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Research article

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Posted Date: September 30th, 2019

DOI: <https://doi.org/10.21203/rs.2.15589/v1>

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Version of Record: A version of this preprint was published at Journal of Clinical Medicine on February 3rd, 2020. See the published version at <https://doi.org/10.3390/jcm9020411>.

Title: Opposite roles of BAP1 in overall survival of uveal melanoma and cutaneous melanoma

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Running title: BAP1 in CM and UM

Abstract

Background: BAP1 germline mutations predispose individuals to a number of cancer types including uveal melanoma (UM) and cutaneous melanoma (CM) which are distinctively different in the oncogenic pathways. BAP1 loss was common in UM and was associated with a worse prognosis. BAP1 loss was rare in CM and the outcome was unclear. **Methods:** This study used TCGA UM and CM databases for survival analysis for patients with different BAP1 status and mRNA expression levels. Cox regression model was used for adjusting to known prognosis factors. **Results:** BAP1- (loss or low expression) predicted a poor overall survival in UM (Cox HR = 0.062, logrank $p = 0.007$) but a contrasting better overall survival in CM (HR = 1.69, $p = 0.009$). Multi-covariate Cox regression analysis indicated BAP1 was a significant predictor for overall survival after adjusting for age of diagnosis, presence of ulceration, Breslow depth and CM stages in patients older than 50 years but not in younger patients. Co-expression analysis revealed no shared genes in BAP1 altered UM and CM tumors, further supporting a completely distinctive role of BAP1 in CM and UM. **Conclusions:** low BAP1 mRNA was significantly associated with a better overall survival in CM patients, in sharp contrast to its tumor suppressor role in UM where low or loss of BAP1 indicated a worse overall survival. Function of BAP1 may be dependent on cellular context.

Keywords: Uveal Melanoma, Cutaneous Melanoma, BAP1, overall survival, age difference, YAF2, SF3B1

Background

Germline mutation in BAP1 (BRCA1-Associated Protein 1) is associated with multiple types of hereditary cancer [1], which is now classified as BAP1-TPDS (BAP1 Tumor Predisposition Syndrome) [2]. The susceptible cancer types include malignant mesothelioma [3], lung adenocarcinoma, meningioma [1], gallbladder cancer [4], renal cell carcinomas [5], cutaneous melanoma [6] and uveal melanoma [1, 7], as well as myelodysplastic syndrome [8]. The BAP1 mutations are generally deletions or loss-of-function, thus BAP1 was defined as a tumor suppressor gene [8]. Overall the germline mutations in BAP1 is rare in CM (<1% of tumors carry BAP1 germline mutations) [9] but common in UM (up to 45%) [10]. Additionally, tumor characteristics the BAP1-TPDS-associated CM are quite unique, exhibiting distinct morphology and histology which are similar to Atypical Spitz Tumors [2], and substantially different from common CM sub-types.

BAP1 is a deubiquitinase that inhibits cell growth in Hela cells and breast cancer cells [11, 12], and promotes DNA damage-associated apoptosis thus reduces cellular transformation [13]. Loss of BAP1 in uveal melanoma cells did not impact cell proliferation or tumorigenesis; rather, loss of BAP1 led to dedifferentiation accompanied by increased stem-like biomarkers [14]. In cutaneous melanoma cell lines, however, stable over-expression of BAP1 promoted cell growth while knockdown of BAP1 suppressed cell proliferation with concomitant decrease of survivin [15]. Therefore, the role of BAP1 in cell growth and tumorigenesis seems to be context-dependent.

BAP1 mutations are associated with worse prognosis and survival in UM patients due to increased metastasis potentials [10, 16]. A meta-analysis of various cancer types with BAP1 mutations indicated that BAP1 mutations were also associated with worse outcome in renal cell carcinoma but not in other cancers [17]. High BAP1 mRNA expression levels were reported to be associated with a better survival in a cohort of primary CM patients [15], which is consistent with BAP1 function as a tumor suppressor in CM, but the author stated that BAP1 level was perhaps confounded by other prognosis factors such as ulceration and Breslow depth in that study [15].

