MEX3A and MEX3B as Potential Prognostic Indicators in Stomach Adenocarcinoma

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Abstract

Stomach adenocarcinoma(STAD) is one of the deadliest cancers in the world. The expression levels of family members of mex-3 RNA that bound MEX3A (member A) and MEX3B (member B) were high expressions in different cancers and interconnected to deficient prognosis. The present research assessed the potential regarding the expression of MEX3A and MEX3B in STAD by analysing the facts of STAD (viz. The Cancer Genome Atlas). TCGA, MEX3A and MEX3B in the cancers were analyzed using TIMER2.0, Kaplan Meier Plotter, and cBioPortal. The data was visualized using version 4.0.3 of R. We found MEX3A and MEX3B had various expressions regarding major cancer and relevant common tissues. Especially, high expression of MEX3A and MEX3B had relationships with the OS (namely overall survival) with deficiency and RFS (viz. relapse-free survival) concerning STAD. The expressions of MEX3B had correlations to T stage with P being 0.012 and to the race with P being 0.049. MEX3B was highly expressed in T3 and T4 stages, and was highly expressed in the white race. MEX3A mutation had a better survival without diseases, with P being 0.0205. However, the situation was different with non-overall survival, with P being 0.194, in comparison with the patients who did not have MEX3A change. MEX3A and MEX3B on tumor pathogenesis might be related to "RNA splicing" and "spliceosomal complex" and "single-stranded RNA binding". We further investigated the association between MEX3A and MEX3B and immune cells. The mast cells of the most connections to MEX3A (R=-0.300, P<0.001) and the NK cells were positively correlation with MEX3B (R=0.590, P<0.001). It showed that they might be potential prognostic molecular biomarkers in patients with STAD.

1. Introduction

Stomach adenocarcinoma (STAD) is one of the deadliest tumors that harm human health, ranking at the fifth place regarding cancer with the most frequency in diagnosis. It was in third place as the trigger of deaths caused by cancer worldwide, based on statistical facts of cancers in the world [1]. The cancer's incidence and mortality has witnessed a constant for ten decades. With the development of the economy, the improvement of living conditions has helped to decrease the popularity of the primary trigger for gastric cancer, known as Helicobacter pylori [2, 3]. Surgical resection or endoscopic resection are major objectives of therapies, although there are better perceptions of gastric cancer from a biological perspective. However, the rate of survival of five years is insignificant [4]. Recently, immunotherapies and targeted therapies, including inhibitors of the checkpoint of immunity specifying PD-L1, indicated prospects regarding improving outcomes among the patients who had microsatellite unstable cancers[5]. But only a minority of people with STAD can benefit from it[6]. Therefore, proposing novel biomarkers has importance concerning its efficiency and quick modification and healing for patients with STAD.

MEX3A and MEX3B belong to the MEX3 family, which includes four constituents clarified based on genes with variety in mammals: MEX3A, MEX3B, and MEX3C, as well as MEX3D. The proteins are clarified consist of two domains of KH with ribonucleoprotein with heterogeneity (K homology). It also has a module of the finger of Ring with the terminal of carboxy. MEX3 is a phosphoprotein binding RNA by the ranger of KH and medium on a pathway of outputs dependent on CRM1 across the nucleus and

cytoplasm [7]. The mammalian importance on the gene of MEX remains unexplored. However, MEX3A of the human has correlations with the dryness of colon cancer cells[8]. One study showed that MEX3A promoted metastasis of adenocarcinoma regarding lungs via the pathway of PI3K/Akt [9]. Other studies have shown that MEX3A promotes cancer progression in glioblastoma[10], pancreatic ductal adenocarcinoma[11], and breast cancer[12]. MEX3B is associated with innate immunity. MEX3B is found to have effects being a co-receptor of TLR3 concerning the response of antiviral of innateness. It binds to dsRNA. Also, it improves the activity that binds dsRNA for TLR3[13]. In one study, the MEX3B of the protein that binds RNA was indicated to be the most capable potential factor for alleviating sensitivity of the cells of melanoma for the elimination of TIL. The increase in the expression of MEX3B had correlations with prevention from the block of PD-1 [14]. Research on cancer showed that MEX3B induces Runx3 ubiquitination and enhances aggression of cells of cancer of gastric [15]. However, whether the expression and prognosis of MEX3A and MEX3B had correlations with clinicopathological parameters of STAD remains unclear.

