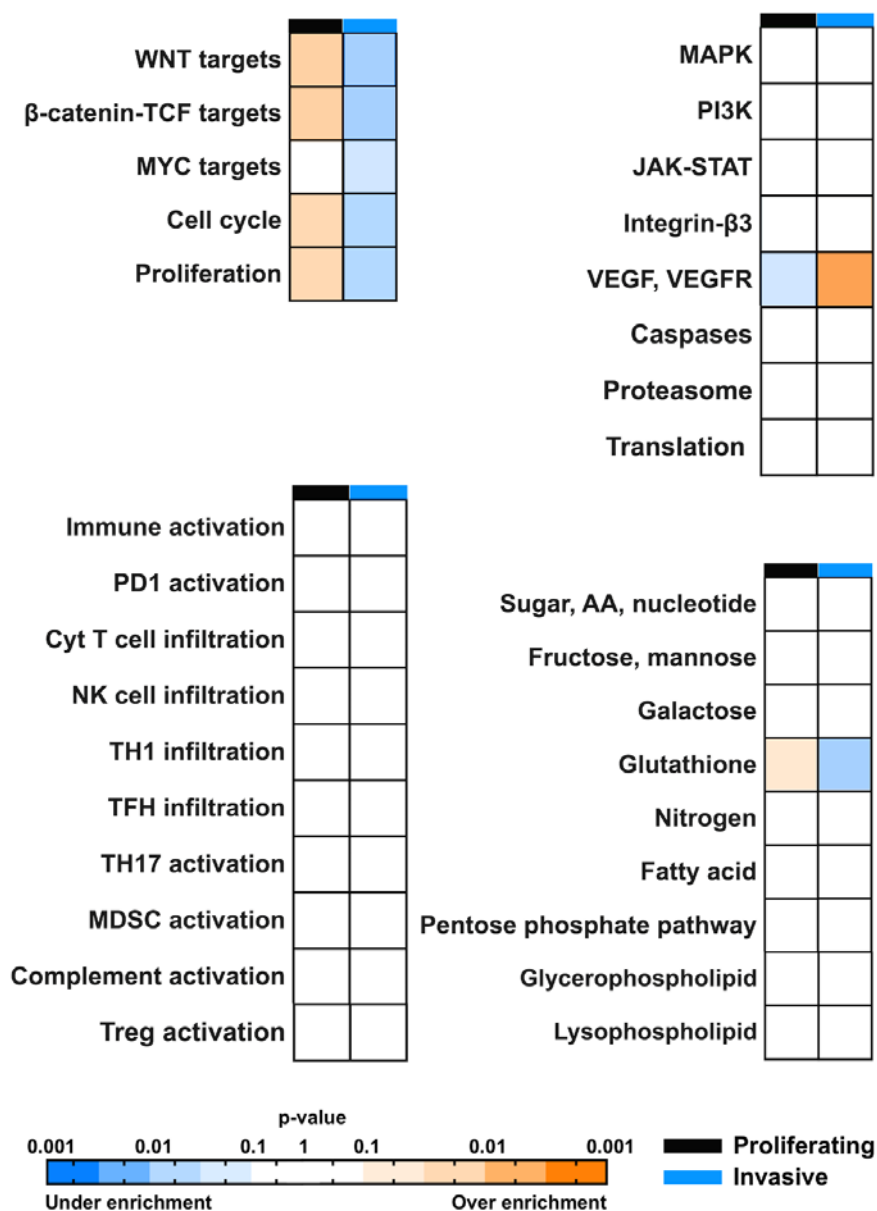


Jin Wang, Tianfang Wang, Yanfang Sun, Yuan Feng, William C. Kisseberth, Carolyn J. Henry, Irene Mok, Susan E. Lana, Kevin Dobbin, Nicole Northrup, Elizabeth W. Howerth and Shaying Zhao

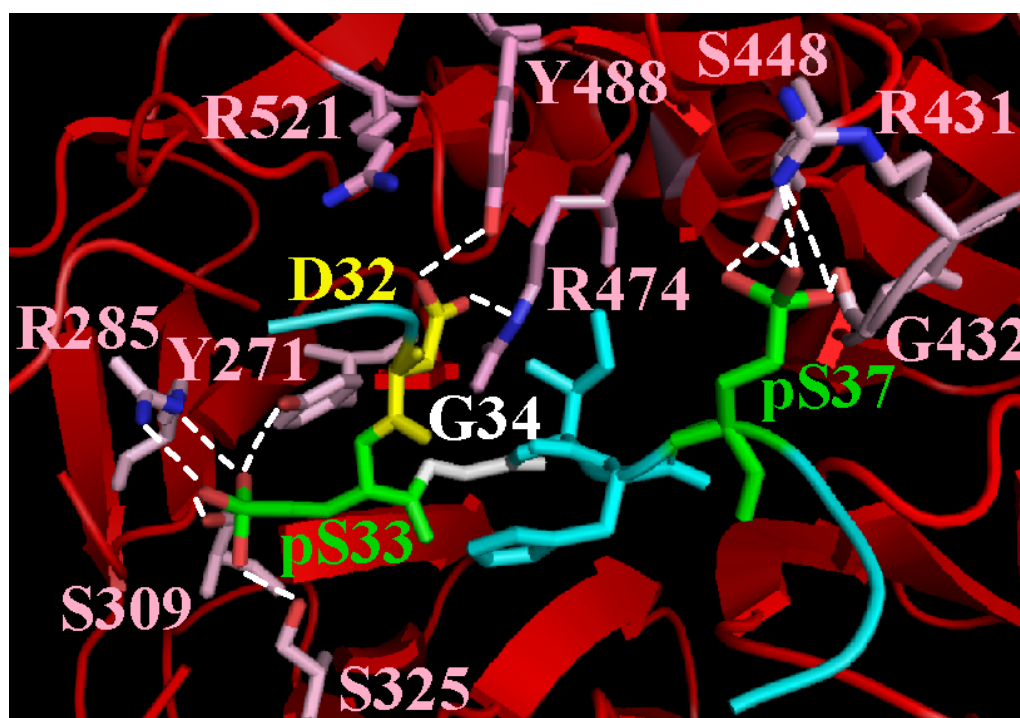
**Figure S1.** Hierarchical clustering, with various numbers of top most variable genes in expression across the 26 canine samples, consistently separates invasive tumors from proliferative tumors. Related to Figure 1B.