Methods

This is a secondary data analysis based on TCGA (the Cancer Genome Atlas) sequencing and patient information. Mutation counts, copy number variation, mRNA expression information and patients characteristics were retrieved from TCGA data portal (cbioportal.org). A total of 471 CM patients and 80 UM patients were included for analysis. Patient and tumor characteristics in UM were not available but those for CM included tumor stage (AJCC), presence or absence of ulceration, Breslow depth, age

and sex of patients, which were used in multivariate Cox regression analysis. All statistical analysis was performed using Stata (IC 13.1) software. Survival analysis was analyzed using Kaplan-Meier method; influence of BAP1 status or expression levels were analyzed by Cox single variate regression model. Influence of other prognostic factors were analyzed using multi-variate Cox model.

Results

Low BAP1 mRNA or loss of BAP1 indicated significant worse survival in UM patients

The TCGA (The Cancer Genome Atlas) CM and UM patient information (level 1 raw data), mRNA expression data, mutations (single nucleotide changes or small insertion/deletions) and copy number variations (SNV) in each tumor (level 3 processed data) were retrieved from TCGA data portal (cBioportal.org) [18, 19]. Z scores based on the mean expression of all samples were used for mRNA expression indicators. Data analysis were performed primarily using Stata software or the cBioportal-embedded analysis tools. As shown in Figure 1a, the UM patients with the bottom 30% of BAP1 mRNA expression (N=24, Z score ≤ -2.291) showed significant worse overall survival as compared to those with the top 30% BAP1 mRNA expression levels (Figure 1A), with Cox hazard ratio HR of 0.062, 95% confidence interval (CI) at 0.008, 0.473, and p value of 0.007. These results were consistent with the role of BAP1 as a tumor suppressor for UM [10].

The BAP1 mRNA was not completely correlated with BAP1 mutation status in UM tumors. Among the 80 UM tumors, 13 carried a BAP1 mutation, with most mutations as loss-of-function type, including frame-shift and non-sense mutations (gain of a stop codon). In the TCGA UM cohort, BAP1 mutation status was not associated with overall survival (N=13, HR=0.89, 95% CI 0.30, 2.64, logrank p = 0.54). When these BAP1 mutations were grouped with low mRNA expression cohort (N= 30) and compared to the rest of the cohort (N=50), the results of overall survival remained similar to the cohort with low BAP1 mRNA expression, with HR of 0.232 (95% confidence interval: 0.094, 0.575, p =0.0009) (Figure 1B). Therefore, in the rest of this report we group the UM with low BAP1 mRNA expression and/or BAP1 mutation as BAP1- group, and the rest as BAP1+ group.

Monosomy 3 was a driver cause for uveal melanoma which led to BAP1 hemizygous deletion [16, 20]. In TCGA UM cohort the hemizygous deletion status in BAP1 locus was correlated with BAP1 mRNA expression levels, with significant difference in the mean Z scores for mRNA expression in the hemizygous deletion group (N= 44) versus the rest of patients (Table 1, p<0.0001). Consequently, the overall survival was also significantly worse in the patients with BAP1 hemizygous deletion (HR =0.08, p = 0.001). Homozygous deletion was not found in UM tumors. Taken together, this data set indicated that

BAP1 status was significantly associated with overall survival in UM, with loss of BAP1 (or low BAP1 mRNA levels) indicating poor survival, consistent with previous reports [21, 22]. No multiple covariate analysis was performed as gender, age and stage information was not available for UM patients [20].

