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Telomeric zinc-finger associated protein (TZAP) in cancer biology: friend or foe?

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ABSTRACT

The new identified protein telomeric zinc-finger associated protein (TZAP) is a negative regulator of telomere length. Since telomere length and telomere maintenance mechanisms are essential to cancer progression, TZAP is considered a new player in cancer biology. Here we aimed to analyze TZAP using the Cancer Genome Atlas data in a Pan-Cancer approach. We gathering data from TCGA Pan-Cancer studies utilizing cBioPortal, GEPIA and UALCAN. In total we analyzed 33 types of cancer (n=9664) and their respective controls (n=711). TZAP is transcribed in all cancers but less than 5% of all tumors show any somatic changes. TZAP was downregulated in kidney chromophobe carcinoma, and upregulated in esophageal cancer, head and neck squamous cell carcinomas, kidney renal clear cell carcinoma and in liver hepatocellular carcinoma. Globally, TZAP expression is related to favorable prognosis, associated to better overall and disease-free survival. Looking to specific tumors, TZAP expression has a dual behavior. Its downregulation is associated with poor prognosis in cervical squamous cell carcinoma, in kidney renal clear cell carcinoma, kidney papillary cell carcinoma, lung adenocarcinoma and pancreas adenocarcinoma. On the contrary, in adrenocortical carcinoma, colon and rectal cancer, brain lower grade glioma and prostate adenocarcinoma the upregulation of TZAP is related with poor prognosis. TZAP expression has a positive correlation with TRF1 and TRF2 in normal tissue but not in cancer. Our analyses indicate that TZAP has an important role in oncology and may be considered as a potential biomarker.

Keywords: Telomere Length; Telomere Maintenance Mechanisms; Telomere Binding Proteins; Pan-Cancer; Cancer Biomarker

INTRODUCTION

Telomeres are nucleoprotein structures at the ends of eukaryotic chromosomes. To achieve replicative immortality, all cancer cells acquire telomere maintenance mechanisms (TMM), which explain the importance of these structures in oncology [1]. Somatic cells undergo

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continuous telomere shortening as a natural consequence of cellular replication in the absence of telomerase. To promote telomere elongation, and maintain replicative viability, 85% of cancer cells reactivate telomerase and 15% active alternative lengthening of telomere (ALT) [2]. In both mechanisms, the telomere length is crucial to cancer survival and carcinogenesis process as a whole [3].

Telomere length (TL) is highly dependent on telomeric proteins. For example, the shelterin complex is composed by six subunits (TRF1, TRF2, POT1, RAP1, TIN2 and TPP1) that bind telomeres to promote their protection and regulation of TL. Telomere dysfunction and shelterin aberrations are present in the vast majority of cancers [4, 5].

Recently, a new protein was identified as a TL regulator. TZAP (telomeric zinc finger-associated protein), or ZBTB48, promotes rapid deletion of telomeric repeats by a process called telomere trimming [6, 7]. Since TZAP acts as a negative regulator of TL, scientists hypothesize its importance in several diseases, such as cancer [8, 9]. In this context, TZAP modulates a novel mechanism that controls the upper limit of TL, a key determinant of cancer probably acting as a tumor suppressor gene [6, 7]. Nevertheless, there are few studies that show the association of TZAP in cancer and none of them uses a Pan-Cancer approach [10-12]. Thus, we aimed to analyze the TCGA (The Cancer Genome Atlas) datasets of 33 types of cancer, to better understand the role of TZAP in this disease.

MATERIALS AND METHODS

Samples: We collected genomic and transcriptome data from 33 different types of cancer, and adjacent normal tissue, from TCGA data sets. In total, we analyzed 9664 samples of cancer and 711 samples of normal tissue. Detailed information, and the code for each cancer, is showed in Table 1.

