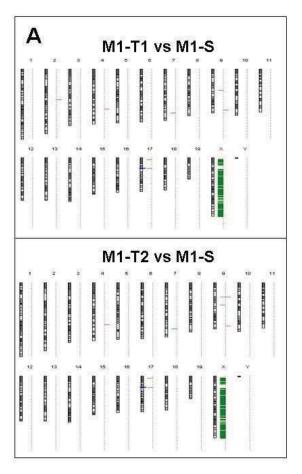
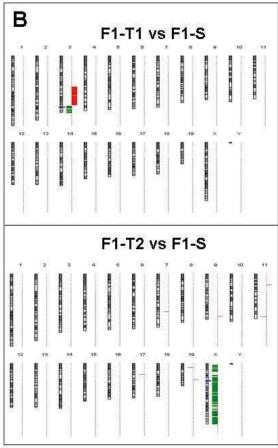
Supplementary Figures and Tables





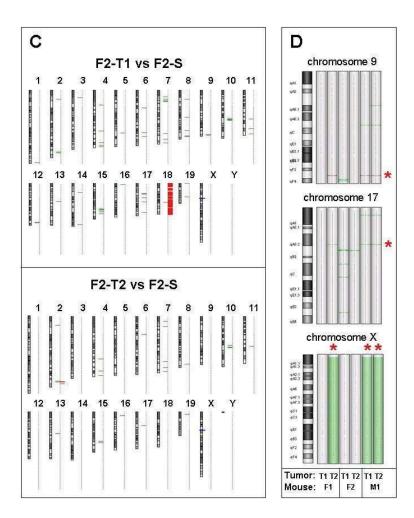


Figure S1. Distribution of chromosomal aberrations in the FIV-induced liver tumors. Comparative genomic hybridization (CGH) was performed on genomic DNA extracted from tumors (T1, T2) obtained from male mouse, M1 and female mice, F1 and F2, and compared to DNA extracted from the surrounding, non-tumorous, tissue (S). Amplifications (red) and deletions (green). (**a-c**) Distribution of aberrations according to chromosome. (**d**) Small aberrations in chromosomes 9 and 17, as well as a complete deletion of the X chromosome, were common to the three tumors, F1-T2, M1-T1 and M1-T2, (marked by a red asterix).

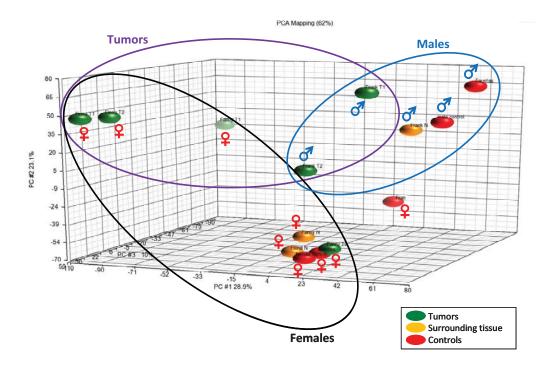


Figure S2. A graphical representation of the Principal Component Analysis (PCA) of genome scale gene expression profiling data obtained from FIV-transduced and control mice. Tumor tissue (T, green); matched non-tumorous liver tissue (N, yellow); liver tissue from healthy untransduced, or from tumor-free FIV-transduced mice (H, red). Male clusters (blue line); female clusters (black line); tumors (purple line).

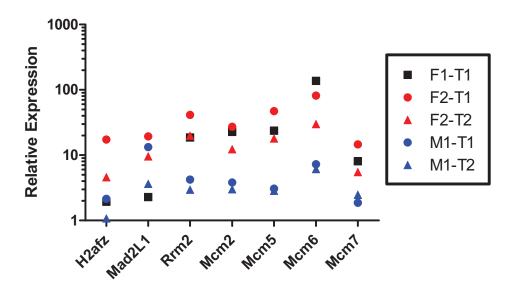


Figure S3. Validation of genome-wide microarray expression data by qRT-PCR. Total RNA was extracted from the five FIV-induced HCCs that shared gene expression patterns. Seven E2F target genes that were significantly upregulated in the genome-wide expression arrays were validated by qRT-PCR. Relative quantitation (RQ) of the tumor tissue was calculated using non-tumorous tissue as the calibrator (RQ=1). HPRT was used as the endogenous control.