Low BAP1 mRNA indicated a significant better survival in CM patients

In contrast to the observations in the UM patient cohort, CM patients with bottom 30% of Z scores (BAP1-low) in BAP1 mRNA expression showed significant better overall survival as compared to patients with the top 30% Z scores (BAP1-high) Cox Hazard Ratio = 1.69, 95% confidence interval 1.14, 2.51, $p = 0.009$), thus suggesting that low expression of BAP1 indicated a better overall survival in CM (Figure 1C). When the patients were stratified into 2 groups based on the BAP1 mRNA Z score (top and bottom 50%), again BAP1-low patients survived significantly longer than BAP1-high group (HR=1.46, 95%CI, 1.11, 1.91, logrank $p = 0.006$). Copy number variations (76 hemizygous deletion and 68 amplification) was not associated with overall survival in CM (Figure 1D). Eleven tumors carried BAP1 mutation, with 4 silent synonymous mutations and 7 missense mutations with unknown significance (I643T, E30K, P629S, R417M, S143N (N=2), L416F and R59W). It was not surprising that these mutations were not associated with overall survival in CM (HR=0.58, $p=0.36$). Therefore, low expression of BAP1 mRNA actually indicated a better overall survival in CM patients, opposite to that in UM patients, and suggesting a tumor-promoting role of BAP1 in CM, rather than a tumor suppressor role as in UM.

Multivariate Cox regression in CM patients

In order to examine whether BAP1 expression levels were confounded by other prognostic factors, multivariate Cox regressions were performed, first with gender and age of diagnosis. In this model adjusted for gender and age of diagnosis, BAP1 mRNA (grouped by top and bottom 50% Z scores) showed borderline significance in patient survival (HR = 1.31, $p = 0.056$). Gender did not play a significant role in survival ($p=0.53$) but age of diagnosis did ($p<0.001$) in this three-variable model. Therefore, patients were stratified by age of diagnosis (≤ 50 and >50 years) for Cox analysis. BAP1 level was not significantly associated with overall survival in the younger age group but was significantly associated with overall survival in the older age group, even after adjusting for age of diagnosis within the strata (HR = 1.42, 95% CI 1.02, 1.98, $p = 0.04$).

When additional prognosis factors (presence of ulceration, Breslow depth, AJCC stages – stage 0-II was grouped as early stage and stage III-IV was grouped as late stage) were included in the Cox model together with age of diagnosis, BAP1 mRNA level did not predict survival (HR= 1.31, $p=0.124$), but age

of diagnosis ($p=0.02$), ulceration ($p=0.004$), Breslow depth ($p = 0.04$) and stage ($p<0.001$) all were significantly associated with survival. However, when the patients were stratified by age of diagnosis, BAP1 mRNA level showed significant predicative value in the all-adjusted model ($HR = 1.59$, 95% CI 1.04, 2.44, $p= 0.032$) in the older group (>50 years), but not in the younger group ($HR=0.77$, $p=0.49$). Therefore, BAP1 mRNA showed good predicative values only in the older patients after adjusting for ulceration, age of diagnosis, Breslow depth and stage of disease.

Low BAP1 mRNA levels were associated with high mutation burden in CM

BAP1 mRNA levels were not significantly associated with Breslow depth, ulceration or stage of CM as analyzed by either Student t-test or a linear regression model (data not shown). As BAP1 was suggested to play a role in DNA damage response [13], the mutation counts were compared in the BAP1-low and BAP1-high CM tumors (30% cut-off). The mean mutation counts in BAP1-low and -high group was 409.6 ($N=114$) and 564.1 ($N=101$), respectively, with a one-sided p value of 0.047, suggesting that a higher BAP1 mRNA is perhaps associated with higher mutation burden in tumors. Further analysis revealed that higher (30% or 50% cut-off) mutation burden was indeed associated with a better overall survival as compared to the cohort with lower mutation burden (for 50% cut-off: $HR=0.62$, 95% CI 0.48, 0.81, $p <0.001$). In order to determine whether mutation burden plays a confounding role in BAP1-associated overall survival, Cox analysis was performed in low and high mutation burden cohort (50% cut off). Low BAP1 mRNA levels were significantly or borderline significantly associated with better overall survival in patients with low mutation burden ($HR=1.68$, $p=0.048$) and high mutation burden ($HR=1.54$, $p=0.078$), respectively. The trend is similar in the two strata with similar hazard ratios; therefore, the tumor burden is perhaps not a confounding factor for BAP1 role in overall survival.