Table 1: TCGA codes and number of samples of each cancer

TCGA code	Cancer	Cancer (n)	Normal (n)
ACC	Adrenocortical carcinoma	77	0
BLCA	Bladder Urothelial Carcinoma	404	19
BRCA	Breast invasive carcinoma	1085	112
CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma	306	3
CHOL	Cholangio carcinoma	36	9
COAD	Colon adenocarcinoma	275	41
DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma	47	0
ESCA	Esophageal carcinoma	182	13
GBM	Glioblastoma multiforme	163	0
HNSC	Head and Neck squamous cell carcinoma	519	44
KICH	Kidney Chromophobe	66	25
KIRC	Kidney renal clear cell carcinoma	523	72
KIRP	Kidney renal papillary cell carcinoma	286	32
LAML	Acute Myeloid Leukemia	173	0
LGG	Brain Lower Grade Glioma	518	0
LIHC	Liver hepatocellular carcinoma	369	50
LUAD	Lung adenocarcinoma	483	59
LUSC	Lung squamous cell carcinoma	486	50
MESO	Mesothelioma	87	0
OV	Ovarian serous cystadenocarcinoma	426	0
PAAD	Pancreatic adenocarcinoma	179	4
PCPG	Pheochromocytoma and Paraganglioma	182	3
PRAD	Prostate adenocarcinoma	492	52
READ	Rectum adenocarcinoma	92	10
SARC	Sarcoma	262	2
SKCM	Skin Cutaneous Melanoma	461	1
STAD	Stomach adenocarcinoma	408	36
TGCT	Testicular Germ Cell Tumors	137	0
THCA	Thyroid carcinoma	512	59
THYM	Thymoma	118	2
UCEC	Uterine Corpus Endometrial Carcinoma	174	13
UCS	Uterine Carcinosarcoma	57	0
UVM	Uveal Melanoma	79	0

Genetic alterations: Genetic alterations in TZAP were assessed using TCGA Pan-Cancer studies deposited in cBioPortal [13, 14]. All images were generated from cBioPortal, with minor style adaptations.

Gene expression analyses: All analyses were performed using the online UALCAN and GEPIA (Gene Expression Profiling Interactive Analysis) platforms [15, 16]. The boxplots represented the TZAP mRNA levels were generated from UALCAN with minor style adaptations. The expression data are first $\log_2$ (TPM+1) transformed for differential analysis and the $\log_2$FC (fold change) is defined as median (Cancer) – median (Normal). Genes with higher $\log_2$FC values and lower q values than pre-set thresholds are considered differentially expressed genes. The survival analyses and Spearman correlations were generated from GEPIA with minor style adaptations. The Kaplan-Meier curves were based on gene expression of all cancer samples, using the highest and lowest quartiles as a cut-off. The hazard ratio was calculated using cox proportional hazard ratio. We set a level of significance of 5% ($p<0.05$).

RESULTS

In the figure 1A, we demonstrate the somatic alteration landscape of TZAP. Structural genetic alterations in TZAP are not common, being present in less than 5% of all samples studied. Tumors with the highest proportion of alterations are adrenocortical carcinoma, cervical adenocarcinoma and mature B-cell neoplasm. Leukemia, seminoma, thymic epithelial tumors and undifferentiated stomach adenocarcinoma showed no alteration. The only fusion was detected in invasive breast carcinoma, in which the TZAP gene was fused with TAS1R1. The presence and proportion of amplifications, deletions and mutations varies in relation to each type of cancer, without following a pattern.