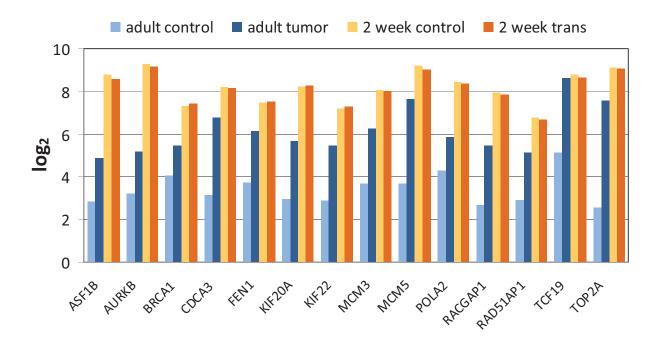


Figure S4. High level of E2F target gene expression in livers of young mice. Expression levels of E2F target genes common to humans and rats that were upregulated in the FIV-induced tumors, as determined by genome-wide array analysis. Microarray analysis was performed on total RNA extracted from FIV-induced liver tumors that developed in adult mice (dark blue) and matched surrounding tissue (light blue), as well as from livers of 10 day old mice untransduced (yellow) and FIV-transduced (orange). The following housekeeping genes were expressed at the same level in all datasets: Arl6ip1, Copb2, Eif2s3x, Man1a, Srp9, Tfg, and Ywhae.

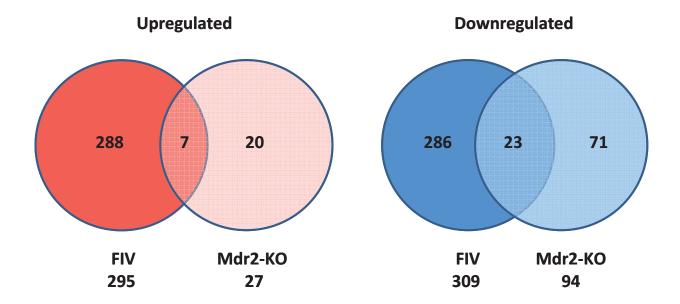


Figure S5. Comparison of deregulated genes between the two murine HCC models, namely, FIV-induced (current study) and inflammation-mediated Mdr2-KO mice³⁴. The Venn diagram demonstrates numbers of gene probes that were either up- or down-regulated in at least four tumors in each dataset. Fold-change threshold for tumor versus non-tumor was ≥ 1.8 for up-regulated and \leq -1.8 for down-regulated genes. Six tumors were analyzed in each HCC model and compared to matched non-tumor tissue (3 samples in FIV dataset and 4 in the Mdr2-KO dataset).

