Supplementary Tables

Table S1 Relationship between *RIP3* promoter methylation and clinico-pathological parameters

Parameter	*RIP3* promoter methylation	*P* value
Age at diagnosis (year)		
≥ 61	143/262 (54.6%)	0.352
< 61	116/257 (45.1%)	
Sex		
Female	69/139 (49.6%)	0.963
Male	190/381 (49.9%)	
Histology grade		
G1	28/62 (45.2%)	
G2	157/304 (51.6%)	0.556
G3/G4	63/132 (47.7%)	
pT		
T1	18/35 (51.4%)	
T2	75/151 (49.7%)	0.881
T3	71/135 (52.6%)	
T4	88/183 (48.1%)	
pN		
N0	81/176 (46.0%)	
N1	33/67 (49.3%)	0.597
N2/N3	91/177 (51.4%)	
Stage		
I	12/20 (60.0%)	
II	46/98 (46.9%)	0.251
III	60/105 (57.1%)	
IV	134/283 (47.3%)	

G1, well differentiated; G2, moderately differentiated; G3, poorly differentiated; G4, Undifferentiated; pT, pathologic T stage; pN, lymph node metastases.

Table S2 Survival analysis according to *RIP3* mRNA expression

***RIP3* mRNA expression**	**N**	**Disease-free survival time (months)**		**Overall survival time (months)**	
		average	**median**	**average**	**median**
positive	211	91.779	71.220	109.944	108.870
negative	181	71.135	53.090	82.109	*
Total	**392**	**90.414**	**67.740**	**105.124**	**108.870**

* The cumulative probability of survival > 50%.

Table S3 Survival analysis according to *RIP3* promoter methylation

***RIP3* promoter methylation**	**N**	**Disease-free survival time (months)**		**Overall survival time (months)**	
		average	**median**	**average**	**median**
unmethylated	189	106.129	*	111.327	108.870
methylated	203	76.223	49.970	98.684	69.650
Total	**392**	**90.414**	**67.740**	**105.124**	**108.870**

***** The cumulative probability of survival > 50%.

Supplementary Figures

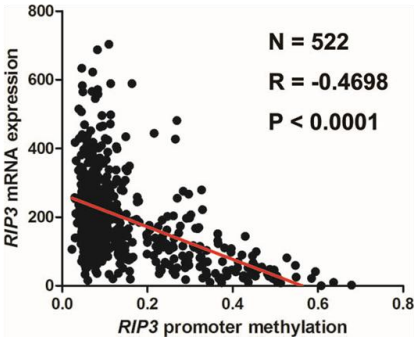

Figure S1. There is a significantly negative correlation between *RIP3* mRNA expression and its promoter methylation in HNSCC tissues (data from TCGA Research Network).

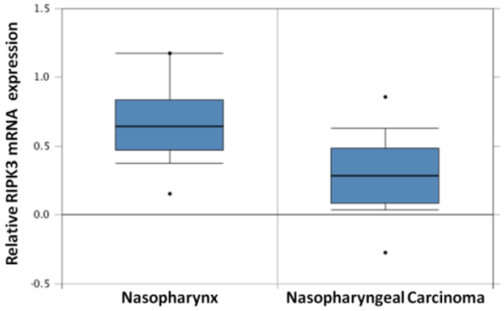

Figure S2. *RIP3* mRNA expression is down-regulated in NPC (*P* < 0.001) (data from Oncomine database [1])

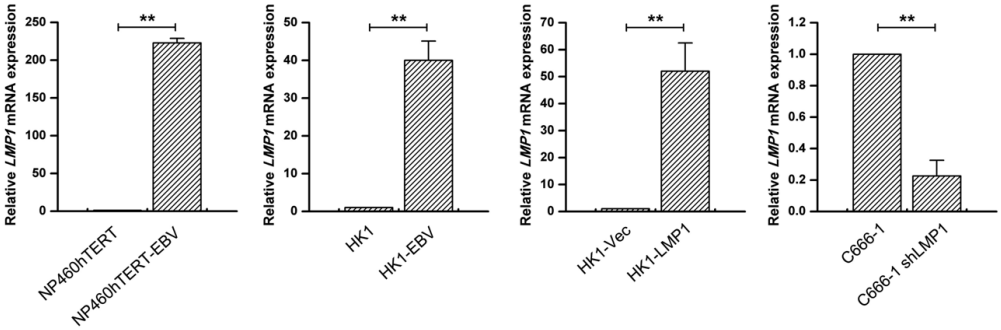

Figure S3. *LMP1* mRNA expression in cell lines determined by realtime PCR.