**Figure S2A.** The GSEA p-values between invasive and proliferative canine tumors with known human CRC pathway and signature genes. Related to Figure 2A.

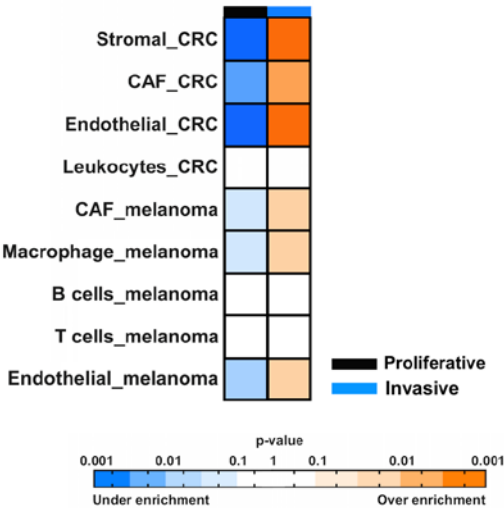
sp B6V8E6 CTNB1_CANLF	MATQADLMELDMAMEPDRKAAVSHWQQQSYLDSGIHSGATTAPSLSGKGNPEEEDVDTT
sp P35222 CTNB1_HUMAN	MATQADLMELDMAMEPDRKAAVSHWQQQSYLDSGIHSGATTAPSLSGKGNPEEEDVDTT
	*****;
sp B6V8E6 CTNB1_CANLF	QVLYEWEGFSQSFTQEQQVADIDGGYAMTRAQVRRAAMPETLDEGMQIPSTQFDAAHP
sp P35222 CTNB1_HUMAN	QVLYEWEGFSQSFTQEQQVADIDGGYAMTRAQVRRAAMPETLDEGMQIPSTQFDAAHP
	*****
sp B6V8E6 CTNB1_CANLF	NVQRLAEPQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEQVVVNKAAMVHQLSK
sp P35222 CTNB1_HUMAN	NVQRLAEPQMLKHAVVNLINYQDDAELATRAIPELTKLLNDEQVVVNKAAMVHQLSK
	*****
sp B6V8E6 CTNB1_CANLF	KEASRHAIMRSPQMVSIVRTMQNTNDVETARCTAGTLHNLSHREGLLAIFKSGGIPAL
sp P35222 CTNB1_HUMAN	KEASRHAIMRSPQMVSIVRTMQNTNDVETARCTAGTLHNLSHREGLLAIFKSGGIPAL
	*****
sp B6V8E6 CTNB1_CANLF	VKMLGSPVDSVLFYAITTLHNLHLLHQQGAKMAVRLAGGLQKQVALLNKTNVKFLAITTDC
sp P35222 CTNB1_HUMAN	VKMLGSPVDSVLFYAITTLHNLHLLHQQGAKMAVRLAGGLQKQVALLNKTNVKFLAITTDC
	*****
sp B6V8E6 CTNB1_CANLF	LQILAYGNQESKLIILASGGPQALVNIMRTYTYEKLWTTSRVLKVLVSVCSNKPATVEA
sp P35222 CTNB1_HUMAN	LQILAYGNQESKLIILASGGPQALVNIMRTYTYEKLWTTSRVLKVLVSVCSNKPATVEA
	*****
sp B6V8E6 CTNB1_CANLF	GGMQALGLHLTDPSQRLVQNCWTLRNLSDAATKQEGMEGLLGTVLQLLGSDDINVVTCA
sp P35222 CTNB1_HUMAN	GGMQALGLHLTDPSQRLVQNCWTLRNLSDAATKQEGMEGLLGTVLQLLGSDDINVVTCA
	*****
sp B6V8E6 CTNB1_CANLF	AGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRHLTSRHQEAEM
sp P35222 CTNB1_HUMAN	AGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRHLTSRHQEAEM
	*****
sp B6V8E6 CTNB1_CANLF	AQNAVRLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLREQGAIPRLVQLL
sp P35222 CTNB1_HUMAN	AQNAVRLHYGLPVVVKLLHPPSHWPLIKATVGLIRNLALCPANHAPLREQGAIPRLVQLL
	*****
sp B6V8E6 CTNB1_CANLF	VRAHQDTQRRTSMTGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNIRIVIRGLNTIPLFV
sp P35222 CTNB1_HUMAN	VRAHQDTQRRTSMTGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNIRIVIRGLNTIPLFV
	*****
sp B6V8E6 CTNB1_CANLF	QLLYSPIENIQRVAAGVLCALQDKEAAEAIEAEGATAPLTELHLSRNEGVAITYAAAVLF
sp P35222 CTNB1_HUMAN	QLLYSPIENIQRVAAGVLCALQDKEAAEAIEAEGATAPLTELHLSRNEGVAITYAAAVLF
	*****
sp B6V8E6 CTNB1_CANLF	RMSEDKPQDYKKRLSVELTSSLFRTEPMAWNETADLGLDIGAQGEPLGYRQDDPSYRSFH
sp P35222 CTNB1_HUMAN	RMSEDKPQDYKKRLSVELTSSLFRTEPMAWNETADLGLDIGAQGEPLGYRQDDPSYRSFH
	*****
sp B6V8E6 CTNB1_CANLF	SGGYGQDALGMDPMMEHEMGHHPGADYPVDGLPDLGHAQDLMDGLPPGDSNQLAWFDTD
sp P35222 CTNB1_HUMAN	SGGYGQDALGMDPMMEHEMGHHPGADYPVDGLPDLGHAQDLMDGLPPGDSNQLAWFDTD
	*****
sp B6V8E6 CTNB1_CANLF	L
sp P35222 CTNB1_HUMAN	L
	*