Table S1. FIV integration sites within liver tumors

Tumor ID	Chromosomal Location ^a	Gene Symbol	Intragenic ^b	Intergenic (k	ops) ^c	Integration orientation ^d
	Chr4: 82315639	Nfib	intron 10			opposite
	Chr4: 106175353				>100kb	
	Chr5: 115025088	Spp13	intron 1			same
	Chr6: 4677827	Sgce	intron 10			same
F1(T1)	Chr13: 77132015	Ankrd32	intron 1			opposite
	Chr14: 22596501	1700112E06Rik	exon 4- intron 5			opposite
	Chr18: 9309351	ccny		upstream	4580	same
	Chr19: 29513373	A930007I19Rik	intron 2			same
	Chr1: 134747726	Syt2	3'UTR			same
	Chr2: 76984794	Ttn		upstream	2500	same
E4/T2\	Chr4: 64586468				>100kb	
F1(T2)	Chr10: 84917375	Ric8b		upstream	241	opposite
	Chr19: 6904891	Prdx5		downstream	4754	same
	Chr19 :61095340	Grk5		downstream	3038	opposite
	Chr1: 15845050	Terf1		downstream	1621	opposite
	Chr1: 13539165	Tram1		downstream	50699	same
	Chr5: 88759162	AK046278	exon1			
F2(T1)	Chr6: 122437822	Rimklb		downstream	9480	opposite
	Chr11: 12876885				>100kb	
	Chr18: 84327800	Zfp407	intron 7			same
	ChrX: 72959054	Nsdh1		downstream	526	opposite
E2/T2\	Chr3: 107325730	AK048987	3'UTR			opposite
F2(T2)	Chr5: 143645250	Cyth3	intron 1			same
M1(T1)	Chr3: 63958416	Slc33a1	intron 1			same
	Chr9: 108531707	Qrich1	intron 2			opposite
	Chr12: 85327916	Nek9	intron 16			same
	Chr16: 31262903	Ppp1r2	intron 2			same
M1(T2)	Chr16: 4626884	Coro7	intron 9			opposite

^a Location of first nucleotide following 3' LTR according to the UCSC Genome Browser, Dec 2011 mouse assembly.

^DLocation of integration within gene.

^cPosition and distance of viral insertion relative to nearest gene within 100kb.

^aOrientation of vector LTR with respect to the direction of transcription of the targeted gene.

Table S2. Syntenic regions of human common fragile sites in the mouse genome.

Fragile site name	Human genome ^a	Size (bp)	Mouse genome ^a	Size (bp)	Tumors bearing a coinciding chromosomal aberration ^b	Location of aberration
FRA1E	chr1: 68362127-156421365	88,059,239	chr3: 86799634-159599772	72,800,139	F1-T1	chr3: 87535405-159870502
FRA1H	chr1: 205641715-225711350	20,069,636	chr1: 181768214-197047501	15,279,288		
FRA2G	chr2: 139785273-188118461	48,333,189	chr2: 39363343-84313407	44,950,065		
FRA3B	chr3: 57917214-63984740	6,067,527	chr14: 8637918-14953921	6,316,004		
FRA4F	chr4: 93567701-93586956	19,256	chr6: 63311998-63322971	10,974		
FRA6E	chr6: 160023022-167303093	7,280,072	chr17: 7175001-13208514	6,033,514		
FRA6F	chr6: 100641521-155090183	54,448,663	chr10: 3011989-51231556	48,219,568		
FRA6H	chr6: 29430682-33405196	3,974,515	chr17: 34042414-37636846	3,594,433	F2-T1, F2-T2	chr17: 34622785-35297915
FRA7E	chr7: 76539913-92524425	15,984,513	chr5: 3144811-20984943	17,840,133		
FRA7G	chr7: 92596878-150189329	57,592,452	chr6: 3320884-48858948	45,538,065		
FRA7K	chr7: 107559442-111923382	4,363,941	chr12: 40896394-45712997	4,816,604		
FRA7H	chr7: 92596878-150189329	57,592,452	chr6: 3320884-48858948	45,538,065		
FRA7I	chr7: 92596878-150189329	57,592,452	chr6: 3320884-48858948	45,538,065		
FRA8C	chr8: 97515808-146131251	48,615,444	chr15: 32717008-76767049	44,050,042		
FRA9E	chr9: 27315071-122528763	95,213,693	chr4: 34896196-70204380	35,308,185		
FRA9G	chr9: 6745997-27290706	20,544,710	chr4: 73894394-94597321	20,702,928		
FRA11E	chr11: 26252973-57510525	31,257,553	chr2: 84322813-110832617	26,509,805	M1-T1	chr2: 85936918-85946800
FRA11F	chr11: 71304680-88990549	17,685,870	chr7: 94258787-109226497	14,967,711		
FRA11G	chr11: 106957827-134348749	27,390,923	chr9: 25880811-53831242	27,950,432	M1-T2	chr9: 37858515-37931443
FRA13A	chr13: 33378325-40146259	6,767,935	chr3: 52065711-56976945	4,911,235		
FRA13E	chr13: 52124034-101887709	49,763,676	chr14: 79986707-125114860	45,128,154		
FRA16D	chr16: 45250774-88637531	43,386,758	chr8: 87782679-126060687	38,278,009		