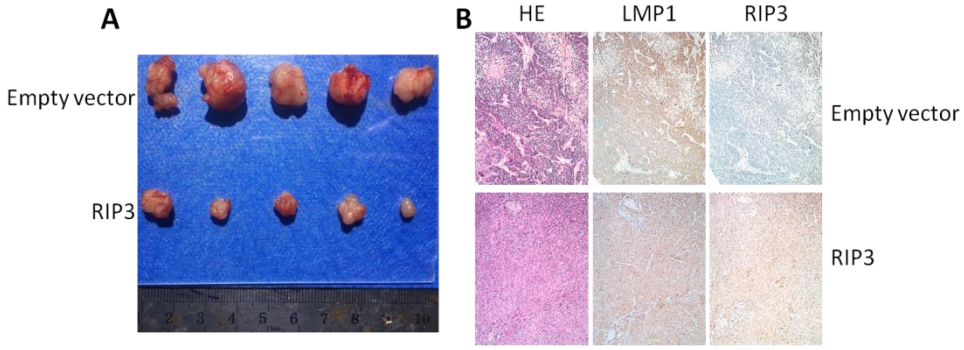

Figure S4. Restoring RIP3 expression in EBV(LMP1)-positive cells inhibits xenograft tumor growth in nude mice. A, representative images of xenograft tumors; B, representative images of HE staining and LMP1/ RIP3 staining by immunohistochemistry in xenograft tumor sections (100×).