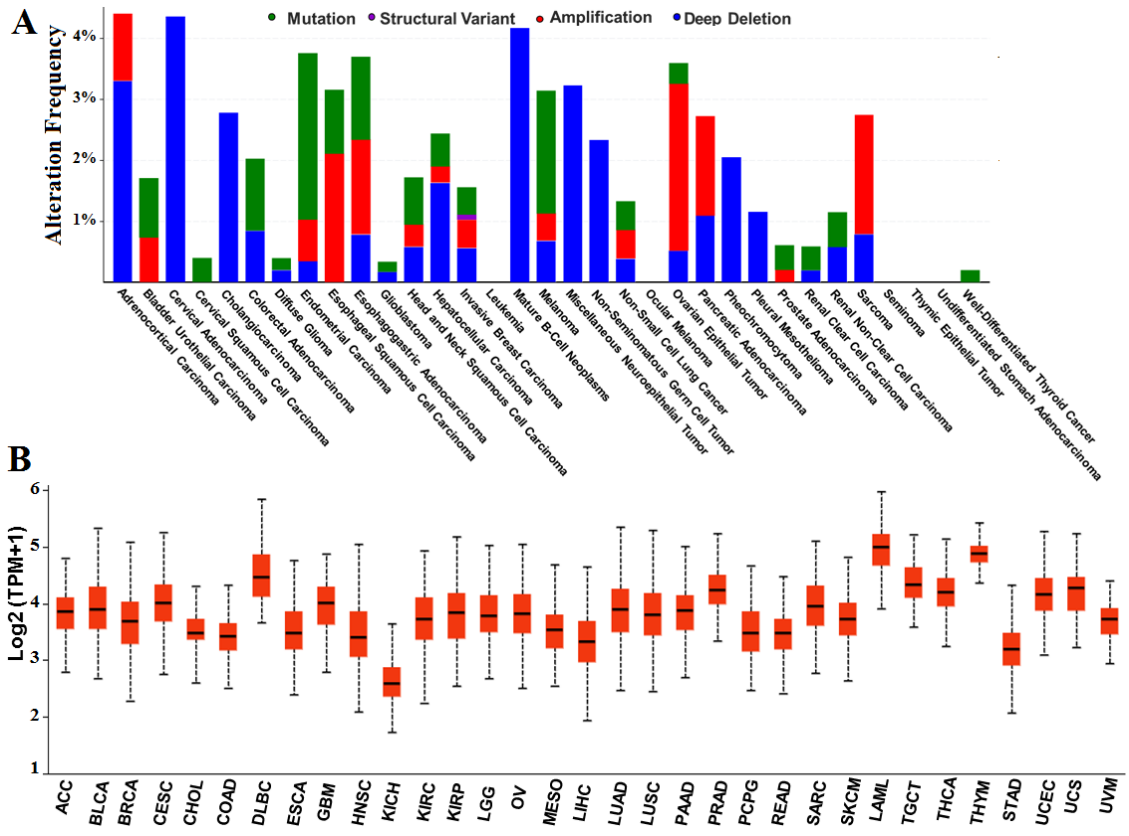

Figure 1: TZAP in cancer. In A we showed the genomic alterations in each type of cancer and their proportions. In B we showed the gene expression level of TZAP in each TCGA cancer.

Figure 1B showed the mRNA levels of TZAP across the cancer of TCGA. The expression of TZAP is present in all tumors, but varies in each site. The highest expressions were present in lymphoid neoplasm diffuse large B-cell lymphoma (DLBC), acute myeloid leukemia (LAML) and thymic epithelial tumor (THYM) and the lowest in kidney chromophobe (KICH) and stomach adenocarcinoma (STAD).

Next, we compare TZAP expression in Tumor and Normal tissue (Fig. 2). Here, it is important to notice that not all types of cancer had the adjacent normal tissue available for analysis. TZAP is significantly downregulated in kidney chromophobe (KICH) and upregulated in esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC) and liver hepatocellular carcinoma (LIHC) when comparing with normal tissue.