 $^{^{\}rm a}{\rm Chromosomal}$ locations according to UCSC Genome Browser assemblies 2006 $^{\rm b}{\rm Chromosomal}$ aberrations as determined by CGH.

Table S3. Summary of FIV integration profiling following high throughput sequencing of transduced AML 12 cells

tnrougnput	t sequencing of transduce	a AIVIL 12 cei	
BIOINFORMATIC ANALYSIS	DEFINITION	NO. OR % OF SEQUENCES ^a	
no. of raw sequences	Number of sequences that were generated by 454 high throughput sequencing.	93,115	
output of sorter	The sorter removes the viral LTR, barcode sequences, and genomic sequences that do not immediately follow the LTR.	72,994	
output of CD-HIT	Redundant sequences are removed from the output of sorter.	32,480	
output of ISA	Sequences that are too small are removed from the output of CD-HIT; remaining sequences are matched to the mouse genome.	19,603	
no hits found	No matches were found in the UCSC Genome Browser.	991	
no gene within 150 kb	No gene was found within 150 kb of the integration site.	1,988	
number of unique sequences	This equals the output of ISA minus (multiple hits + no hits).	17,576	
RESULTS			
hits in gene	Number of integrations occurring within a gene.	6,437	
% of integrations within genes	Number of integrations within genes/number of unique sequences.	37 <u>+</u> 2	
number of integrations in repeat sequences	Number of sequences in LINEs, SINEs, LTRs.	1,036	
% of integrations in repeat sequences	Percentage of sequences in LINEs, SINEs, LTRs.	9 <u>+</u> 4.8	
number of integrations upstream of closest gene		5,818	
% of integrations upstream of closest gene	Of integrations occurring between genes, the percentage that were upstream of the closest gene.	38 <u>+</u> 1	
number of integrations downstream of closest gene		9,241	
% of integrations downstream of closest gene	Of integrations occurring between genes, the percentage that were		

asum or average of four experiments+SD

Table S4: Genes deregulated in livers of tumor-free, transduced mice, compared to untransduced controls