The present research aimed to investigate the differential expression of MEX3A and MEX3B in patients with STAD and the correlations with parameters of clinics based on the data from TCGA. Besides, the mutation pathway and the predictive function of MEX3A and MEX3B were analyzed. The paper reveals potential new therapeutic targets for STAD.

2. Methods

2.1 Data collocation

We downloaded the data regarding of presentation of genes and the relevant features of the data in clinics concerning gastric cancer from The Cancer Genome Atlas (https://portal.gdc.cancer.gov/). Four hundred and seven samples of TCGA were retrieved. Of them, 375 had gastric cancer, and 32 were normal. Three hundred and seventeen gastric cancer samples contained complete clinical information.

2.2 Genes expression profiles

Then, we used the Timer2 online database (http://timer.cistrome.org/) analysis of MEX3A and MEX3B expression in the case of 33 kinds of tumors[16]. The significance assessed using the test of Wilcoxon is expressed through how many asterisks there are (*** being p-value less than 0.001; ** being p-value less than 0.01; and * being p-value less than 0.05). We explored how MEX3A and MEX3B were presented amongst gastric cancer and normal tissues, as well as those of tumor and paired non-tumor ones, according to the database of TCGA.

2.3 Survival analysis

Kaplan Meier Plotter is a website whose primary purpose is the discovery and validation of survival biomarkers based on meta-analysis. Database sources include GEO database (viz. Gene Expression Omnibus, https://www.ncbi.nlm.nih.gov/geo/), TCGA, and EGA database (viz. The European Genome-

phenome Archive, https://ega-archive.org/) [17]. Kaplan Meier Plotter performs survival analysis following level of expression of genes and evaluations of hypotheses through the test of log ranks. We used Kaplan Meier Plotter to investigate the correlations of presentation and prognosis of the MEX3A and MEX3B in cancer of gastric (including databases of TCGA and GEO). We regrouped the patients using auto select with the most optimal cutoff into two cohorts. The MEX3A and MEX3B with an expression at a low level was referred to black. The one at a high level was shown in the red curve. The X axis or the horizontal axis denotes to months as the time factor. The Y axis or the vertical axis refers to the surviving likeliness.

2.4 Mutation profiles

A practical online tool named cBioPortal is used via http://cbioportal.org. The datasets of genomics of cancers with multidimensions are searched. The data of samples of tumors are collected from over 20 cancer studies[18]. We used this database to study MEX3A and MEX3B mutations in STAD and analyze the genomic variation types and mutation frequencies of STAD.

2.5 Constructing network of PPI (Protein–protein interaction) and enrichment analysis

The present paper indicated the regulation of synergistic protein of MEX3A and MEX3B. It also assessed interactions of functions crossing nodes based on the database of STRING via the link http://string-db.org [19]. The interaction that showed a score larger than 0.4 referred to significance. Analysis of GO (viz. Gene ontology) such as CC (cellular component) and MF (molecular function), as well as BP (biological process). The P value less than 0.05 meant significance [20]. Moreover, an analysis of the pathway of KEGG (namely Kyoto encyclopedia of genes and genomes) was conducted [21].

2.6 Immune infiltration

We used the GSVA R package to explore whether there was correlation between MEX3A and MEX3B and the cells of immunity (NK CD56bright cells; T cells; DC; Eosinophils; activated DC [aDC]; Mast cells; CD8 T cells; Neutrophils; B cells; Cytotoxic cells; T effector memory [Tem]; T helper cells; Plasmacytoid DC [pDC]; Macrophages; immature DC [iDC]; NK CD56dim cells; NK cells; T central memory [Tcm]; T follicular helper [Tfh]; T gamma delta [Tgd]; cells of Th1; cells of Th2; cells of Th17; Treg)[22]. The markers of 24 immune cells are derived from an article on Immunity[23]. The P-values and correlation (cor) values were obtained via the Spearman's rank correlation test.

2.7 Statistical analysis

R (version 4.0.3) was used to analyze the data. The test of Wilcoxon rank-sums was adopted for a comparison of how MEX3A and MEX3B were presented between gastric cancer and the normal group. The test of Wilcoxon signed ranks was applied to estimate whether the correlation existed between MEX3A and MEX3B and clinicopathological variables. If P was less than 0.05, there was significance.