**Figure S2B.** The protein alignment indicates that except for a T60S change, canine  $\beta$ -catenin is identical to human  $\beta$ -catenin. Related to Figure 2.

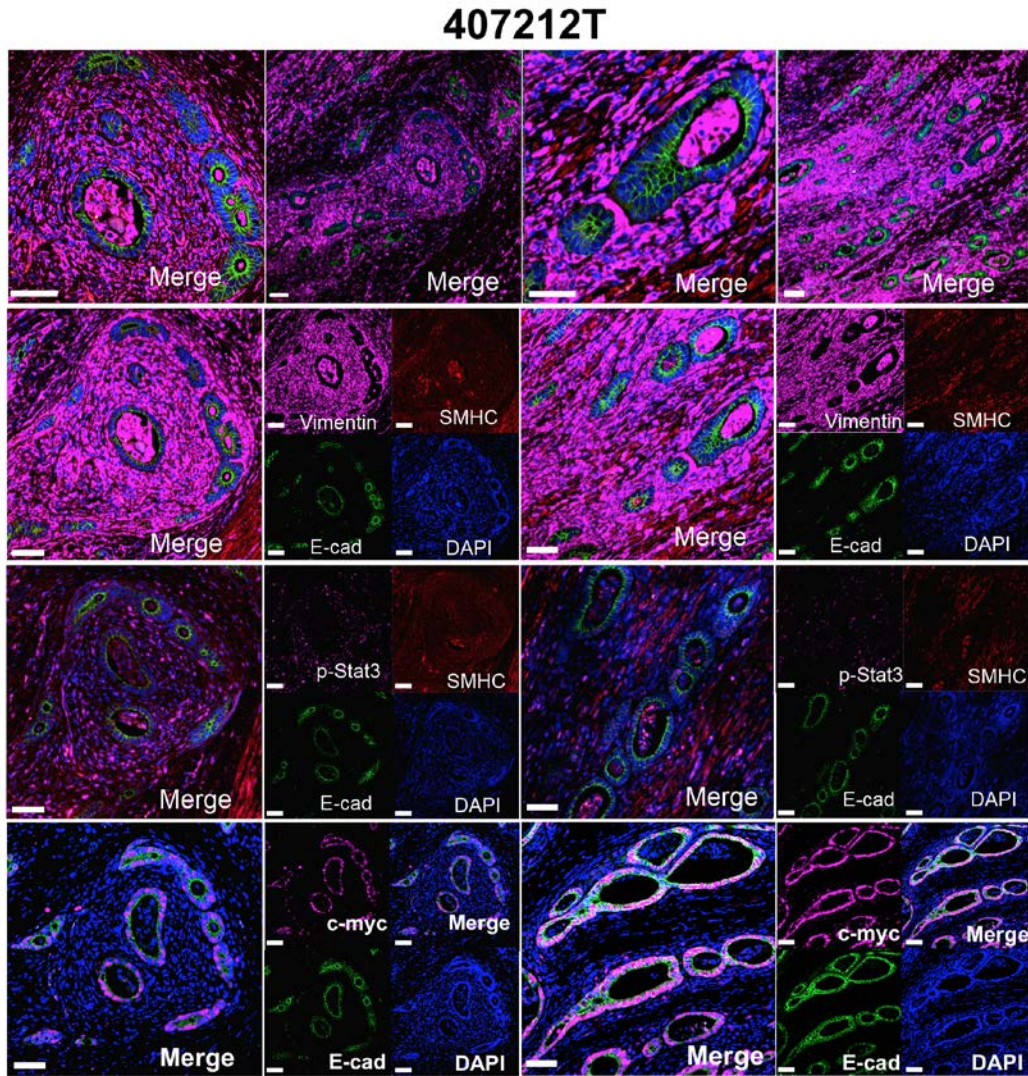


**Figure S2C.** The N-terminal phosphorylated peptide of  $\beta$ -catenin binds  $\beta$ -TrCP1 via hydrogen bonds and electrostatic interactions, based on a published human crystal structure (33). Related to Figure 2.

