type 2 (FcaPV-2) is a virus which commonly infects the skin of domestic cats. While most infections are asymptomatic, there is growing evidence that FcaPV-2 may play a role in the development of a subset of feline cutaneous squamous cell carcinomas (SCCs).

In the first part of this thesis, the natural history of FcaPV-2 infection was investigated with the aim of determining when cats become infected with the virus. A real-time PCR assay was developed to quantify FcaPV-2 DNA in feline skin swabs. This assay was then used to measure the FcaPV-2 DNA load in serial samples from two populations of cats. Results from these studies showed that most kittens are exposed to FcaPV-2 in the first few days of life. Additionally, the primary source of exposure is likely to be direct contact with other cats in the household, particularly their queen, as some of the queens appeared to be shedding large amounts of virus. FcaPV-2 mRNA was also detected in some of the kittens, confirming that they had become infected with FcaPV-2 soon after birth.

The aim of the second part of this thesis was to determine the quantity and transcriptional activity of the FcaPV-2 DNA present in feline cutaneous SCCs in order to determine if the virus was involved in cancer development or just present as an innocent bystander. Real-time PCR assays were developed to measure FcaPV-2 gene expression in SCCs and the results clearly distinguished two subsets of feline cutaneous SCCs. The majority of the SCCs had low copy numbers of FcaPV-2 DNA and no FcaPV-2 gene expression, suggesting the virus was an incidental finding. In contrast, around a third of the SCCs had detectable FcaPV-2 gene expression and high copy numbers of FcaPV-2 DNA, similar to that found in the FcaPV-2-induced premalignant lesions. There was also a significant association between FcaPV-2 gene expression and alterations in a host cell cycle regulatory protein (p16). Taken together, these results strongly suggest that FcaPV-2 played a role in the development of around a third of the feline cutaneous SCCs.

The results from the studies reported in this thesis support a causative role of FcaPV-2 in a proportion of feline cutaneous SCCs. However, as infection of cats is common and appears to occur early in life, there may be little opportunity to prevent SCC development by preventing FcaPV-2 infection.

Acknowledgements

The journey to the publication of this thesis, while trying at times, has been made worthwhile by the wonderful people I have met along the way.

My utmost thanks go to my primary supervisor John Munday, who supported me from start to end, and mostly managed to stop me from taking myself too seriously along the way. In all seriousness though John, you've been an excellent supervisor, thank-you.

I am also very grateful to Keren Dittmer and Magda Dunowska, for their enthusiasm, patience and technical skills. Countless times I barged into Keren's office eager to share a new idea or result, before realising that she probably had more important work to do. Thank-you Keren for sharing my excitements and frustrations. To Magda, I am most grateful for the time and effort you put in to help me get the first real-time PCR assay working well, it proved to be immensely useful.

This thesis would not have been possible without the many people who helped me collect samples. In particular, I am very grateful to the people who let me collect swabs and hair plucks from their cats, and to the veterinarians who sent me biopsies. Genevieve Rogerson and Robyn Jarrett deserve special mention, thank-you both. The staff at the Feline Centre for Nutrition at Massey University, and Adrienne French, at New Zealand Pathology Limited, were also very helpful in this regard.

I would also like to acknowledge the financial support I received from a Massey Doctoral Scholarship and from the grants which funded the research presented in this thesis, including the Morris Animal Foundation, Maurice and Phyllis Paykel Trust, IVABs Postgraduate Research Fund and the Massey University Research Fund.

Finally, I could not have done this without the love and support of my family, especially my mother Barbara, who provided lots of moral support and proofread this thesis. Nor could I have done this without the encouragement of my partner Sam; thank-you Sam for all the ways you made me smile, even when I was tired and grumpy, throughout this journey.