3. Results

3.1 Transcriptional levels concerning MEX3A and MEX3B among various cancer categories

The levels of expressions in the dataset of TCGA were adopted to assess various presentations regarding MEX3A and MEX3B among different tumor tissues and normal issues by TIMER2.0. Figure 1A indicated that MEX3A had high expressions in carcinoma of urothelial of bladder (viz. BLCA), cholangiocarcinoma (viz. CHOL), carcinoma of invasiveness of breast (viz. BRCA), head and neck squamous cell carcinoma (viz. HNSC), kidney renal papillary cell carcinoma (viz. KIRP), prostate adenocarcinoma (viz. PRAD), esophageal carcinoma (viz. ESCA), colon adenocarcinoma (viz. COAD), stomach adenocarcinoma (viz. STAD), GBM (viz. glioblastoma multiforme), lung squamous cell carcinoma (viz. LUSC), rectum adenocarcinoma (viz. READ), lung adenocarcinoma (viz. LUAD), kidney renal clear cell carcinoma (viz. KIRC), liver hepatocellular carcinoma (viz. LIHC), thyroid carcinoma (viz. THCA), and uterine corpus endometrial carcinoma (viz. UCEC) in comparison with relevant normal tissues. Furthermore, MEX3A had high presentations in metastasis of HPV-HNSC+ and that of cutaneous skin melanoma (viz. SKCM). However, expression of MEX3A had a lower level in kidney chromophobe (viz. KICH) in comparison with related normal tissues. According to Figure 1B, MEX3B had more LUAD, ESCA, pheochromocytoma and paraganglioma (viz. PCPG), LIHC, KIRC, CHOL, HNSC, KIRP, LUSC, metastasis of STAD and SKCM. However, it had a lower level in KICH, esophageal carcinoma (viz. ESCA), and UCEC in comparison with relevant normal tissues.

3.2 MEX3A and MEX3B were highly expressed in STAD

The test of Wilcoxon-rank sum was used to evaluate how MEX3A and MEX3B were expressed among the features of various tissues. It was found that MEX3A and MEX3B were presented among tissues of gastric cancers had greater relationships, compared with that in normal tissues (Figure 2A: MEX3A, $P=7.419\times10^{-16}$; Figure 2C: MEX3B, $P=1.873\times10^{-5}$). Subsequently, we used Wilcoxon-rank test to determine MEX3A and MEX3B expression in 27 gastric cancer tissues and matched normal tissues. The results showed that the expression of MEX3A and MEX3B in normal tissues was significantly lower than that in cancer tissues (Figure 2B: MEX3A, $P=3.18\times10^{-10}$; Figure 2D: MEX3B, P=0.021).

3.3 Prognostic of MEX3A and MEX3B in STAD

We investigated whether MEX3A and MEX3B expression had relationships with patients with cancer of prognosis. The database of Kaplan Meier Plotter was used for analyzing the prognostic value regarding MEX3A and MEX3B following Affymetrix microarrays. We regrouped the patients using auto choosing with the most satisfying cutoff into two cohorts. Interestingly, we found that all of the probes associated with MEX3A with the expression of MEX3A at a high level. It had relationships with OS at a poor level. Figure 3A indicated that probe expression was at a high level of 226346. It had relationships with OS at a poor level (95% CI being 1.06 -1.7, HR being 1.34, logrank P being 0.016). The same result was observed in probe 236885_at (Figure 3B, 95% CI being 1.09 -1.73, HR being 1.37, logrank P being 0.0077). The 227512 was_at (Figure 3C, 95% CI being 1.34 -2.22, HR being 1.73, logrank P being 1.6×10^{-5}). Only one

probe was associated with the MEX3B gene, and the results indicated that MEX3B had a high level of expression. It had relationships with OS at a poor level (Figure 3F, 95% CI being 1.11 -1.75, HR being 1.4, logrank P being 0.0041). The data of sequences of RNA among TCGA were adopted for further analysis for figuring out whether the MEX3A and MEX3B had prognostic potential among gastric cancer. Similarly, results of Affymetrix microarrays showed that high expression of MEX3A had correlations with OS at a poor level (Figure 3D, 95% CI being 1.01 -2.19, HR being 1.49, logrank P being 0.043) and RFS (Figure 3E, HR=2.4, 95% CI=1.25 -4.6, logrank P =0.0067). As shown in Figures 3G and 3H, MEX3B had expression at a high level. It had relationships with OS at a poor level (Figure 3G, HR being 1.59, logrank P being 0.011, 95% CI being 1.11 -2.27). It was the same with RFS (Figure 3H, 95% CI being 1.15 -6.63, HR being 2.76, logrank P being 0.018).