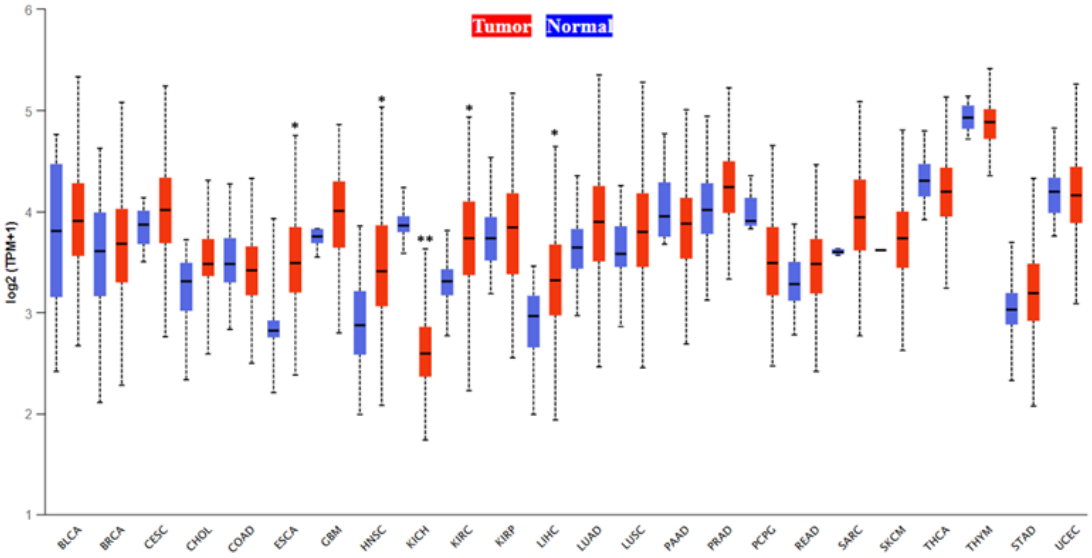

Figure 2: Comparison in TZAP expression between normal and cancer tissues. The boxplots are grouped in pairs for each cancer, the control tissue is blue(left) and the tumor tissue in red(right). **Log_2FC Cutoff: 1.0 q<0. 01. *Log_2FC Cutoff: 0.5 q<0.01.

Interestingly, TZAP expression can predict survival and recurrence. When we analyzed all cancer samples as a whole, the increase in TZAP expression was related to favorable tumor outcome for both, overall survival (Fig. 3A) and disease-free survival (Fig. 3B).

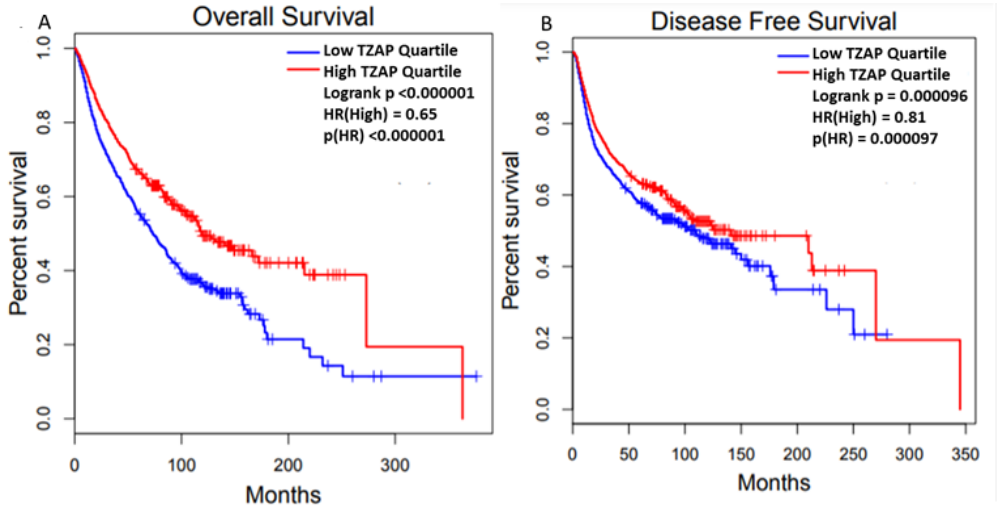

Figure 3: TZAP expression associated with cancer survival. In A we have overall survival and in B disease free survival. HR= Hazard Ratio

Considering each cancer individually, the Table 2 represents a summary of the hazard ratio of these analyzes. Highlighting only the statistically significant results (or with a marginal p-value), data show that the downregulation of TZAP was associated with the worst prognosis in cervical squamous cell carcinoma and endocervical adenocarcinoma (CESC, overall survival), kidney renal clear cell carcinoma (KIRC, disease free survival), kidney renal papillary cell carcinoma (KIRP, overall survival), lung adenocarcinoma (LUAD, overall and disease-free survival) and pancreatic adenocarcinoma(PAAD, overall and disease-free survival). On the contrary, the overexpression of TZAP was related to unfavorable prognosis in adrenocortical carcinoma (ACC, overall and disease-free survival), colon adenocarcinoma (COAD, overall survival), brain lower grade glioma (LGG, overall and disease-free survival) and prostate adenocarcinoma (PRAD, disease free survival).