**Figure S3A.** Heatmaps indicate differential expression of signature genes for tumor microenvironment and for epithelial and mesenchymal features between proliferative and invasive tumors. Related to Figure 3.

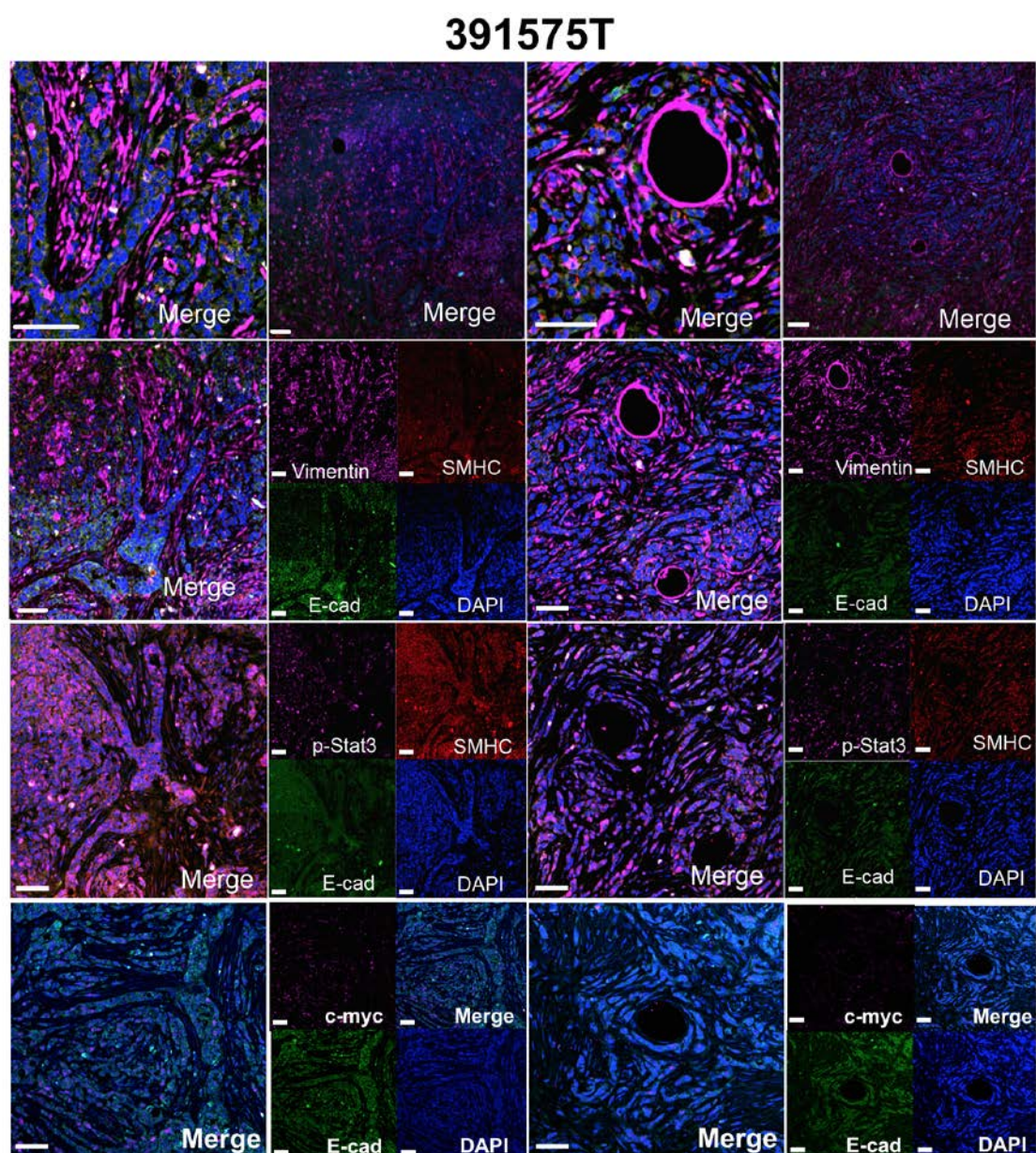


**Figure S3B.** GSEA p-values of under- or over-enrichment of signature genes for tumor microenvironment between proliferative and invasive canine tumors. Related to Figure 3.

