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

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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.

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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	*Felis catus* papillomavirus type 1 Formerly Felis domesticus papillomavirus 1	Lambdapapillomavirus	oral mucosa
FcaPV-2	*Felis catus* papillomavirus type 2 Formerly Felis domesticus papillomavirus 2	Dyothetapapillomavirus	skin
FcaPV-3	*Felis catus* papillomavirus type 3	Taupapillomavirus	skin
FcaPV-4	*Felis catus* 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	*Canis familiaris* oral papillomavirus Formerly COVP	Lambdapapillomavirus	oral mucosa
CPV-2	*Canis familiaris* papillomavirus type 2	Taupapillomavirus	skin
Domestic cattle			
BPV-1	*Bos taurus* papillomavirus type 1	Deltapapillomavirus	skin
BPV-2	*Bos taurus* papillomavirus type 2	Deltapapillomavirus	skin
BPV-3	*Bos taurus* papillomavirus type 3	Xipapillomavirus	skin
BPV-4	*Bos taurus* papillomavirus type 4	Xipapillomavirus	oral/ oesophageal mucosa
BPV-13	*Bos taurus* papillomavirus type 13	Deltapapillomavirus	skin
BPV-14	*Bos taurus* papillomavirus type 14	Deltapapillomavirus	skin
Horses			
EcPV-2	*Equus caballus* papillomavirus type 2	Dyoiotapapillomavirus	genital mucosa
Rabbits			
SfPV-1	*Sylvilagus floridanus* papillomavirus type 1 Formerly cottontail rabbit papillomavirus	Kappapapillomavirus	skin
OcPV-1	*Oryctolagus cuniculus* papillomavirus type 1	Kappapapillomavirus	oral mucosa
Mice			
MnPV-1	*Mastomys natalensis p*apillomavirus type 1	Iotapapillomavirus	skin
MmuPV-1	*Mus musculus* papillomavirus type 1	Pipapillomavirus	skin