BAP1- status is associated with SF3B1 mutations in UM

Enriched gene mutations were investigated in UM cohort with BAP- and BAP+ groups using the cBioportal-embedded “enrichments” analysis tools and selected patient identifiers. Mutation rates of UM oncogenes GNAQ and GNA11 were similar in BAP1 mutation/low tumors as compared to the rest of tumors (data not shown). Two genes, SF3B1 and EIF1AX, exhibited significant exclusivity with BAP1- in UM ($p =0.042$, and 0.025, respectively), which was consistent with previous reports [10, 22], and supported classification of UM in three sub-types by mutations in 3 genes: BAP1, SF3B1 and EIF1AX [22]. SF3B1 copy number variation was not common in the UM cohort, with 1 homozygous deletion, and 8 hemizygous amplification out of the 80 tumors. SF3B1 mRNA levels were not associated with overall survival ($HR = 1.29$, $p=0.66$, bottom 30% vs. top 30%); but SF3B1 mutation alone or mutation plus amplification indicated better overall survival (supplemental Figure S1). This outcome was perhaps

due to the presence of SF3B1 mutation/amplification exclusively in the BAP+ group. Neither EIF1AX mRNA levels nor the mutation status (N=10) was associated with UM overall survival.

Differential molecular networks of the BAP1 in CM and UM

Next, in order to understand the potential mechanism of BAP1 function in UM and CM, differential molecular networks of the BAP1 in each tumor were analyzed using the cBioportal-embedded MEMo software [23]. In CM patients with a Z score cut off at ± 2.0 , 33 (9.0%) tumors showed high mRNA levels. The top 10 co-expressed genes in the 33 BAP1-high tumors are listed in Table 2. YAF2 (YY1-associated factor 2) and GPATCH3 (G-patch domain containing 3) exhibited the highest negative and positive correlations with high BAP1 mRNA levels, respectively (Figure 2A and 2B), as reflected by the highest Spearman's correlation coefficient (-0.55 and 0.49, respectively), and significant p values and false discovery q values (Table 2). YAF2 or GPATCH3 alone did not predict survival. A total of 65 genes showed Spearman's coefficient of 0.45 or greater with significant p values and false discovery rates (Table S1), with genes on chromosome 3 excluded as they are likely linked with BAP1.

In UM patients, a total of 2238 genes showed significant co-expression with BAP1 status using the same screen standards as in CM (Table S2 shows the top 65 genes). None of these genes over-lapped with the BAP1 co-expressed genes in CM. HTR2B (5-Hydroxytryptamine Receptor 2B, or Serotonin Receptor 2B) and FBXO17 (F-Box Protein 17) ranked top negatively and positively correlated genes with BAP1-status (Figure 2C and 2D, Table 2). Neither of these two genes predicted survival.

Discussion

This study described opposite roles of BAP1 in survival of two types of melanoma patients. The worse outcome of BAP1- (loss or low mRNA expression) was validated in UM, while a new discovery of low BAP1 indicating a better overall survival in CM patients was described. Furthermore, low BAP1 mRNA seemed to be an important predictor for CM patients of older age (>50 years) but did not predict survival for younger patients. The age-differentiated BAP1 role in CM survival is different than that in UM where loss of BAP1 predicted worse outcome in patients of all age [16]. UM and CM diagnosis was usually at younger age in the BAP1-TPDS group as compared to the general population [24-26], but UM tumors carrying germline mutations required a longer time to progress to metastasis than those carrying somatic mutations [24].

These results are consistent with the cellular role of BAP1 in CM cell lines A375 and C918 where depletion of BAP1 expression led to inhibition of cell growth [15], but were different with the survival

outcome in the same Kumar et. al study [15]. The difference may be because CM cases were all primary tumors in the Kumar et. al study but the TCGA contained a whole spectrum of tumor stages.

Molecular network analysis revealed that BAP1 was associated with completely different molecular profiles in CM and UM. Although both melanomas produce melanin, their oncogenic pathways and mutation spectra are different. The primary oncogenic mutations in UM are GNAQ and GNA11 while that in CM are BRAF and NRAS. Nevertheless, BAP1 status was not associated with none of these oncogenes in either tumors (data not shown). Further understanding of BAP1 network regulation in these melanomas may provide opportunities for future therapy.