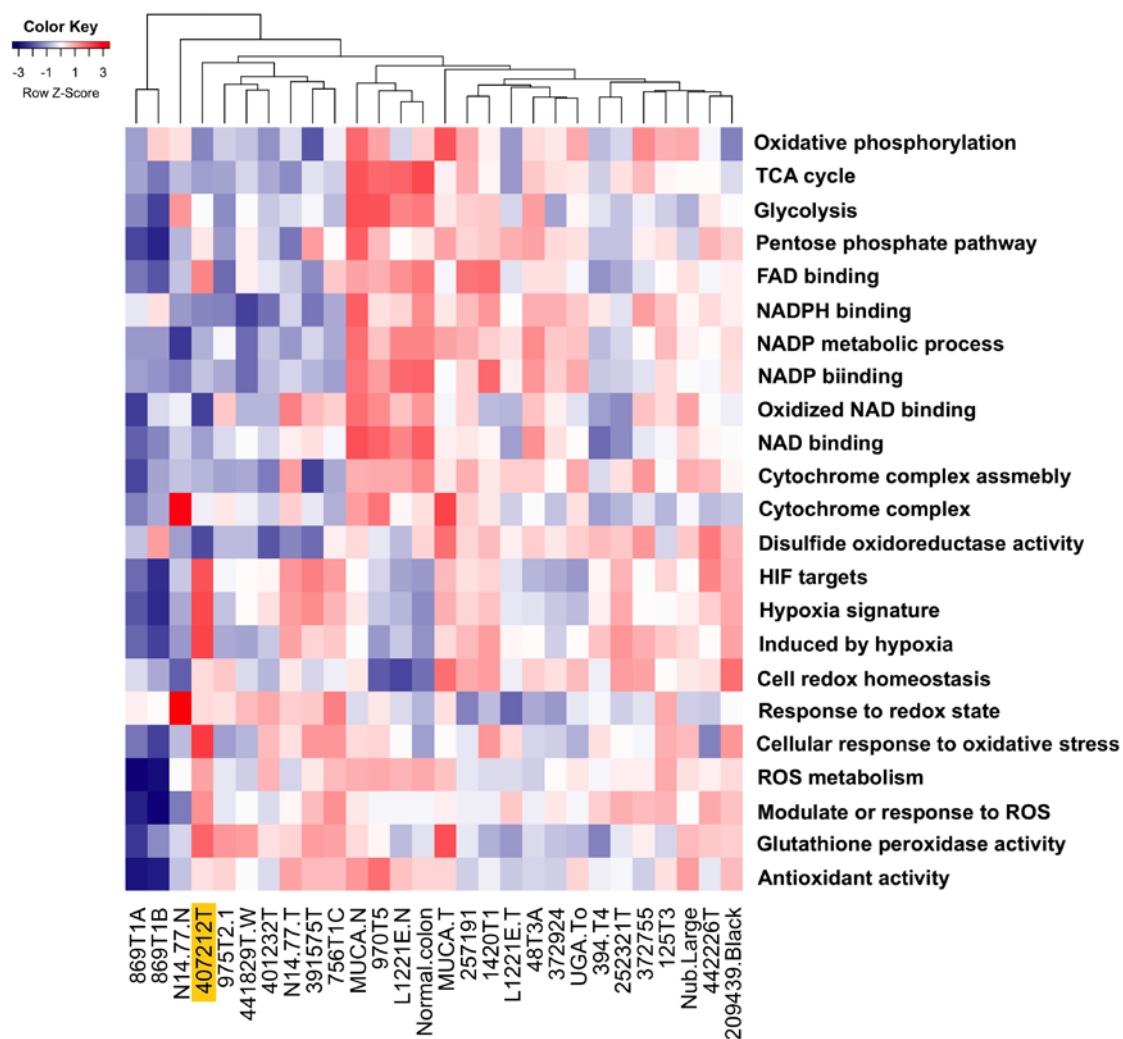


**Figure S3C-1.** Crypt-like invasion: with indicated marker staining. Related to Figure 3.

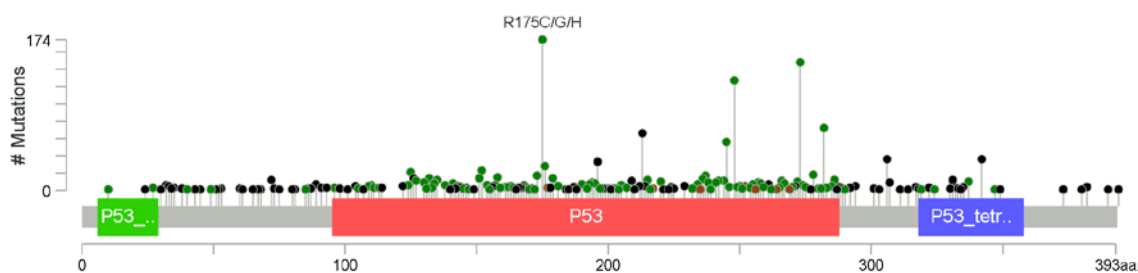




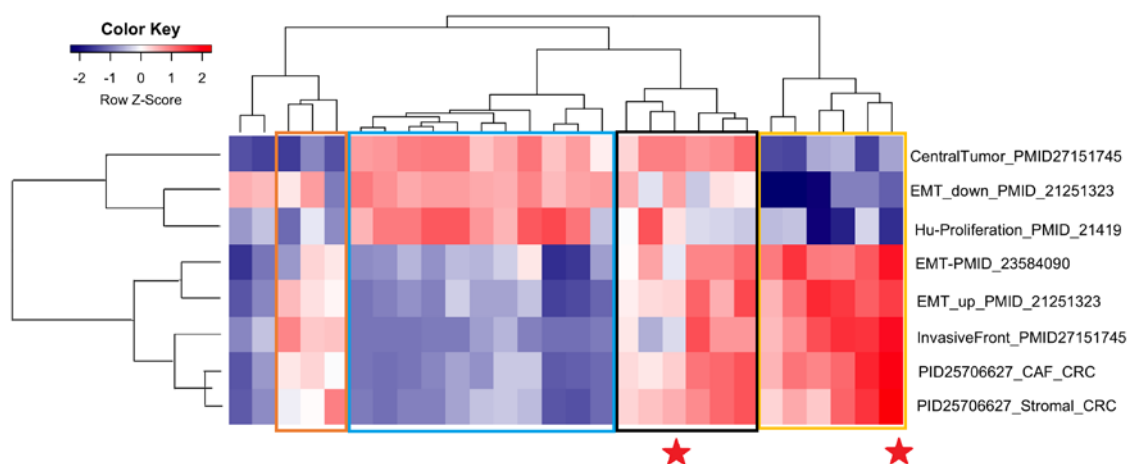
**Figure S3C-2.** EMT invasion: with indicated marker staining. Related to Figure 3.



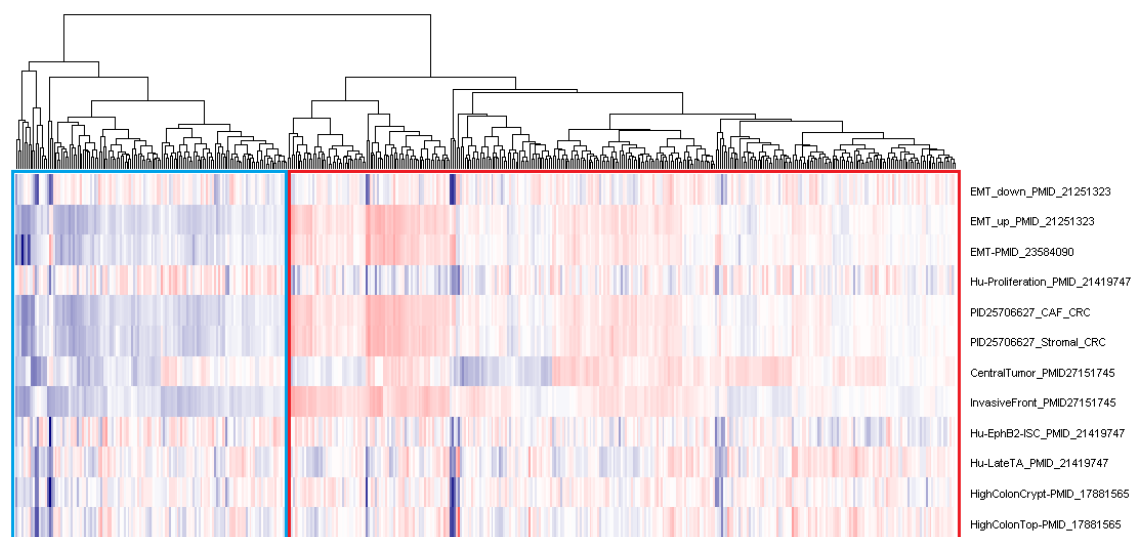
**Figure S3D.** Crypt-like invasion, as exemplified by the tumor highlighted in yellow, harbor activated signatures of hypoxia and cellular response to oxidative stress. Related to Figure 3.



**Figure S4.** TP53 mutations in human CRCs from TCGA. The data are downloaded from the cBioportal cancer genome database (<http://www.cbioportal.org/>). Related to Figure 5.

