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Prognostic Value of TZAP Expression in Various Cancers: TCGA Data Analysis

Won Jin Park, Yu Ran Heo, Jae Ho Lee, M.D.

Department of Anatomy, Keimyung University School of Medicine, Daegu, Korea

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Corresponding Author: Jae Ho Lee, M.D., Department of Anatomy, Keimyung University School of Medicine, 2800 Dalgubeol-daero, Dalseo-gu, Daegu 42601, Korea
Tel: +82-53-580-3833
E-mail: anato82@dsmc.or.kr

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The zinc finger protein ZBTB48 is a telomere-associated factor and renamed it as telomeric zinc finger-associated protein (TZAP). It binds preferentially to long telomeres competing with TRF1 and TRF2. However, its expression in cancers has not been performed. In the present study, we analyzed the prognosis of TZAP expression in 22 kinds of cancers by using TCGA data analysis. TZAP expression had a prognostic value in cervical, colon, and pancreatic cancers. When sorting the patients differently, it got the significance in bladder, breast, kidney, brain, and lung cancers. TZAP expression was associated with better prognosis in bladder, breast, cervical, lung, and pancreatic cancers. However, it showed poorer survival results in colon, kidney, and brain cancers. This result suggested that TZAP expression appears to be a possible prognosis marker in various cancers.

Keywords: TCGA, Telomere, TZAP, ZBTB48

Introduction

Telomeres, composed of 6-bp TTAGGG repeat sequences, are nucleoprotein complexes capping each end of eukaryotic chromosomes [1,2]. In normal human somatic cells, telomeres have an average length of 5 to 15 kilobases and are shortened by approximately 30 to 200 base pairs at every cell division. Telomere shortening is counteracted by the reverse transcriptase telomerase in stem cells and most types of cancer, while the remaining cancers maintain telomeres with alternative lengthening of telomeres (ALT) mechanism [3-5]. A telomere trimming mechanism is induced in the presence of overly long telomeres, which are cut back to normal length by rapid telomere shortening [6-8]. Though the specific

regulation of this process has not been identified, recent studies have discovered a special protein that is necessary for regulating telomere [9]. They identified the zinc finger protein ZBTB48, as a telomere-associated factor, and renamed it telomeric zinc finger-associated protein (TZAP). It binds preferentially to long telomeres competing with telomeric repeat factor 1 and 2 (TRF1 and TRF2). In addition, the study showed that overexpression of TZAP caused progressive telomere shortening. TZAP localizes to chromosome 1p36, a region that is frequently rearranged or deleted in various cancers [10-12]. This genetic change of TZAP may be associated with cancer pathogenesis, however, a genetic analysis of TZAP has not been performed in any specific type of cancer.

The Cancer Genome Atlas Project (TCGA) as a National Cancer Institute-funded consortium project is to profile about 10,000 cases of 33 tumor types using genomic, transcriptomic, epigenomic and clinical platforms [13]. The data are centralized at the TCGA data portal and can be downloaded for academic use. Though TZAP expression has not been analyzed in cancer tissues, we can get the prognostic value of ZBTB48 in various cancer using TCGA data. In this study, we evaluated the prognosis of TZAP expression in 22 kinds of cancers for the first time to determine whether TZAP have clinical characteristics and prognostic values in cancers.

Materials and Methods

To investigate the clinical significance of TZAP, we used the TCGA database from OncoLnc and cBioPortal. TZAP mRNA expression data were downloaded from TCGA's data portal (https://tcga-data.nci.nih.gov/tcga/) on January, 2018 [13]. Its prognostic values were analyzed. To compare its prognosis, patients were sorted by TZAP expression level. We compared bottom third versus top third, or bottom quartile versus top quartile, so 33:33, or 25:25. If there is a small number of patients, 50:50 was also analyzed.

Survival curves, constructed using the univariate Kaplan-Meier estimators, were compared using the log-rank test. A p value of <0.05 denoted significance for all statistical analyses performed in this study.

Results

Prognostic value of TZAP expressions in various cancers

We examined TCGA data of survival analysis to clarify the prognostic significance of the TZAP expression in various cancers. The prognostic value of TZAP was presented in Table 1. TZAP expressions in cervical, colon, and pancreatic cancers have a prognostic value in all sorting percentile. When sorting the patients as 50:50, TZAP expressions got a significance in bladder, breast, kidney, and lung cancers. And the prognosis of glioma was associated with TZAP expression when comparing bottom third versus top third.