Gene symbol Gene Title Genes up-regulated in FIV-transduced liver Arntt aryl hydrocarbon receptor nuclear translocator-like Cdkn1a cyclin-dependent kinase inhibitor 1A (P21) TS P53 V Cdkn2 choline kinase alpha O Ditle DNA-damage-inducible transcript 4 Dusp6 dual specificity phosphatase 6 GO/TS Egr1 early growth response 1 GO/TS P53 V GOS2 GO/C1 switch gene 2 Gadd45a growth arrest and DNA-damage-inducible 45 alpha Heat shock protein 1 Roff platelet-derived growth factor binding protein 1 Norg1 N-myc downstream regulated gene 1 Proft printer-inducible are scency coactivator 1 Ppp173c protein phosphatase 1, regulatory (inhibitor) subunit 3C St5 suppression of tumorigenicity 5 Trim34 Tripartite motif protein 34 Genes down-regulated in FIV-transduced liver Armacx3 armadillo repeat containing, X-linked 3 Cish cytokine inducible SH2-containing protein Dact1 dapper homolog 1, antagonist of beta-catenin (xenopus) Myc myelocytomatosis oncogene Per3 period homolog 3 (Drosophila) Pylkish 3 p-lopsophriduse 3 (Drosophila) Pylkish 3 p-lopsophriduse 3 (Drosophila) Pylkish 3 polo-like kinase 3 (Drosophila) Pylkish 3 polo-like kinase 3 (Drosophila) Firef thyrotroph embryonic factor Thrsp thyroid hommone responsive SPOT14 homolog (Rattus)		compared to unitransduced contr	(O)		нсс
Arntt aryl hydrocarbon receptor nuclear translocator-like P53 Cdkn1a cyclin-dependent kinase inhibitor 1A (P21) TS P53 V Chka choline kinase alpha O Ddit4 DNA-damage-inducible transcript 4 TS P53 V Dusp6 dual specificity phosphatase 6 O/TS Egr1 early growth response 1 O/TS P53 V G0s2 G0/G1 switch gene 2 PPAR Gadd45a growth arrest and DNA-damage-inducible 45 alpha P53 V Hspb1 heat shock protein 1 P53 V Hspb1 insulin-like growth factor binding protein 1 P53 V Pdgfc platelet-derived growth factor conditionation of tumorigenicity 5 TS St5 suppression of tumorigenicity 5 TS St5 suppression of tumorigenicity 5 TS St5 suppression of tumorigenicity 5 Ts St6 St6 cytokine inducible St2-containing protein Dact1 dapper homolog 1, antagonist of beta-catenin (xenopus) TS Wnt V Port of forkhead box Q1 Mcm10 minichromosome maintenance deficient 10 (S.cerevisiae) Myc myelocytomatosis oncogene O Myc Pflk3 polo-like kinase 3 (Drosophila) TS Rb V Pflk3 polo-like kinase 3 (Drosophila) TS Rb V Firsh Armc3 Rho family GTPase 3 TS Rb V Pflk63 Rho family GTPase 3 TS Rb V Trimsp thyroid homonoer responsive SPOT14 homolog (Rattus)		Gene Title	Oncogene or (TS)	" "	
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Ddit4 DNA-damage-inducible transcript 4 TS P53 V Dusp6 dual specificity phosphatase 6 O/TS Egr1 early growth response 1 O/TS P53 V GGs2 G0/G1 switch gene 2 PPAR Gaddd45a growth arrest and DNA-damage-inducible 45 alpha P53 V Hspb1 heat shock protein 1 P53 N-Hspb1 insulin-like growth factor binding protein 1 P53 N-Hspb1 insulin-like growth factor binding protein 1 P53 N-Hyr downstream regulated gene 1 TS P53 V Pdgfc platelet-derived growth factor, C polypeptide O V Pdk4 pyruvate dehydrogenase kinase, isoenzyme 4 Phrc1 proline-rich nuclear receptor coactivator 1 Pppp1r3c protein phosphatase 1, regulatory (inhibitor) subunit 3C P53 St5 suppression of tumorigenicity 5 TS TS Tbx3 T-box 3 O Trim34 Tripartite motif protein 34 Genes down-regulated in FIV-transduced liver armadillo repeat containing, X-linked 3 Cytokine inducible SH2-containing protein Dact1 dapper homolog 1, antagonist of beta-catenin (xenopus) TS Wnt V Dbp D site albumin promoter binding protein myelocytomatosis oncogene O Myc Per3 period homolog 3 (Drosophila) TS V Pfkfb3 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 Phlda1 pleckstrin homology-like domain, family A, member 1 TS PIR Rb V Rnd3 Rho family GTPase 3 TS TS Rb V thyroid homone responsive SPOT14 homolog (Rattus)	Cdkn1a	cyclin-dependent kinase inhibitor 1A (P21)	TS	P53	٧
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PIk3 polo-like kinase 3 (Drosophila) TS V Rnd3 Rho family GTPase 3 TS Rb V Tef thyrotroph embryonic factor Thrsp thyroid hormone responsive SPOT14 homolog (Rattus)	Pfkfb3				
Rnd3 Rho family GTPase 3 TS Rb √ Tef thyrotroph embryonic factor Thrsp thyroid hormone responsive SPOT14 homolog (Rattus)	Phlda1	pleckstrin homology-like domain, family A, member 1	TS		
Tef thyrotroph embryonic factor Thrsp thyroid hormone responsive SPOT14 homolog (Rattus)	Plk3	polo-like kinase 3 (Drosophila)	TS		٧
Thrsp thyroid hormone responsive SPOT14 homolog (Rattus)	Rnd3	Rho family GTPase 3	TS	Rb	٧
	Tef	thyrotroph embryonic factor			
Usp2 ubiquitin specific peptidase 2 P53 √	Thrsp	thyroid hormone responsive SPOT14 homolog (Rattus)			
	Usp2	ubiquitin specific peptidase 2		P53	٧