Table 2: Association of survival outcomes and hazard ratio of each type of cancer

TCGA code	Overall Survival		Disease Free Survival	
	Hazard Ratio (HR)	p(HR)	Hazard Ratio (HR)	p(HR)
ACC	4.3	**0.027**	5.2	**0.0037**
BLCA	0.78	0.25	0.67	0.1
BRCA	0.73	0.21	0.89	0.66
CESC	0.28	**0.0012**	1.3	0.58
CHOL	0.41	0.22	0.31	0.11
COAD	2.1	0.056	1.5	0.24
DLBC	0.19	0.14	0.84	0.87
ESCA	1.2	0.63	1.3	0.44
GBM	1.2	0.43	0.66	0.17
HNSC	0.83	0.36	1.3	0.37
KICH	0.51	0.44	1.3	0.7
KIRC	0.96	0.86	0.6	**0.041**
KIRP	0.45	0.063	0.5	0.1
LAML	1.5	0.34	-	-
LGG	2.2	**0.0019**	2.3	**0.00022**
LIHC	1.1	0.62	1.1	0.69
LUAD	0.67	0.056	0.67	0.068
LUSC	0.93	0.73	0.99	0.97
MESO	0.76	0.44	0.58	0.16
OV	1.1	0.73	0.94	0.73
PAAD	0.39	**0.0001**	0.36	**0.0023**
PCPG	0.48	0.55	0.38	0.12
PRAD	2.4	0.48	2.5	**0.0034**
READ	1.5	0.57	3	0.11
SARC	0.95	0.85	0.88	0.6
SKCM	0.76	0.16	0.88	0.45
STAD	1.1	0.57	1.2	0.46
TGCT	1	1	0.74	0.64
THCA	1.2	0.8	0.89	0.77
THYM	0.64	0.54	0.62	0.42
UCEC	1.7	0.39	0.83	0.88
UCS	1	0.99	1.2	0.71
UVM	3	0.16	1	1

Then, we group all TCGA samples to correlate the TZAP expression with two shelterin components TRF1 and TRF2, as they compete for the same telomere binding site. We observe that although there is a positive correlation between them in normal tissue, in cancer we have a weak negative correlation (Figure 4).

Finally, to further evaluate the relationship between TZAP and TRF1/TRF2 we repeated the correlation analysis but using each cancer individually (Table 3). We can observe that we have a prevalence of negative correlation (considering all the results or only the significant ones), which indicates an imbalance between the expression of TZAP and these two shelterin components in cancer. To better illustrate these results, we have compiled the expression of TRF1 (Supplementary1) and TRF2 (Supplementary 2) in each TCGA cancer.

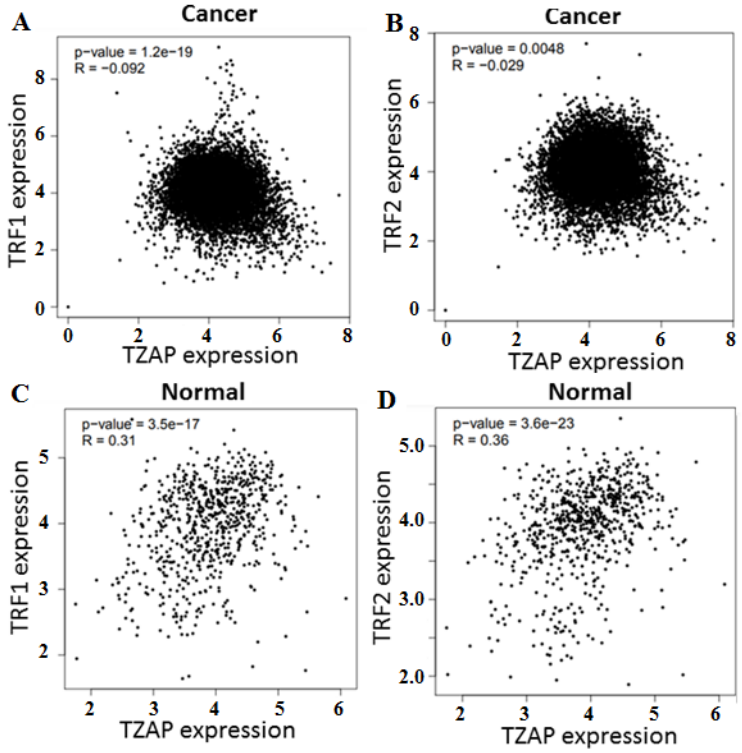

Figure 4: Correlation between TZAP and TRF1/TRF2 expression. In A and B we have the correlation in Cancer. In C and D we have the correlation in normal tissues.