Higher expression of TZAP had a better prognosis in bladder, breast, cervical, lung, and pancreatic cancers (Fig. 1). However, it was associated with poorer survival results in colon, kidney, and brain cancers (Fig. 2).

Discussion

In this study, we demonstrated the prognostic value of TZAP expression for the first time in various cancers by using TCGA data. ZBTB48 is a Kruppel-like C2H2 zinc finger protein consisting of

Table 1. Significances of prognosis of TZAP expression in various cancers according to sorting percentile of patients

Cancer type	Sorting percentile		
	50:50	33:33	25:25
Bladder urothelial carcinoma	0.0175*	0.117	0.356
Breast invasive carcinoma	0.0495*	0.312	0.0853
Cervical squamous cell carcinoma	0.0529*	0.000889*	0.000439*
Colon adenocarcinoma	0.00149*	0.0381*	0.0197*
Esophageal carcinoma	0.715	0.592	0.0898
Glioblastoma multiforme	0.925	0.745	0.446
Head and neck squamous cell carcinoma	0.923	0.847	0.851
Kidney renal clear cell carcinoma	0.182	0.114	0.0139*
Kidney renal papillary cell carcinoma	0.336	0.0624	0.241
Acute myeloid leukemia	0.324	0.736	0.863
Brain lower grade glioma	0.0813	0.0065*	0.0771
Liver hepatocellular carcinoma	0.576	0.412	0.156
Lung adenocarcinoma	0.185	0.0901	0.00301*
Lung squamous cell carcinoma	0.817	0.753	0.895
Ovarian serous cystadenocarcinoma	0.376	0.391	0.422
Pancreatic adenocarcinoma	0.00141*	0.000143*	0.0018*
Rectum adenocarcinoma	0.951	0.422	0.15
Sarcoma	0.75	0.701	0.191
Skin cutaneous melanoma	0.148	0.758	0.641
Stomach adenocarcinoma	0.073	0.788	0.965
Uterine corpus endometrial carcinoma	0.493	0.821	0.892

* $p < 0.05$.

11 tandem zinc finger domains located C-terminal to the BTB/POZ domain [14]. Both studies establish that ZBTB48, renamed by Li *et al*. [9] as TZAP for telomeric zinc finger-associated protein, has a greater tendency to bind hyperextended telomeres in mouse stem cells and cancer cells, irrespective of whether telomerase or ALT is operational. TZAP appears to compete with TRF1 and TRF2 for binding to telomeres, and its association could be contingent on the exhaustion of free shelterin, possibly as telomeres replicate and elongate [8,9]. Therefore, its genetic change may be associated with chromosomal instability and associated disease, especially cancers. Based on this hypothesis, we searched ZBTB48 (TZAP) expression level in TCGA data. Its expression level was studied in 22 kinds of cancers and their prognosis could be calculated according to cancer types. In many cancers, TZAP was highly expressed and showed a prognostic values. Interestingly, higher expression of TZAP was