Conclusion

BAP1 plays distinctively different roles in the overall survival of UM and CM patients. It is a new finding that low BAP1 mRNA levels were significantly associated with a better overall survival in CM patients, especially in older patients. These results may reflect how distinct oncogenic signals impact BAP1 function in these two types of melanomas. Further investigation on cell context and oncogene-dependent function of BAP1 may provide molecular explanations of the observed epidemiological data.

List of abbreviations

BAP1, BRCA-associated Protein 1

UM, Uveal melanoma

CM, cutaneous melanoma

TCGA, the Cancer Genome Atlas

HR, Hazard ratio

95% CI, 95% confidence interval

Declarations**Ethics approval and consent to participate:**

As all data were de-identified, an exempt IRB review was approved by University of California Irvine Office of Research. The original written consent to participate were obtained by the original researchers and described in the TCGA database.

Consent for publication: yes

Availability of data and materials: all data are publicly available

Competing interests: none

Funding: The author is supported by MRA young investigator award (#509278) and an anti-cancer pilot award from Chao Family Comprehensive Cancer Center at UCI.

Authors' contributions: single author, from conceiving the idea to extract and process data to analysis and writing, and editing.

Acknowledgements

Liu-Smith is supported by an MRA young investigator award (#509278) and an anti-cancer pilot award from Chao Family Comprehensive Cancer Center, UCI.

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Figure legends

Figure 1. Kaplan-Meier survival curves in UM and CM. A and C, survival curves of patients with BAP1-low vs. BAP1-high (mRNA level, bottom 30% vs top 30%) tumors. A, UM, C, CM. B, survival curves of BAP1- vs BAP1+ tumors in UM. BAP1- includes tumors with bottom 30% mRNA or with BAP1 mutations. These two categories contained all BAP1 hemizygous deletion tumors in UM. D, survival curves of CM patients with various BAP1 copy number variations.

Figure 2. Top BAP1 co-expressed genes in UM and CM. CM tumors were grouped by median mRNA Z scores (± 2.0) and screened for BAP1 co-expressed genes. YAF2 and GPATCH3 showed negative and positive correlation with high BAP1 mRNA expression in CM (A and B). Similarly, HTR2B and FBXO17 showed negative and positive correlation in UM tumors grouped by BAP status (low mRNA or mutation) (C and D). RSEM, RNA abundance calculated by RSEM (RNA-Seq by Expectation Maximization) algorithm.

Table 1, mean mRNA Z scores in BAP1 hemizygous deletion and BAP1 2N tumors

BAP1 status	# patients	mean Z score (mRNA)	standard error	95% CI	
Hemizygous deletion	44	-2.199	0.109	-2.418	-1.979
Normal 2N	36	-0.064	0.162	-0.335	0.322
p<0.0001					