3.4 Correlations of MEX3A with MEX3B and patients' parameters of clinicopathology with STAD

For demonstrating the relationships and potential mechanism to present MEX3A and MEX3B in cancer, the correlations were studied between MEX3A and MEX3B on the expression and the features of clinics of patients who had gastric cancer in the database of TCGA. The levels of MEX3A and MEX3B expressions, the patients were regrouped into two cohorts at a high level and low level of expression. The correlation was calculated between the levels of MEX3A and MEX3B expression and features in clinics. We used chi-square test and T test to carry out data analysis (as shown in Table 1). The expression of MEX3A had no correlation with features in clinics. However, expression of MEX3B had relationships with race (P being 0.049) and T stage (P being 0.012). We found that MEX3B was highly expressed in T3 and T4 stages, and was highly expressed in the white race. The MEX3B was expressed with a relationship with pathologic type (P being 0.056) and pathologic stage (P being 0.069), but not significantly.

Table 1. Relationship between expression of MEX3A and MEX3B and clinicopathological features

Characteristic	Low expression of MEX3A	High expression of MEX3A	p	Low expression of MEX3B	High expression of MEX3B	p
n	187	188		187	188	
T stage, n (%)			0.286			0.012
T1	12 (3.3%)	7 (1.9%)		14 (3.8%)	5 (1.4%)	
T2	42 (11.4%)	38 (10.4%)		48 (13.1%)	32 (8.7%)	
T3	75 (20.4%)	93 (25.3%)		81 (22.1%)	87 (23.7%)	
T4	53 (14.4%)	47 (12.8%)		41 (11.2%)	59 (16.1%)	
N stage, n (%)			0.955			0.205
N0	54 (15.1%)	57 (16%)		53 (14.8%)	58 (16.2%)	
N1	51 (14.3%)	46 (12.9%)		48 (13.4%)	49 (13.7%)	
N2	38 (10.6%)	37 (10.4%)		45 (12.6%)	30 (8.4%)	
N3	37 (10.4%)	37 (10.4%)		32 (9%)	42 (11.8%)	
M stage, n (%)			0.965			0.668
M0	163 (45.9%)	167 (47%)		167 (47%)	163 (45.9%)	
M1	13 (3.7%)	12 (3.4%)		11 (3.1%)	14 (3.9%)	
Pathologic stage, n (%)			0.914			0.069
Stage I	27 (7.7%)	26 (7.4%)		35 (9.9%)	18 (5.1%)	
Stage II	57 (16.2%)	54 (15.3%)		49 (13.9%)	62 (17.6%)	
Stage III	75 (21.3%)	75 (21.3%)		73 (20.7%)	77 (21.9%)	
Stage IV	17 (4.8%)	21 (6%)		19 (5.4%)	19 (5.4%)	
Gender, n (%)			0.221			0.884
Female	73 (19.5%)	61 (16.3%)		68 (18.1%)	66 (17.6%)	
Male	114 (30.4%)	127 (33.9%)		119 (31.7%)	122 (32.5%)	
Race, n (%)			0.956			0.049
Asian	37 (11.5%)	37 (11.5%)		41 (12.7%)	33 (10.2%)	

Characteristic	Low expression of MEX3A	High expression of MEX3A	p	Low expression of MEX3B	High expression of MEX3B	p
Black or African American	6 (1.9%)	5 (1.5%)		8 (2.5%)	3 (0.9%)	
White	122 (37.8%)	116 (35.9%)		104 (32.2%)	134 (41.5%)	
Age, n (%)			0.953			0.422
<=65	81 (21.8%)	83 (22.4%)		77 (20.8%)	87 (23.5%)	
>65	104 (28%)	103 (27.8%)		107 (28.8%)	100 (27%)	
Histological type, n (%)			0.180			0.056
Diffuse Type	41 (11%)	22 (5.9%)		26 (7%)	37 (9.9%)	
Mucinous Type	8 (2.1%)	11 (2.9%)		6 (1.6%)	13 (3.5%)	
Not Otherwise Specified	99 (26.5%)	108 (28.9%)		105 (28.1%)	102 (27.3%)	
Papillary Type	2 (0.5%)	3 (0.8%)		2 (0.5%)	3 (0.8%)	
Signet Ring Type	6 (1.6%)	5 (1.3%)		4 (1.1%)	7 (1.9%)	
Tubular Type	31 (8.3%)	38 (10.2%)		44 (11.8%)	25 (6.7%)	
Age, meidan (IQR)	68 (58, 72)	67 (59, 74)	0.919	66.53 ± 10.75	65.14 ± 10.54	0.212

