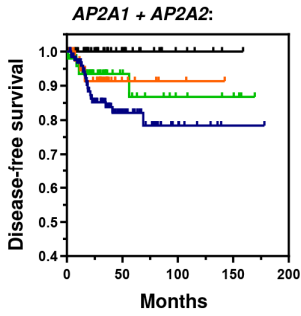


SUPPLEMENTARY FIGURE S6

A BRAF-like ($n = 260$)



■ Low/ Low ($n = 44$)
■ Low/ High ($n = 40, P = NS$)
■ High/ Low ($n = 50, P = NS$)
■ High/ High ($n = 126, P = 0.0084$)

B THCA: BRAF-like RAI-treated ($n = 137$)

Gene #1	Gene #2	Expression Group				Disease-Free Survival (L/L vs H/H)		Frequency of Recurrence (L/L vs H/H)	
		Low/Low		High/High		P	q	P	q
		N_{tot}	N_{rec}	N_{tot}	N_{rec}				
AP2A1	AP2A2	29	0	62	15	0.006	0.038	0.002	0.013
AP2A1	AP2B1	31	1	51	11	0.034	0.071	0.026	0.055
AP2A1	AP2M1	34	2	42	5	0.411	0.432	0.450	0.473
AP2A1	AP2S1	23	2	55	8	0.619	0.557	0.714	0.643
AP2A2	AP2B1	31	2	39	12	0.020	0.063	0.015	0.047
AP2A2	AP2M1	42	1	38	4	0.151	0.238	0.185	0.291
AP2A2	AP2S1	32	2	54	8	0.260	0.328	0.310	0.391

C TCGA: Differential Expression - AP2A2 (High vs Low) $n = 859$ genes ($q < 0.001$; Supp Fig. S6D)

Pathway Analysis (DAVID, TOPPgene)

$n = 72$ endocytic genes (Supp Fig. S6E and S6F)

14 NIS Interactors (Fig. 1A)

67 Endocytic accessory genes (Bhave *et al.*, PNAS 2020)

$n = 137$ unique genes (Fig. 3F, \log_2FC (C vs N))

Assess clinical relevance (Supp Fig. S7)

ROC analysis ($AUC > 0.575$ or < 0.425)

Kaplan-Meier analysis

Univariate Cox regression analysis

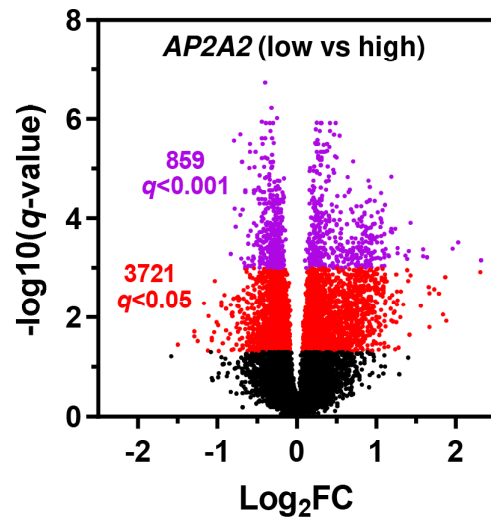
Determine prognostic utility (Supp Fig. S8 and S9; Table 1)

Hierarchical cluster analysis

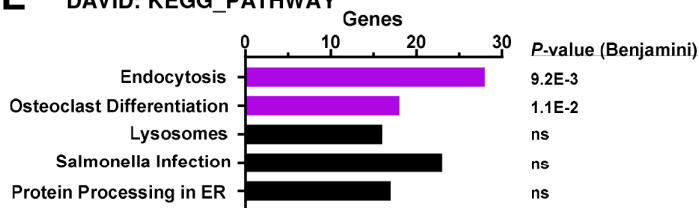
Risk score analysis

Multivariate Cox regression analysis

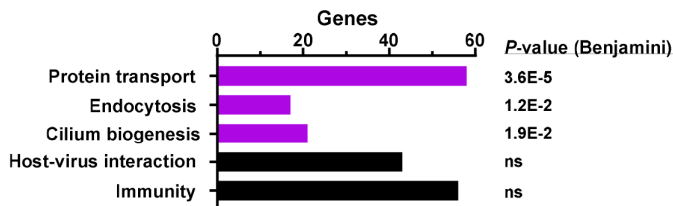
D THCA: BRAF-like RAI-treated ($n = 137$)



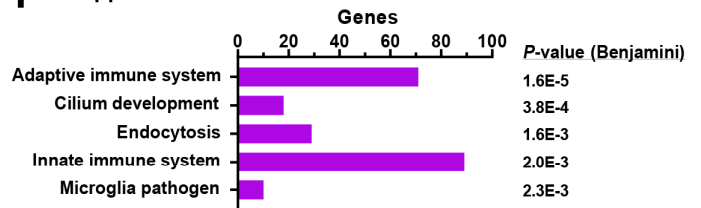
E DAVID: KEGG_PATHWAY



DAVID: BIOLOGICAL PROCESS



F ToppGene: PATHWAY



ToppGene: GO BIOLOGICAL PROCESS

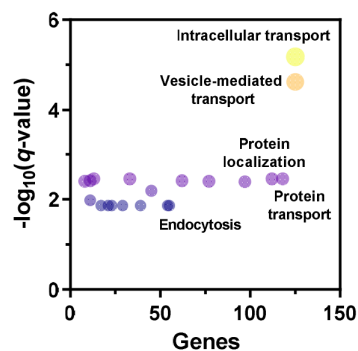


Figure S6. Identification of endocytic gene biomarkers for recurrence. **A**, Representative Kaplan-Meier analysis of DFS for the BRAF-like THCA cohort stratified on high vs low tumoral expression of *AP2A1* and *AP2A2*; log-rank test. Number (*n*) of patients per sub-group (high/low) and *P*-values are shown. **B**, Kaplan-Meier analysis of the BRAF-like, RAI-treated THCA cohort stratified on high (H/H) versus low (L/L) tumoral expression of either *AP2A1* or *AP2A2* combined with other AP2 genes; log-rank test. Number (N_{tot}) of patients and recurrent cases (N_{rec}) in each stratified group are shown, as well as *P*- and *q*-values. Fisher's exact test used to determine significance for incidence of recurrence between groups with high (H/H) vs low (L/L) tumoural gene expression. **C**, Bioinformatic pipeline used to filter and identify potential clinical biomarkers of PTC recurrence. **D**, Volcano plot comparing $\log_2\text{FC}$ with *q*-value ($-\log$ base 10) for the BRAF-like, RAI-treated THCA dataset [high vs low *AP2A2* expression; $n = 137$]. Top 859 genes ($q < 0.001$; purple spots) were filtered based on functional classification. **E**, DAVID functional classification of top 859 differentially expressed genes as described in **D**. KEGG pathway (*upper*) and biological process (*lower*) categories of greatest significance ($P < 0.05$ or lower, purple bars; ns, not significant, black bars) and number of genes per category are indicated. **F**, Same as **E** but ToppGene used to classify the top 859 differentially expressed genes ($q < 0.001$).