Table S5. HCC-associated oncogenes and tumor suppressors

HCC- associated oncogenes	HCC-associated tumor suppressors			
Akt	Ache	Hic1	Rprm	
Birc2	Apc	Igfals	Runx3	
Birc5	Arid2	Irf2	Scara5	
Bmi1	Axin1	KI	Sfn	
Ccnd1	Blm	KIf4	Sfrp1	
Cks1b	Brms1	KIf6	Sfrp2	
Ctnnb1	Btbd9	Lats1	Sirt3	
Ect2	Cacna1g	Lats2	Socs1	
Egf	Cadm1	Men1	Sox1	
Egfr	Casp8	Mxi1	Sparc	
Eif5a2	Cdh1	Ndrg2	Stk11	
Ezh2	Cdkn1a	Nf2	Sulf1	
Hgf	Cdkn1b	Nr1h4	Trp53	
ld1	Cdkn2a	Nrsn2	Tsc1	
Jun	Cdkn2b	Pax5	Tsc2	
Mad2l1	Creb3l3	Per3	Vac14	
Met	Cyr61	Plagl1	Wrn	
Mtdh	Dapk1	Plk4	Xpo4	
Мус	Dcc	Pml	Zbbx	
Pdgfb	Ddx20	Prdm2		
Pdgfra	Dlc1	Ptgs2		
Pdgfrb	Dleu2	Pycard	33 20000013 33 30000013 30000013 30000013 30000013	
Psmd10	Dpyd	Rassf1	3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3 3	
Rhoc	Fgf6	Rassf2		
Sirt1	Fgl1	Rassf5		
Smo	Fstl5	Rb1		
Sulf2	Gjd4	Rbl1		
Tgfa	Glo1	Rbl2		
Vegfa	Gorab	Recql		
Yap1	Gstp1	Recql5		

Table S6. Primer sequences of E2F target genes used for qRT-PCR

gene	orientation ^a	sequence
H2afz	F	GAAATCTAGGACAACCAGCCAC
	R	AAGTCTTTTGACGCATTTCCTG
Mad2L1	F	GTATCTCAATAATGTGGTGGAACAG
IVIAUZLI	R	ATATCAAACTGCCATCTTTCAAGG
Rrm2	F	GCTCTGAAACCCGATGAGAG
IXIIIZ	R	GCCTCTGTAACTTGAACTTCTTGG
Mcm2	F	AAGAAGAGGATGGAGAGGAACTC
IVICITIZ	R	CCTCCACATCTTCATCATCCAG
Mcm5	F	AGATGAGCTGCTCCAAGACATC
IVICITIS	R	CAGAGGCTGAAATGATGATGC
Mcm6	F	GAGAAACACGCTGGTTGTGAG
	R	AAGGTCTTCAAGGCTCGACAC
Mcm7	F	ATTGTCACTCGTGTGTCTGAAGTC
	R	ACATGATCAGAGGCATGAAAGTG

^aF forward; R reverse