Table 2: co-expressed genes with BAP1 in CM and UM

	Gene	Approved Name	cytoband	spearman's correlation	pvalue	qvalue
CM	YAF2	YY1 associated factor 2	12q12	-0.545	1.4E-37	1.2E-34
	C12ORF4	chromosome 12 open reading frame 4	12p13.32	-0.529	4.3E-35	3.1E-32
	UBXN4	UBX domain protein 4	2q21.3	-0.524	2.4E-34	1.6E-31
	PPP1R12A	protein phosphatase 1 regulatory subunit 12A	12q21.2-q	-0.505	1.2E-31	6.4E-29
	TANK	TRAF family member associated NFKB activator	2q24.2	-0.503	2.3E-31	1.2E-28
	USP15	ubiquitin specific peptidase 15	12q14.1	-0.499	7.8E-31	3.8E-28
	FAS	Fas cell surface death receptor	10q23.31	-0.498	9.9E-31	4.8E-28
	GPATCH3	G-patch domain containing 3	1p36.11	0.494	3.7E-30	1.7E-27
	THAP1	THAP domain containing 1	8p11.21	-0.491	8E-30	3.6E-27
	RPAP3	RNA Polymerase II Associated Protein 3	12q13.11	-0.490	1.10E-29	4.9E-27
UM						
	HTR2B	5-hydroxytryptamine receptor 2B	2q37.1	-0.785	4.7E-17	5.7E-14
	FBXO17	F-box protein 17	19q13.2	0.775	2.1E-16	1.8E-13
	ACSF2	acyl-CoA synthetase family member 2	17q21.33	0.774	2.5E-16	2E-13
	PXDC1	PX domain containing 1	6p25.2	0.770	4.2E-16	2.8E-13
	LIMS2	LIM zinc finger domain containing 2	2q14.3	0.767	6.7E-16	4E-13
	PCBD2	pterin-4 alpha-carbinolamine dehydratase 2	5q31.1	-0.765	9.1E-16	4.7E-13
	HSPA1L	heat shock protein family A (Hsp70) member 1 like	6p21.33	0.763	1.1E-15	5.4E-13
	PPM1K	protein phosphatase, Mg ²⁺ /Mn ²⁺ dependent 1K	4q22.1	-0.761	1.5E-15	6.5E-13
	GTF2H4	general transcription factor IIH subunit 4	6p21.33	0.760	1.8E-15	7.4E-13
	PHYHD1	phytanoyl-CoA dioxygenase domain containing 1	9q34.11	0.757	2.5E-15	1E-12

A.

C.

B.

D.

Liu-Smith, Figure 1

Liu-Smith, Figure 2

Table S1, co-expressed genes with BAP1 in CM

Gene	cytoband	Spearman's correlation	pvalue	qvalue
YAF2	12q12	-0.545	1.40E-37	1.20E-34
C12ORF4	12p13.32	-0.529	4.30E-35	3.10E-32
UBXN4	2q21.3	-0.524	2.40E-34	1.60E-31
PPP1R12A	12q21.2-q21.31	-0.505	1.20E-31	6.40E-29
TANK	2q24.2	-0.503	2.30E-31	1.20E-28
ABCF3	3q27.1	0.502	2.90E-31	1.50E-28
USP15	12q14.1	-0.499	7.80E-31	3.80E-28
FAS	10q23.31	-0.498	9.90E-31	4.80E-28
GPATCH3	1p36.11	0.494	3.70E-30	1.70E-27
THAP1	8p11.21	-0.491	8.00E-30	3.60E-27
RPAP3	12q13.11	-0.490	1.10E-29	4.90E-27
RAP1B	12q15	-0.490	1.30E-29	5.50E-27
CAB39	2q37.1	-0.488	2.00E-29	8.20E-27
TOP1P1	1q24.3	-0.486	4.70E-29	1.90E-26
JAK2	9p24.1	-0.484	6.70E-29	2.60E-26
ASF1A	6q22.31	-0.484	7.00E-29	2.60E-26
SCAF11	12q12	-0.484	7.00E-29	2.60E-26
NUCB2	11p15.1	-0.483	9.20E-29	3.40E-26
PEX10	1p36.32	0.481	1.90E-28	6.70E-26
INTS1	7p22.3	0.481	1.90E-28	6.70E-26
NBN	8q21.3	-0.480	2.20E-28	7.50E-26
RAP2C	Xq26.2	-0.479	3.50E-28	1.10E-25
ST3GAL3	1p34.1	0.478	4.10E-28	1.30E-25
ZEB1	10p11.22	-0.477	5.10E-28	1.60E-25
MIS18BP1	14q21.2	-0.476	6.70E-28	2.10E-25
ZNF362	1p35.1	0.475	1.10E-27	3.40E-25
ATP11C	Xq27.1	-0.475	1.10E-27	3.50E-25
ERGIC2	12p11.22	-0.473	1.80E-27	5.30E-25
TOP1	20q12	-0.473	2.00E-27	5.90E-25
IBTK	6q14.1	-0.472	2.60E-27	7.40E-25
MIA2	14q21.1	-0.472	2.60E-27	7.50E-25
RETREG2	2q35	0.470	3.90E-27	1.10E-24
ZNF267	16p11.2	-0.470	4.00E-27	1.10E-24
RESF1	12p11.21	-0.469	6.50E-27	1.80E-24