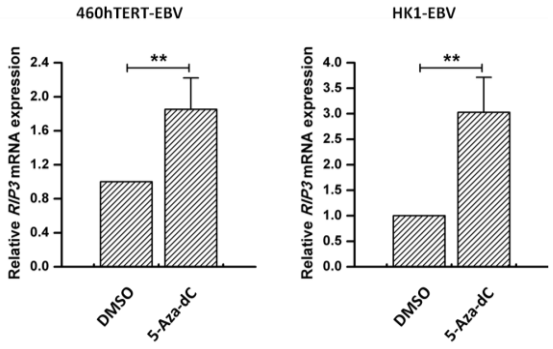

Figure S5. *RIP3* mRNA re-expressed with 5-aza-dC treatment

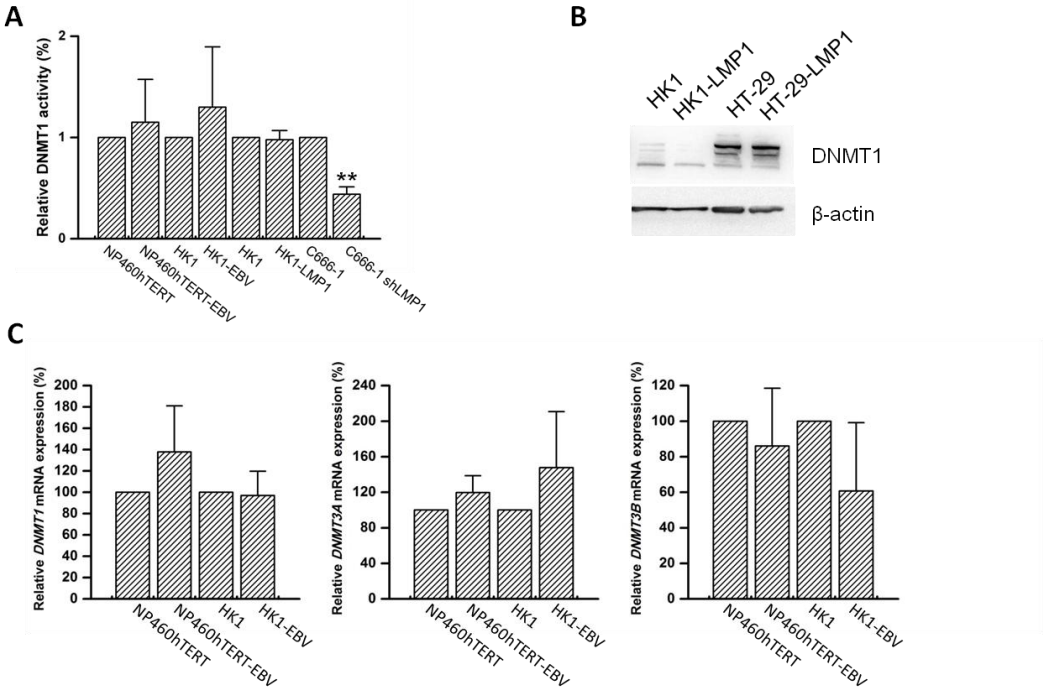

Figure S6. DNMTs enzymatic activity and expression were not affected by EBV(LMP1).

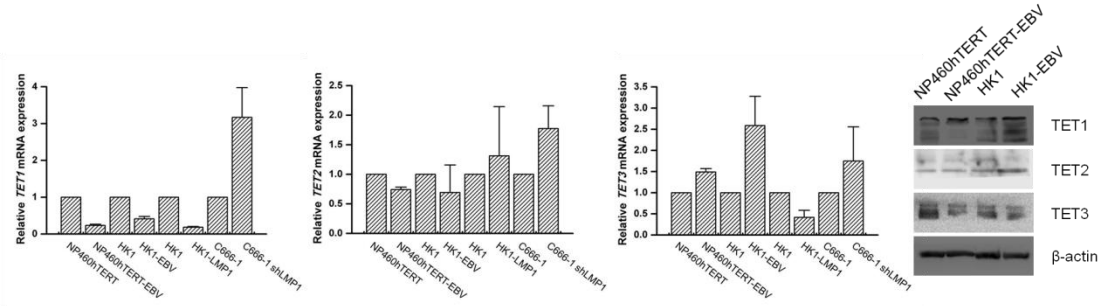

Figure S7. The expression of TETs was not affected by EBV(LMP1).

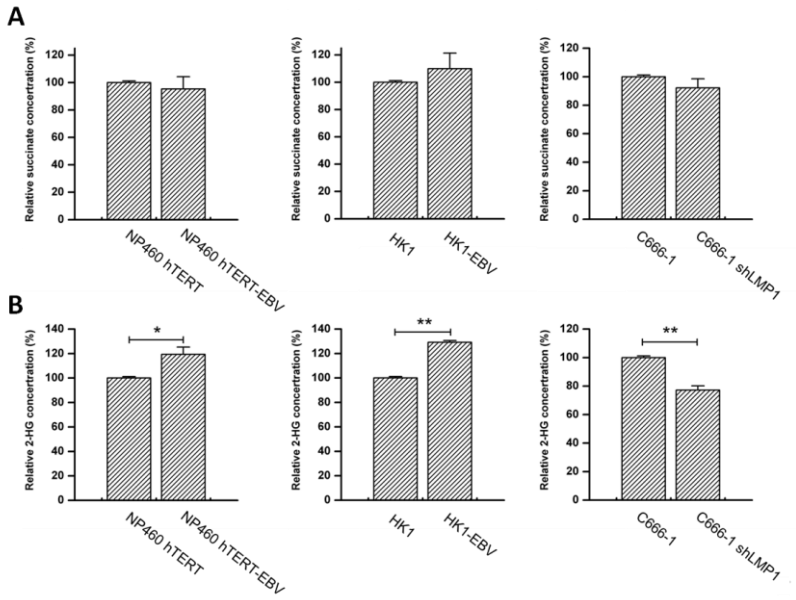

Figure S8. The cellular levels of succinate and 2-HG were confirmed by specific kits in three pairs of cell lines.

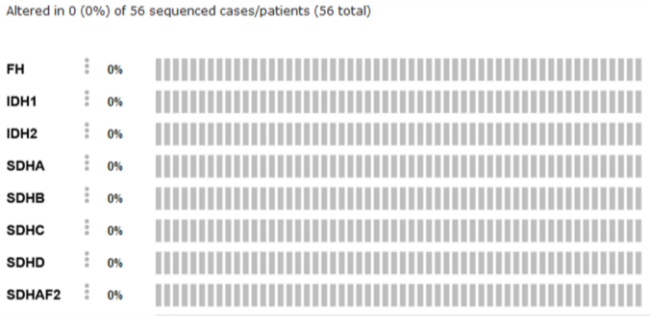

Figure S9. No mutation of indicated genes was found in 56 NPC tissues (data from cBioPortal for Cancer Genomics [2]).