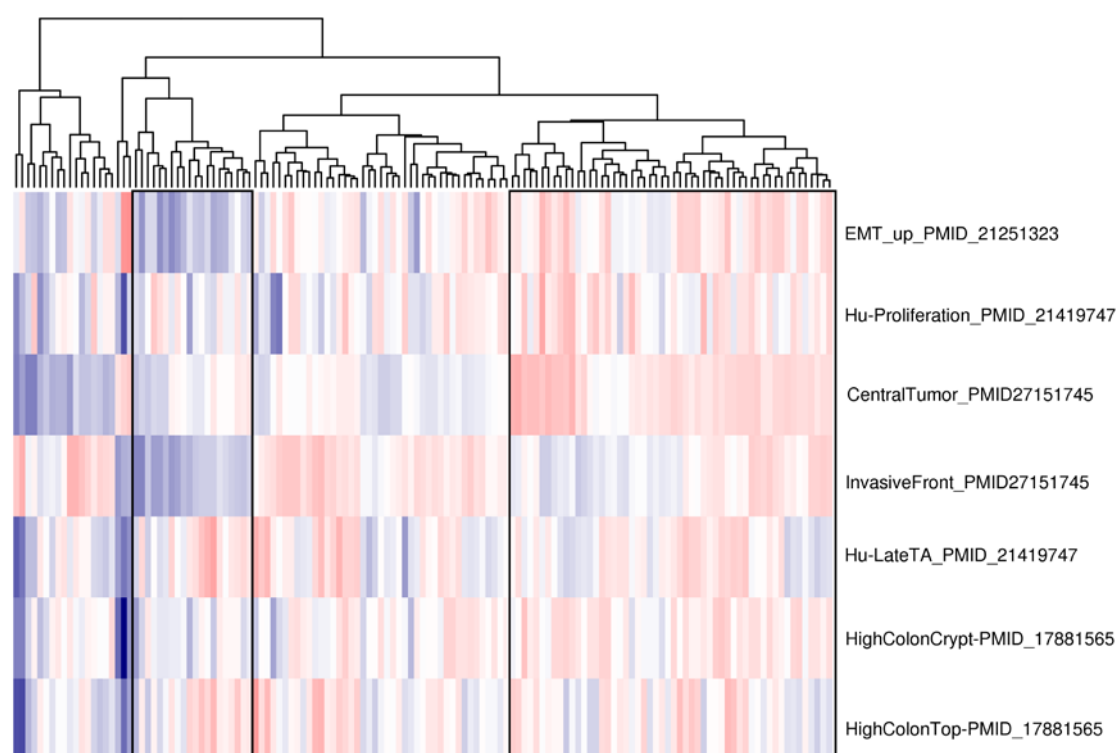


**Figure S5A.** Canine samples are clustered into five groups/subtypes: normal colon tissues (left), collective invasion (enclosed in orange box), proliferative (in blue box), crypt-like (in black box), EMT or stromal subtype (in yellow box), based on ssGSEA enrichment scores of published human CRC signatures shown. Red stars indicate the canine tumors that exemplify crypt-like invasion (left) and EMT invasion (right).

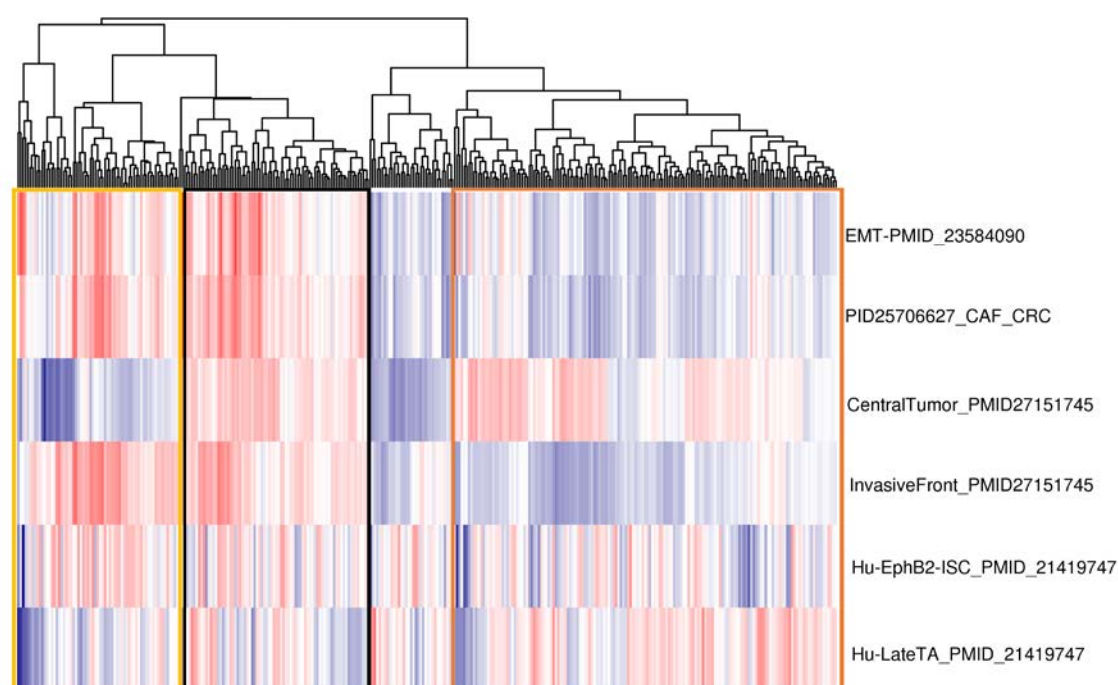


**Figure S5B-1.** Heatmap indicates that 478 human colon cancers of TCGA are clustered into two groups, proliferative (left, enclosed in blue box) and invasive (right, enclosed in red box), based on the ssGSEA enrichment scores of the 12 signatures indicated.