SGPP1	14q23.2	-0.468	7.10E-27	1.80E-24
SLC3A2	11q12.3	0.468	7.50E-27	1.90E-24
CCDC91	12p11.22	-0.466	1.20E-26	2.90E-24
EFR3A	8q24.22	-0.466	1.20E-26	3.00E-24
ACTR2	2p14	-0.466	1.30E-26	3.10E-24
ATF1	12q13.12	-0.465	1.60E-26	3.60E-24
RHOA	1q42.13	-0.465	1.70E-26	4.00E-24
PPIG	2q31.1	-0.465	1.90E-26	4.30E-24
ATP2B1	12q21.33	-0.463	2.70E-26	6.10E-24
PYROXD1	12p12.1	-0.462	3.50E-26	7.80E-24
GABPB1	15q21.2	-0.462	4.20E-26	9.30E-24
UNC45A	15q26.1	0.461	4.70E-26	1.00E-23
ERI3	1p34.1	0.461	5.40E-26	1.20E-23
NMI	2q23.3	-0.461	5.80E-26	1.20E-23
RGS18	1q31.2	-0.459	9.60E-26	2.00E-23
GABPA	21q21.3	-0.458	1.30E-25	2.60E-23
SPCS3	4q34.2	-0.457	1.60E-25	3.20E-23
PUS7L	12q12	-0.457	1.70E-25	3.40E-23
STAM2	2q23.3	-0.456	2.40E-25	4.70E-23
MED24	17q21.1	0.454	3.50E-25	6.90E-23
ITGA4	2q31.3	-0.454	3.50E-25	6.90E-23
MANEA	6q16.1	-0.454	3.80E-25	7.20E-23
ST8SIA4	5q21.1	-0.454	4.10E-25	7.70E-23
CEP290	12q21.32	-0.453	4.10E-25	7.70E-23
MECR	1p35.3	0.453	4.40E-25	8.20E-23
HCFC2	12q23.3	-0.452	5.80E-25	1.10E-22
UBE2D1	10q21.1	-0.452	6.10E-25	1.10E-22
VRK2	2p16.1	-0.452	6.10E-25	1.10E-22
TMX3	18q22.1	-0.451	8.90E-25	1.60E-22
PCIF1	20q13.12	0.450	9.80E-25	1.70E-22
ATP6V0A1	17q21.2	0.450	1.00E-24	1.80E-22

Table S2, top 65 co-expressed genes with BAP1 in UM

UM, BAP loss correlated	Gene	cytoband	spearman's correlation	pvalue	qvalue
1	HTR2B	2q37.1	-0.785	4.70E-17	5.70E-14
2	FBXO17	19q13.2	0.775	2.10E-16	1.80E-13
3	ACSF2	17q21.33	0.774	2.50E-16	2.00E-13
4	PXDC1	6p25.2	0.770	4.20E-16	2.80E-13
5	LIMS2	2q14.3	0.767	6.70E-16	4.00E-13
6	PCBD2	5q31.1	-0.765	9.10E-16	4.70E-13