3.5 Genetic alteration analysis

Recently, it has been shown that TMB (namely, tumor mutation burden) has relationships with increased immunotherapeutic responses in clinics [24]. Therefore, we analyzed the mutation of MEX3A and MEX3B and their correlation with prognosis with the tool of cBioPortal in the cohort of TCGA STAD. Currently, various changes in genes regarding MEX3A and MEX3B included mutation, amplification, deep deletion, multiple alterations, as shown in Figure 4A,4B. MEX3A and MEX3B altered in 8.99% (39) of 434 cases in STAD, and Mutation (24 cases) was the most frequently altered form. In addition, we analyzed potential relationships of alteration of genes between MEX3A and MEX3B and survival prognosis in clinics of gastric cancer. Data in Figure 4D, 4C showed the patients who had MEX3A mutation showed a better survival without diseases (P being 0.0205); instead of all the survival (P being 0.194), in comparison of the patients without MEX3A change. We found that the MEX3B gene alteration was not associated with prognosis (Figure 4E, 4F).

3.6 Interaction networks and enrichment analysis of MEX3A and MEX3B

The mechanism of molecules of genes of MEX3A and MEX3B in tumorigenesis was investigated. We tried to screen out targeted MEX3A and MEX3B binding proteins for analyzing enrichment of the pathways. We obtained a total of 50 MEX3A and MEX3B-binding proteins through the STRING website. According to Figure 5A, the interaction network was among the proteins. These proteins were analyzed using enrichment of GO and KEGG. The data of GO was in Figure 5B. The influence of MEX3A and MEX3B on tumor pathogenesis might be related to "RNA splicing" and "spliceosomal complex" and "single-stranded RNA binding". The data to analyze pathway of KEGG showed the majority of such genes were involved in spliceosome and RNA degradation (Figure 5C).

3.7 Immune infiltration

The cells of immunity that infiltrated tumors are crucial to the microenvironment of tumors. They have close correlations with the occurrence, progression or metastasis of cancer[25]. Figure 6A showed a negatively correlation between MEX3A and cells of T helper, macrophages, cells of Th17, TFH, Treg, cells of T of CD8, neutrophils, cells of Th1, iDC, aDC, mast cells, eosinophils, NK D56dim cells, B cells, DC, T cells, pDC, cells of cytotoxins. However, a positive correlation was found between MEX3A and Th2 cells, Tgd cells (all $P < 0.05$). Figure 6C shows the mast cells have the strongest relationships compared with MEX3A (Spearman R being -0.300, P less than 0.001). In contrast to the results of MEX3A, MEX3B had positive relationships with the majority of cells of immunity. According to Figure 6B, MEX3B had positive relationships with iDC, NK cells, Tem, mast cells, macrophages, pDC, TFH, eosinophils, cells of B, Tgd, cells of Th1, DC, Tcm, cells of T of CD8, cells of cytotoxin, T cells, Treg, but was negatively correlated with Th17 cells (all $P < 0.05$). Moreover, in Figure 6D, NK cells had a higher level of expression at a high level in the cohort of MEX3B (Spearman R being 0.590, P less than 0.001).

4. Discussion

Regulating the procedures of post-transcriptions of mRNA is essential for controlling the presentations of genes of eukaryotes. RBP (namely, RNA-binding protein) is a key determinant of mRNA fate, and abnormal expression of RBP has correlations with the development in different diseases, such as cancer[26, 27]. Human MEX3 is one of the new groups of RBPs with novel conservation, which had two KH RBDs, including MEX3A, -3B, and -3C, as well as -3D. They are found at various chromosomes such as 15q25.2, 1q22, and 18q21.1, as well as 19p13.3 [7]. Their roles in tumorigenesis remain to be elucidated. Our current study focused on the prognostic value of MEX3A and MEX3B in STAD.