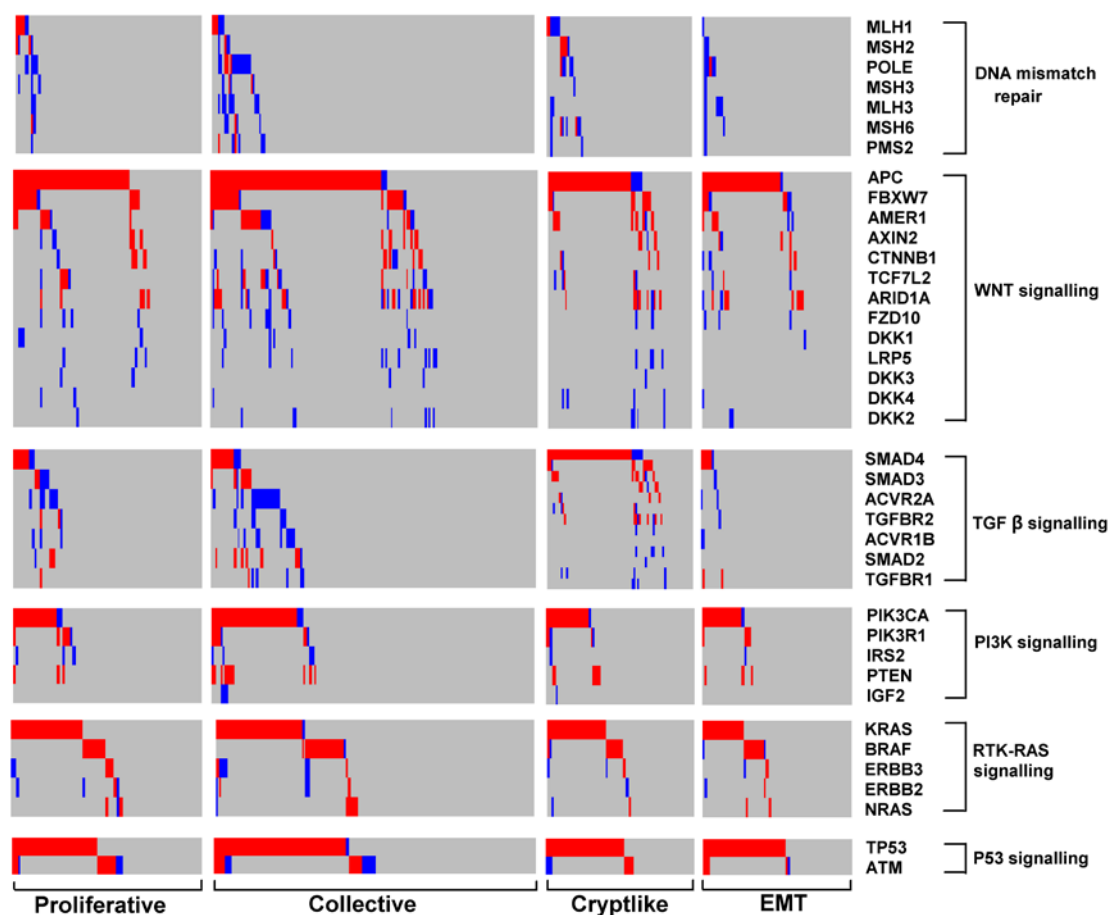




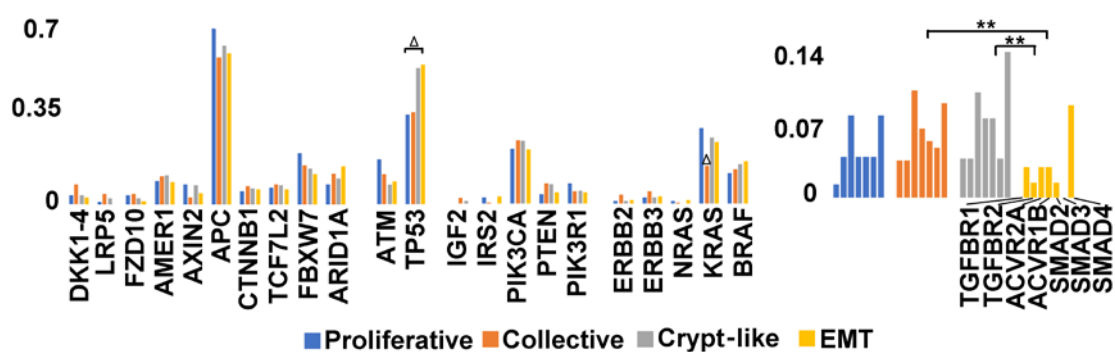
**Figure S5B-2.** Proliferative human colon cancers, enclosed in blue box in Figure S5B-1, are further clustered based on 7 signatures, selected based on ssGSEA enrichment score distributions among the samples. Clusters that are 1) enriched in central tumor and proliferation signatures and 2) depleted in invasive front signature, enclosed in black boxes, are classified as the primarily proliferative subtype shown in Figure 6A.



**Figure S5B-3.** Invasive human colon cancers, enclosed in red box in Figure S5B-1, are further clustered based on 6 signatures, selected based on ssGSEA enrichment score distributions among the samples. Three clusters are identified, including EMT (left, in yellow box), crypt-like (middle, in black box), and collective (right, in orange box).



**Figure S5C-1.** Somatic driver (red) and passenger (blue) mutations of canonical pathway genes of human colon cancers of TCGA. Each column represents a tumor sample and each row represents a gene as shown. The data are from the cBioportal and detailed in Supplementary Table S6C-1.



**Figure S5C-2.** The sample mutation rate of each gene in each human subtype shown in Figures 6C and S5C-1. The data are from the TCGA and detailed in Supplementary Table S6C-2.