7	HSPA1L	6p21.33	0.763	1.10E-15	5.40E-13
8	PPM1K	4q22.1	-0.761	1.50E-15	6.50E-13
9	GTF2H4	6p21.33	0.760	1.80E-15	7.40E-13
10	PHYHD1	9q34.11	0.757	2.50E-15	1.00E-12
11	SCGB1B2P	19q13.11	0.757	2.60E-15	1.00E-12
12	TFAP2A	6p24.3	0.755	3.30E-15	1.20E-12
13	GPR153	1p36.31	0.751	5.40E-15	1.90E-12
14	C16ORF86	16q22.1	0.751	5.90E-15	2.00E-12
15	ZNF835	19q13.43	0.750	6.00E-15	2.00E-12
16	DAXX	6p21.32	0.748	7.80E-15	2.60E-12
17	DLL4	15q15.1	-0.748	8.50E-15	2.70E-12
18	TBC1D22B	6p21.2	0.747	8.80E-15	2.80E-12
19	SERPINB6	6p25.2	0.746	1.00E-14	3.20E-12
20	CLEC11A	19q13.33	0.742	1.60E-14	4.60E-12
21	SAP30	4q34.1	-0.742	1.80E-14	4.90E-12
22	PLEKHG4	16q22.1	0.740	2.20E-14	5.80E-12
23	ZSCAN1	19q13.43	0.740	2.30E-14	6.10E-12
24	RTL8B	Xq26.3	0.739	2.40E-14	6.10E-12
25	ZBTB12	6p21.33	0.739	2.60E-14	6.20E-12
26	ANG	14q11.2	0.738	2.70E-14	6.40E-12
27	HEXB	5q13.3	-0.738	2.80E-14	6.60E-12
28	GREB1L	18q11.1- q11.2	-0.737	3.10E-14	7.00E-12
29	CAMSAP3	19p13.2	0.735	4.10E-14	9.00E-12
30	CEBPA-DT	19q13.11	0.735	4.30E-14	9.30E-12
31	SH2D5	1p36.12	-0.734	4.30E-14	9.30E-12
32	CADM1	11q23.3	-0.734	4.60E-14	9.50E-12
33	ABT1	6p22.2	0.733	4.90E-14	9.80E-12
34	TPTE2P3	13q14.3	0.733	5.20E-14	1.00E-11
35	PPP1R14C	6q25.1	-0.732	5.60E-14	1.10E-11
36	LINC00518	6p24.3	0.730	7.60E-14	1.40E-11
37	TWINK	10q24.31	0.729	8.40E-14	1.60E-11
38	COQ6	14q24.3	-0.729	8.70E-14	1.60E-11
39	CTF1	16p11.2	0.728	9.30E-14	1.70E-11
40	PLEKHG6	12p13.31	-0.726	1.10E-13	2.10E-11
41	FAM120C	Xp11.22	-0.725	1.30E-13	2.20E-11
42	RNF43	17q22	0.723	1.60E-13	2.80E-11
43	RXRB	6p21.32	0.723	1.70E-13	2.80E-11
44	COL9A3	20q13.33	-0.723	1.70E-13	2.80E-11
45	MANEAL	1p34.3	0.722	1.90E-13	3.10E-11
46	PLN	6q22.31	-0.721	2.00E-13	3.30E-11
47	SOCS2	12q22	-0.719	2.60E-13	4.00E-11
48	ALG5	13q13.3	-0.717	3.10E-13	4.70E-11

49	TOB2P1	6p22.1	0.717	3.10E-13	4.70E-11
50	LYRM4	6p25.1	0.715	4.10E-13	6.00E-11
51	TPD52L2	20q13.33	0.714	4.50E-13	6.50E-11
52	C6ORF226	6p21.1	0.713	4.80E-13	6.80E-11
53	DUSP22	6p25.3	0.713	4.80E-13	6.80E-11
54	ATP8B2	1q21.3	-0.713	5.20E-13	7.20E-11
55	HTRA1	10q26.13	-0.711	6.10E-13	8.30E-11
56	SDC2	8q22.1	-0.711	6.40E-13	8.50E-11
57	PCDHB9	5q31.3	0.709	7.60E-13	1.00E-10
58	ENPP2	8q24.12	0.709	7.70E-13	1.00E-10
59	ATP5CKMT	5p15.2	-0.709	8.00E-13	1.00E-10
60	FAM50B	6p25.2	0.708	8.20E-13	1.00E-10
61	SIPA1L2	1q42.2	-0.708	8.20E-13	1.00E-10
62	PSD2	5q31.2	-0.708	9.00E-13	1.10E-10
63	RNF208	9q34.3	0.707	9.10E-13	1.10E-10
64	CARD11	7p22.2	-0.705	1.10E-12	1.40E-10
65	CDK2	12q13.2	0.705	1.20E-12	1.40E-10

Figure S1: role of SF3B1 in UM melanoma survival