Our study showed that MEX3A had high expressions in the majority of tissues of tumor in comparison to common tissues. The same results were observed in gastric cancer. This is consistent with previously published studies, and they found that small interfering RNA silencing of MEX3A effectively inhibited proliferation of the cells in cancer of gastric of AGS and those in SNU-16 [28]. Another study has shown

that depletion of MEX3A induces a pathway of PPAR (namely, peroxisome proliferator-activated receptor) regarding the intestinal crypt, as well as a reduction for signaling of the Wnt and deficiency of signaling of cells of LGR5 plus stem [29]. In patients with PDAC (viz. pancreatic ductal carcinoma), rising expression of MEX3A have relationships with the stage of disease at a higher level and prognosis at a poorer level. Fewer MEX3A in the cells of PDAC made gemcitabine more sensitive to chemotherapy[30]. The present research indicated that expression of MEX3A at a high level had relationships with poor prognosis in the databases of GEO and TCGA. However, we did not find an association between MEX3A and clinical features.

At present, there is little research on the MEX3B gene, especially in relation to tumor. Studies have shown that Mex3b is a novel therapeutic target for infecting the HBV and liver cancer relating to HBV of prognosis at a poor level [31]. In some studies, the role of MEX3B as RNA binding protein and as a ubiquitination enzyme was mainly explored[13, 32]. Our study showed that MEX3B had expressions at a high level in the tissues of gastric cancer tumor in comparison to common ones. It also had expression at a high level regarding MEX3B. It had relationships with RFS and OS at a poor level. We further explored whether MEX3B had relationships with features in clinics. We found that MEX3B had expressions at a high level at the stages of T3 and T4. It was highly expressed in the white race. However, MEX3B had relationships on expressions with the stage of pathology and its categories, but not significantly.

Recently, it has been suggested that TMB (namely, tumor mutation burden) has relationships with prognosis[33]. Therefore, we further analyzed the mutation of MEX3A and MEX3B and its correlation with prognosis. In this study, the changes of MEX3A and MEX3B accounted for 8.99%, among which mutations (24 cases) had the most changes. In addition, we also studied the potential correlation between the changes of MEX3A and MEX3B genes and the clinical survival prognosis of gastric cancer. The results showed that patients with modified MEX3A had better disease-free survival compared with patients without modified MEX3A. Considering the cohort of the patients who had mutation was not large, there might be unreliable findings. In this study, MEX3A and MEX3B were investigated using the analysis of GO. It had enrichment for the "RNA splicing" and "spliceosomal complex" and "single-stranded RNA binding". The data of the pathway of KEGG was investigated. It found that the majority of such genes were involved in spliceosome and RNA degradation.

Since immune cells are critical to the tumor existence and its progression [34], we studied the correlation between MEX3A and MEX3B and the cells of immunity. The MEX3A had negative relationships with the majority of the cells of immunity. It shows the reasons that the patients who had MEX3A expression at a high level revealed a prognosis at a low level. However, MEX3B is positively correlated with most immune cells, especially NK cells, which is contrary to the result that its high expression leads to a poor prognosis. Therefore, further experimental verification is needed.

The present paper is the first research that explores the potential prognostic functions that MEX3A and MEX3B perform in STAD. MEX3A and MEX3B had potential value as biomarkers for the prognosis of gastric cancer. However, there are some limitations. First, the data was only based on a single public

database. Therefore, future studies should eliminate analytical bias considering the retrospect of this paper. Second, this paper is based on high-throughput gene sequencing data from the TCGA database, and we need further experimental validation to continue our efforts to explore their direct mechanisms in gastric cancer. In conclusion, the levels at which MEX3A and MEX3B were expressed had been elevated among the tissues of gastric cancers. They had relationships with prognosis at a poor level. It shows that they may be potential prognostic molecular predictors in patients with STAD. These findings contribute unprecedented insights regarding gastric cancer treatments.

Declarations

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Data Availability Statament

The data of the article comes from public database, which is open access.

Author Contribution Statement

C.Xing, R.Wang:Study design. J. Zou: Data collection and major analysis. C.Xing, R.Wang: Study supervision. J. Zou and Y. Huang: Data analysis and data interpretation. Z. Wu and H. Xie: Statistical analysis. J. Zou and Y. Huang: Manuscript draft. All authors read and approved the final manuscript.