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Abbreviations

Common Abbreviations

28Sr	Reference gene coding for the 28s ribosomal sub-unit
ABL2	Abelson proto-oncogene 2 non-receptor tyrosine kinase RNA reference gene
ACTB	Beta actin RNA reference gene
ANOVA	Analysis of variance statistical method
B2M	Beta-2 microglobulin RNA reference gene
BISC	Bowenoid in situ carcinoma
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
Cq	Number of PCR cycles when threshold reached
CV	Coefficient of variation
DSH	Domestic short hair
EV	Epidermodysplasia verruciformis
FFPE	Formalin fixed paraffin embedded
FIV	Feline immunodeficiency virus
FVP	Feline viral plaque
GAPDH	Glyceraldehyde 3-phosphate dehydrogenase RNA reference gene
GUSB	Beta glucuronidase RNA reference gene
H&E	Haematoxylin and eosin stain
IgG	Immunoglobulin G
MHC	Major histocompatibility molecules
NRQ	Normalised relative quantity
ORF	Open reading frame
p16	Cyclin dependant kinase inhibitor p16 ^{INK4A}
p53	Tumour suppressor p53 protein
pRb	Retinoblastoma protein
PCR	Polymerase chain reaction
PV	Papillomavirus
qPCR	Quantitative PCR
RPL17	Ribosomal protein L17 RNA reference gene
RPS7	Ribosomal protein S7 RNA reference gene
RPS19	Ribosomal protein S19 RNA reference gene
RT	Reverse transcriptase
SCC	Squamous cell carcinoma
SNP	Single nucleotide polymorphism
VLP	Virus-like particle
YWHAZ	Tyrosine 3-monooxygenase/ 5 tryptophan 5-monooxygenase activation protein zeta

Papillomavirus Abbreviations

Domestic cats		Phylogeny- genus	Tissue infected
FcaPV-1	<i>Felis catus</i> papillomavirus type 1 Formerly <i>Felis domesticus</i> papillomavirus 1	Lambdapapillomavirus	oral mucosa
FcaPV-2	<i>Felis catus</i> papillomavirus type 2 Formerly <i>Felis domesticus</i> papillomavirus 2	Dyothetapapillomavirus	skin
FcaPV-3	<i>Felis catus</i> papillomavirus type 3	Taupapillomavirus	skin
FcaPV-4	<i>Felis catus</i> papillomavirus type 4	Taupapillomavirus	unknown
Humans			
HPV-1	Human papillomavirus type 1	Chipapillomavirus	skin
HPV-2	Human papillomavirus type 2	Alphapapillomavirus	skin
HPV-4	Human papillomavirus type 4	Gammapapillomavirus	skin
HPV-5	Human papillomavirus type 5	Betapapillomavirus	skin
HPV-6	Human papillomavirus type 6	Alphapapillomavirus	genital mucosa
HPV-8	Human papillomavirus type 8	Betapapillomavirus	skin
HPV-9	Human papillomavirus type 9	Betapapillomavirus	skin
HPV-11	Human papillomavirus type 11	Alphapapillomavirus	genital mucosa
HPV-16	Human papillomavirus type 16*	Alphapapillomavirus	genital mucosa
HPV-17	Human papillomavirus type 17	Betapapillomavirus	skin
HPV-18	Human papillomavirus type 18*	Alphapapillomavirus	genital mucosa
HPV-27	Human papillomavirus type 27	Alphapapillomavirus	skin
HPV-38	Human papillomavirus type 38	Betapapillomavirus	skin
HPV-57	Human papillomavirus type 57	Alphapapillomavirus	skin
HPV-76	Human papillomavirus type 76	Betapapillomavirus	skin
HPV-93	Human papillomavirus type 93	Betapapillomavirus	skin
Domestic dogs			
CPV-1	<i>Canis familiaris</i> oral papillomavirus Formerly COVP	Lambdapapillomavirus	oral mucosa
CPV-2	<i>Canis familiaris</i> papillomavirus type 2	Taupapillomavirus	skin
Domestic cattle			
BPV-1	<i>Bos taurus</i> papillomavirus type 1	Deltapapillomavirus	skin
BPV-2	<i>Bos taurus</i> papillomavirus type 2	Deltapapillomavirus	skin
BPV-3	<i>Bos taurus</i> papillomavirus type 3	Xipapillomavirus	skin
BPV-4	<i>Bos taurus</i> papillomavirus type 4	Xipapillomavirus	oral/ oesophageal mucosa
BPV-13	<i>Bos taurus</i> papillomavirus type 13	Deltapapillomavirus	skin
BPV-14	<i>Bos taurus</i> papillomavirus type 14	Deltapapillomavirus	skin
Horses			
EcPV-2	<i>Equus caballus</i> papillomavirus type 2	Dyoiotapapillomavirus	genital mucosa
Rabbits			
SfPV-1	<i>Sylvilagus floridanus</i> papillomavirus type 1 Formerly cottontail rabbit papillomavirus	Kappapapillomavirus	skin
OcPV-1	<i>Oryctolagus cuniculus</i> papillomavirus type 1	Kappapapillomavirus	oral mucosa
Mice			
MnPV-1	<i>Mastomys natalensis</i> papillomavirus type 1	Iotapapillomavirus	skin
MmuPV-1	<i>Mus musculus</i> papillomavirus type 1	Pipapillomavirus	skin