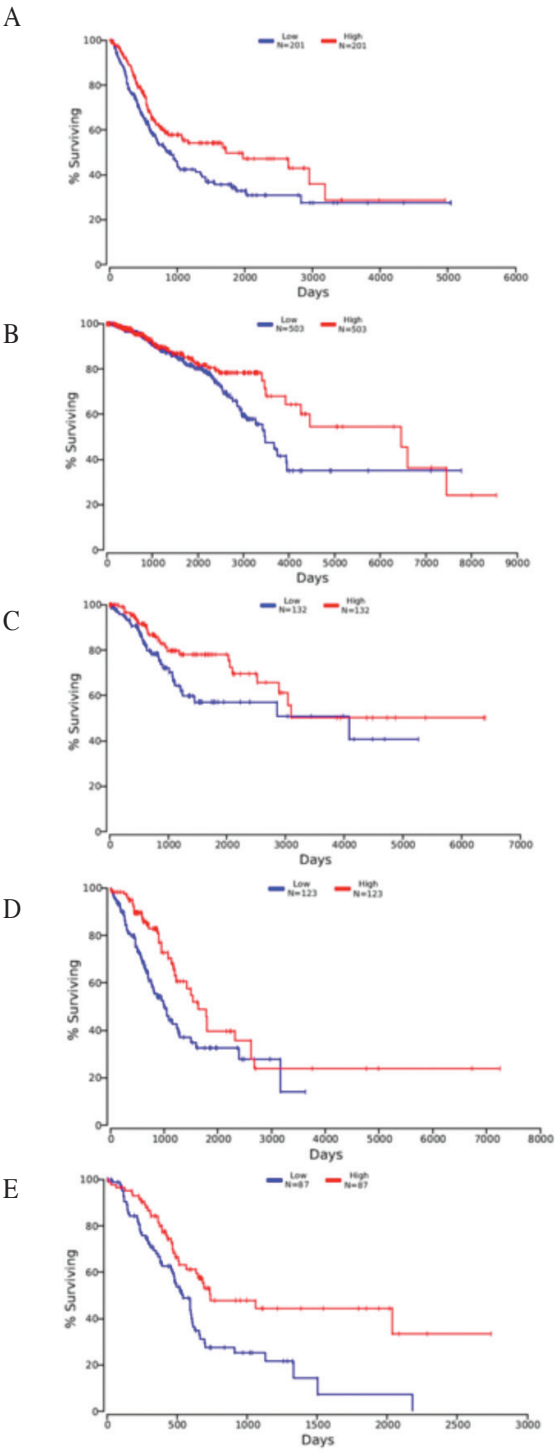

Fig. 1. TZAP expression showing good prognosis in cancers. (A) Bladder urothelial carcinoma, (B) Breast invasive carcinoma, (C) Cervical squamous cell carcinoma, (D) Lung adenocarcinoma, (E) Pancreatic adenocarcinoma.

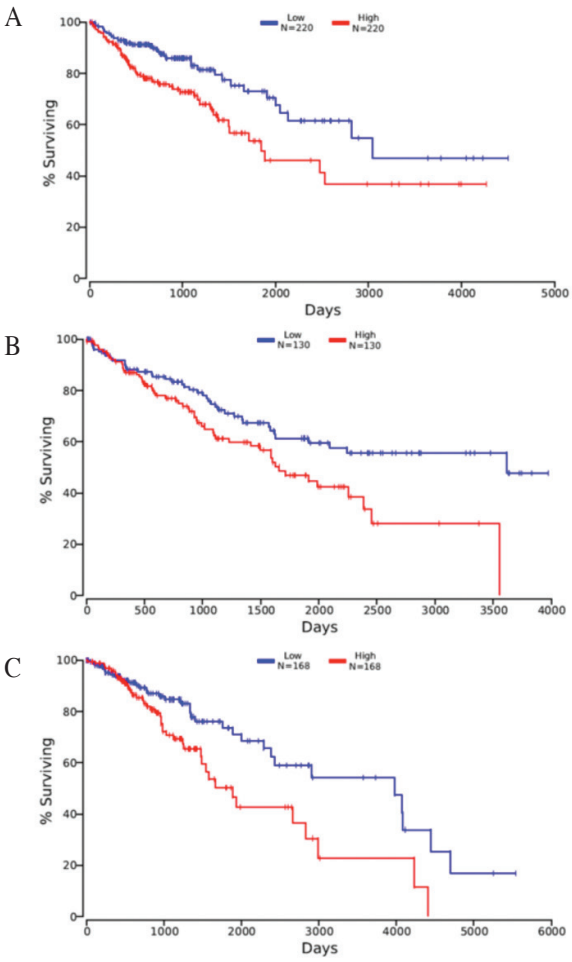

Fig. 2. TZAP expression showing poor prognosis in various cancers, (A) Colon adenocarcinoma, (B) Kidney renal clear cell carcinoma, (C) Brain lower grade glioma.

associated with better survival result in some cancers, however, it expected a poorer prognosis in other cancers. The authors suggested that TZAP may have a different role and produce a different effect on telomere regulation and cancer cell survival according to cancer type. Further study about its clinico-pathological characteristics according to cancer types may give us more interesting information.

Mutations in TZAP gene have been reported rarely in various cancers [15]. However, there was

no cancer study only focused on TZAP mutation. Therefore, TZAP mutation and expression should be studied in Korean patients with cancer further and detail molecular mechanism of TZAP function also should be identified.

In conclusion, we studied the prognostic characteristics of TZAP expression in various cancers. The results of the present study warrant future large-scale studies to elucidate the underlying molecular mechanisms of TZAP and to determine the potential clinical utility.

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