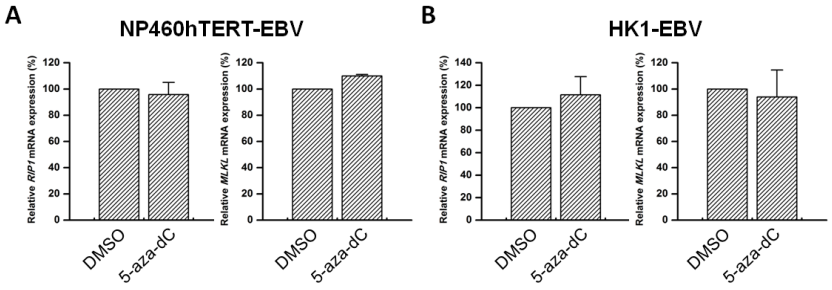

Figure S10. *RIP1* and *MLKL* mRNA were not affected by 5-aza-dC treatment.

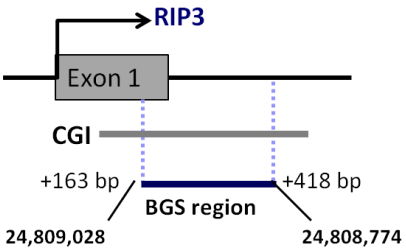

Figure S11. Structure of the *RIP3* promoter CpG island (CGI).

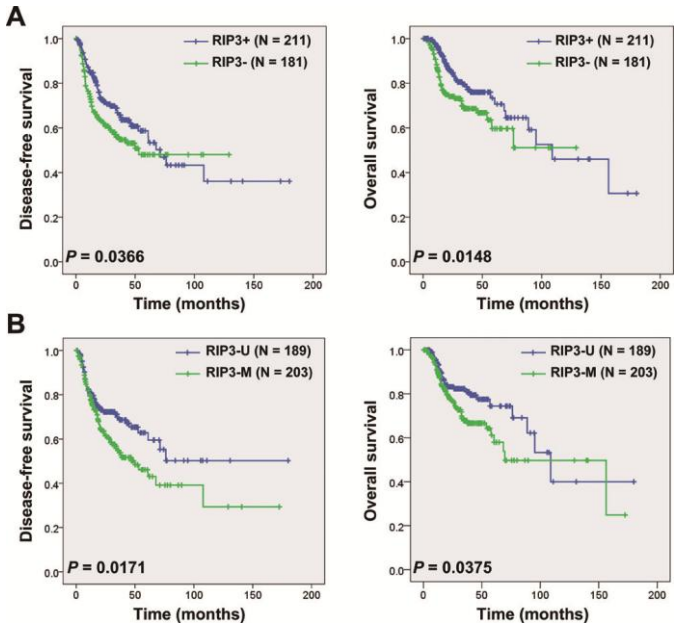

Figure S12. Kaplan–Meier analysis according to *RIP3* promoter methylation and mRNA expression status in 392 HNSCC patients with both DFS and OS information.

A, Disease-free survival (left) and overall survival (right) analysis according to *RIP3* mRNA expression. HNSCC patients were divided into two groups: good prognosis (positive expression of *RIP3* mRNA) and poor prognosis (negative expression of *RIP3* mRNA; "-", negative; "+", positive).

B, Disease-free survival (left) and overall survival (right) analysis according to *RIP3* promoter methylation. HNSCC patients were divided into two groups: good prognosis (unmethylated *RIP3* promoter) and poor prognosis (methylated *RIP3* promoter). U, unmethylated; M, methylated.

References

1. Sengupta S, den Boon JA, Chen IH, Newton MA, Dahl DB, Chen M, et al. Genome-wide expression profiling reveals EBV-associated inhibition of MHC class I expression in nasopharyngeal carcinoma. Cancer Res. 2006; 66: 7999-8006.

2. Lin DC, Meng X, Hazawa M, Nagata Y, Varela AM, Xu L, et al. The genomic landscape of nasopharyngeal carcinoma. Nat Genet. 2014; 46: 866-71.