Table 3: Correlation between TZAP and TRF1 and TRF2 in each cancer

	TRF1		TRF2	
	R	P-value	R	P-value
ACC	0.2	0.08	0.22	0.055
BLCA	-0.2	<0.0001	-0.16	0.0009
BRCA	-0.23	<0.0001	-0.15	<0.0001
CESC	-0.12	0.031	-0.032	0.57
CHOL	0.015	0.93	-0.024	0.89
COAD	-0.1	0.085	0.19	0.0013
DLBC	-0.6	<0.0001	-0.44	0.002
ESCA	0.16	0.031	0.16	0.026
GBM	0.19	0.017	0.39	<0.0001
HNSC	0.037	0.4	-0.067	0.13
KICH	0.071	0.57	0.3	0.015
KIRC	-0.004	0.92	0.0087	0.84
KIRP	-0.35	<0.0001	-0.16	0.0077
LAML	-0.026	0.73	0.37	<0.0001
LGG	-0.26	<0.0001	-0.19	<0.0001
LIHC	-0.23	<0.0001	-0.084	0.11
LUAD	-0.054	0.24	0.047	0.3
LUSC	0.11	0.016	0.15	0.001
MESO	-0.11	0.31	-0.17	0.13
OV	0.23	<0.0001	0.2	<0.0001
PAAD	-0.18	0.015	-0.12	0.11
PCPG	-0.39	<0.0001	-0.35	<0.0001
PRAD	-0.5	<0.0001	-0.41	<0.0001
READ	-0.13	0.2	-0.0081	0.94
SARC	-0.29	<0.0001	-0.14	0.025
SKCM	0.0017	0.97	0.0069	0.14
STAD	0.27	<0.0001	0.21	<0.0001
TGCT	-0.31	0.0002	-0.18	0.031
THCA	0.083	0.036	0.0039	0.38
THYM	-0.66	<0.0001	-0.63	<0.0001
UCEC	-0.31	<0.0001	-0.38	<0.0001
UCS	-0.39	0.0027	-0.2	0.13
UVM	0.22	0.05	0.4	0.0002

DISCUSSION

Telomere homeostasis is essential to maintain cell replication and cancer cells must activate TMM to promote telomere elongation and achieve immortalization. TL is mainly regulated by proteins and, in this context; the newly identified TZAP has a potentially key role in cancer [17]. This study is the first to try to understand the general role of TZAP in cancer. Mutations in TZAP already been associated with poor prognosis in breast cancer, but as shown, the genetic alterations are uncommon in cancer, and probably they are not driven tumor mutations [12].

On the other hand, the TZAP expression may have a role in both initiation and progression of cancer. In the literature, the upregulation of TZAP was already reported in colorectal cancer, where this protein was negative correlated with age and TL and positive correlated with TERT (catalytic unit of telomerase) [10]. TCGA datasets showed that TZAP is differentially expressed in KICH, ESCA, HNSC, KIRC and LIHC. These changes in expression may contribute directly to the carcinogenesis process by regulating the TL and, therefore, influencing in the cancer cell stemness, replicative potential, gene expression pattern and DNA damage responses [18-20]. It is interesting to note that the behavior of TZAP was different in KICH and KIRC reinforcing the completely different pathways from different tumors in the same organ [21, 22].

When we check whether the expression of TZAP can predict survival in cancer as a whole, we see that this protein can act as a cancer suppressor, which has already been hypothesized by Donatti et al [9]. But when we study each TCGA cancer individually, we observed that TZAP can have opposite roles in different types of cancer. TZAP expression has already been associated with poor prognostic in colorectal and cervical cancers [10, 11].

TZAP main function is to promote rapid telomere shortening by telomere trimming, which probably alters all the telomere dynamics in cancers cells [23]. This process probably has different impacts in relation to the TMM adopted by each type of cancer (telomerase or ALT) [24]. Our analysis of TCGA datasets suggest that the downregulation of TZAP in CESC, KIRC, KIRP, LUAD and PAAD increase cancer aggressiveness, which is interesting because these tumors are highly dependent of telomerase and with few events of ALT [25]. On the other hand, the increase of TZAP expression is associated with the poor prognosis in ACC, LGG, PRAD and COAD. ACC and LGG are tumors which ALT is relatively common [25]. PRAD and COAD are also dependent on telomerase but they have very short tumoral TL in comparison with normal tissue [25, 26]. This indicates that the TMM mechanism may influences the role of TZAP in cancer and this protein probably modulates telomere shortening in tumors with short TL.

TZAP compete with the shelterin proteins TRF1 and TRF2 to bind telomeric DNA, in a way that reduced concentration of these proteins (mainly on long telomeres) results in TZAP binding and initiation of telomere trimming [7]. In this sense, our analyses demonstrate that in normal tissue we have a positive correlation between TZAP and TRF1 and TRF2, which suggests that the balance in expression may be important for telomere homeostasis.

Our further analyzes showed that this correlation is reversed in cancer, being negative when considering all tumor samples as a whole (despite a very weak correlation coefficient), which probably favors telomere dysfunction present in most cancers [27]. Still, considering each tumor individually, we again have a higher proportion of negative correlations, but some tumors follow the normal trend of positive correlations. These data are important because, for example, in a cancer cell with high expression of TRF1 or TRF2 we can have a suppression of telomere triming even without a very low expression of TZAP, blocking the tumor suppressor potential of this protein (and the opposite is also true). TZAP is already positively correlated with the expression of TERT in cancer [28]. Thus, the expression of TRF1 and TRF2 are probably important to understand the role of TZAP in each context, especially considering that we have extensive literature of these proteins in oncology [4, 29 , 30].

In summary, we provided the first report about the TZAP role in a Pan-Cancer approach, which suggest that it is an important player in carcinogenesis and may be a new biomarker.

Future experimental studies must be conducted to better understand the function of this protein in cancer.

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Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-674.
2. De Vitis M, Berardinelli F, Sgura A. Telomere Length Maintenance in Cancer: At the Crossroad between Telomerase and Alternative Lengthening of Telomeres (ALT). Int J Mol Sci 2018;19:606.
3. Yuan X, Dai M, Xu D. Telomere-related markers for cancer. Curr Top Med Chem 2020;20:410-432.
4. Patel TN, Vasan R, Gupta D, Patel J, Trivedi M. Shelterin proteins and cancer. Asian Pac J Cancer Prev 2015;16:3085-3090.
5. Luo Z, Liu W, Sun P, Wang F, Feng X. Pan-cancer analyses reveal regulation and clinical outcome association of the shelterin complex in cancer. Brief Bioinform 2021.
6. Jahn A, Rane G, Paszkowski-Rogacz M, Sayols S, Bluhm A, Han CT, Draskovic I, Londono-Vallejo JA, Kumar AP, Buchholz F, Butter F, Kappei D. ZBTB48 is both a vertebrate telomere-binding protein and a transcriptional activator. EMBO Rep 2017;18: 929-946.
7. Li JS, Miralles Fusté JM, Simavorian T, Bartocci C, Tsai J, Karlseder J, Denchi EL. TZAP: A telomere-associated protein involved in telomere length control. Science 2017;355:638-641.
8. Zlotorynski E. Chromosome biology: TZAP trims telomeres. Nat Rev Mol Cell Biol 2017; 18:140.
9. Donati B, Valenti L. Telomeric zinc-finger associated protein (TZAP): a new player in telomere diseases? Ann Transl Med 2017;5:472.
10. Jung SJ, Seo YR, Park WJ, Heo YR, Lee YH, Kim S, Lee JH. Clinicopathological Characteristics of TZAP Expression in Colorectal Cancers. Onco Targets Ther 2020;13: 12933-12942.
11. Park WJ, Park JH, Shin HY, Lee JH. Clinical and prognostic significance of TZAP expression in cervical cancer. Medicina (Kaunas) 2020;56:207.
12. Heo YR, Lee MH, Kwon SY, Cho J, Lee JH. TZAP mutation leads to poor prognosis of patients with breast cancer. Medicina (Kaunas) 2019;55:748.
13. Gao J, Aksoy BA, Dogrusoz U, Dresdner G, Gross B, Sumer SO, Sun Y, Jacobsen A, Sinha R, Larsson E, Cerami E, Sander C, Schultz N. Integrative analysis of complex cancer genomics and clinical profiles using the cBioPortal. Sci Signal 2013;6:pl1.
14. Cerami E, Gao J, Dogrusoz U, Gross BE, Sumer SO, Aksoy BA, Jacobsen A, Byrne CJ, Heuer ML, Larsson E, Antipin Y, Reva B, Goldberg AP, Sander C, Schultz N. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. Cancer Discov 2012;2:401-404.
15. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res 2019;47:W556-W560.
16. Chandrashekar DS, Bashel B, Balasubramanya SAH, Creighton CJ, Ponce-Rodriguez I, Chakravarthi BVSK, Varambally S. UALCAN: A portal for facilitating tumor subgroup gene expression and survival analyses. Neoplasia 2017;19:649-658.

17. Bie YN, Gu P, Chen YT, Zhou XX, Tian YG, Yang Q, Li HY, Lin X, Guan YH, Lin TY, Lu X, Shen HF, Fang TX, Liu YM, Xiao D, Gu WW. TZAP plays an inhibitory role in the self-renewal of porcine mesenchymal stromal cells and is implicated the regulation of premature senescence via the p53 pathway. J Transl Med 2019;17:72.
18. Kim W, Shay JW. Long-range telomere regulation of gene expression: Telomere looping and telomere position effect over long distances (TPE-OLD). Differentiation 2018;99:1-9.
19. Hannen R, Bartsch JW. Essential roles of telomerase reverse transcriptase hTERT in cancer stemness and metastasis. FEBS Lett 2018;592:2023-2031.
20. Wu J, Crowe DL. Telomere DNA damage signaling regulates prostate cancer tumorigenesis. Mol Cancer Res 2020;18:1326-1339.
21. Montironi R, Cheng L, Scarpelli M, Lopez-Beltran A. Pathology and genetics: Tumours of the urinary system and male genital system: Clinical implications of the 4th edition of the WHO classification and beyond. Eur Urol. 2016;70:120-123.
22. Linehan WM, Srinivasan R, Schmidt LS. The genetic basis of kidney cancer: a metabolic disease. Nat Rev Urol 2010;7:277-285.
23. Lossaint G, Lingner J. TZAP or not to zap telomeres. Science 2017;355:578-579.
24. Garcia-Exposito L, O'Sullivan RJ. TZAP-ing telomeres down to size. EMBO Rep 2017;18: 861-863.
25. Heaphy CM, Subhawong AP, Hong SM, Goggins MG, Montgomery EA, Gabrielson E, Gabrielson E, Netto GJ, Epstein JI, Lotan TL, Westra WH, Shih LM, Donahue CA, Maitra A, Li Q, Eberhart CG, Taube JM, Rakheja D, Kurman RJ, Wu T, Roden RB, Argani P, Marzo AM, Terracciano L, Torbenson M, Meeker AK. Prevalence of the alternative lengthening of telomeres telomere maintenance mechanism in human cancer subtypes. Am J Pathol. 2011;179:1608-1615.
26. Herrmann M, Pusceddu I, März W, Herrmann W. Telomere biology and age-related diseases. Clin Chem Lab Med 2018;56:1210-1222.
27. Cleal K, Norris K, Baird D. Telomere length dynamics and the evolution of cancer genome architecture. Int J Mol Sci 2018;19:482.
28. Heo YR, Park WJ, Lee JH. Positive correlation between TZAP and TERT in most cancers: a new player in cancer diseases. Ann Transl Med 2018;6:197.
29. Donate LE, Blasco MA. Telomeres in cancer and ageing. Philos Trans R Soc Lond B Biol Sci 2011;366:76-84.
30. De Boeck G, Forsyth RG, Praet M, Hogendoorn PC. Telomere-associated proteins: cross-talk between telomere maintenance and telomere-lengthening mechanisms. J Pathol 2009; 217:327-344.