Conflict of Interest Statament

None declared.

Ethics Statement

None.

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Figures

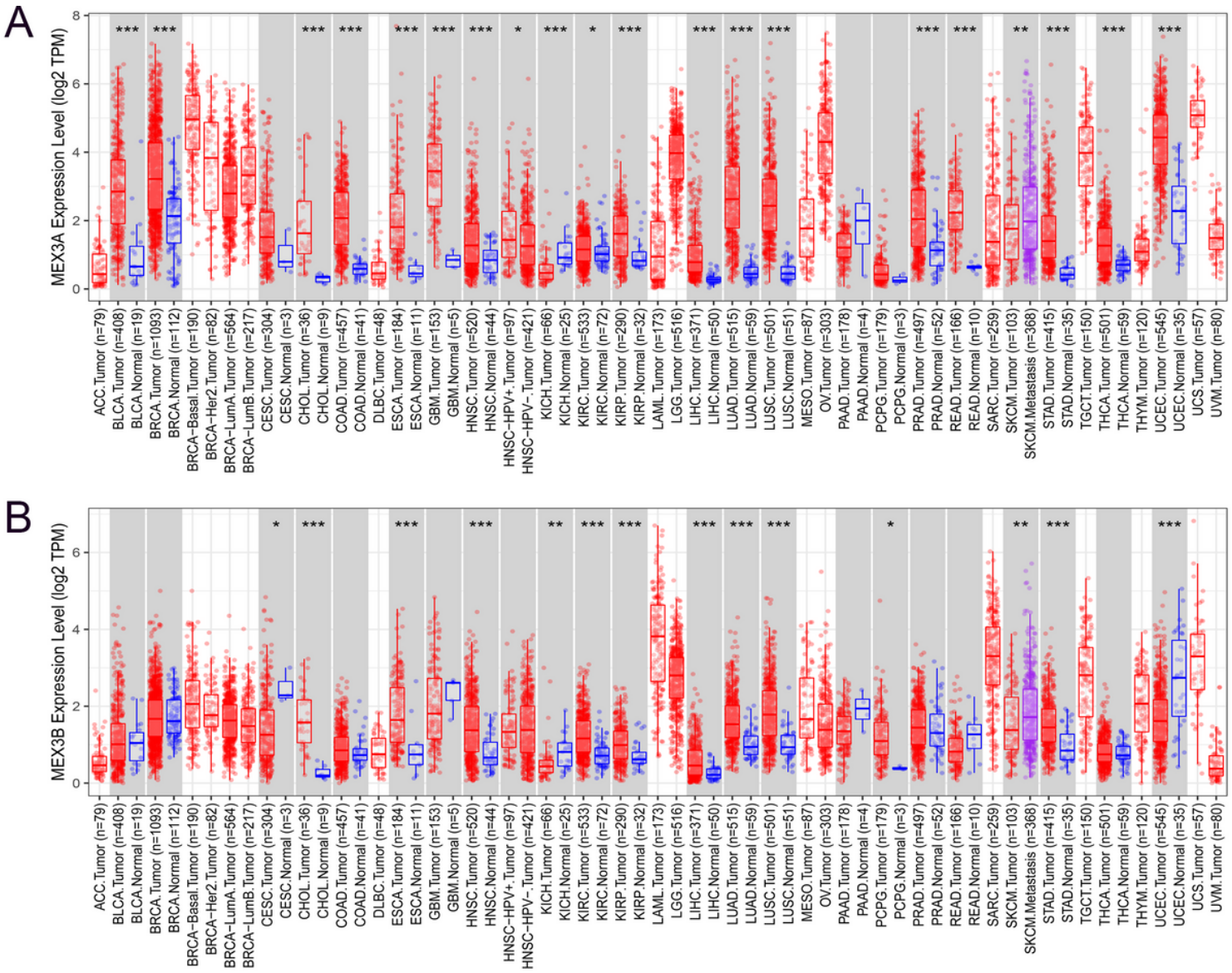

Figure 1

Levels of transcribing MEX3A and MEX3B among various cancer categories. 1A: Levels of transcribing MEX3A among various cancer categories. 1B: Levels of transcribing MEX3B among various cancer categories.

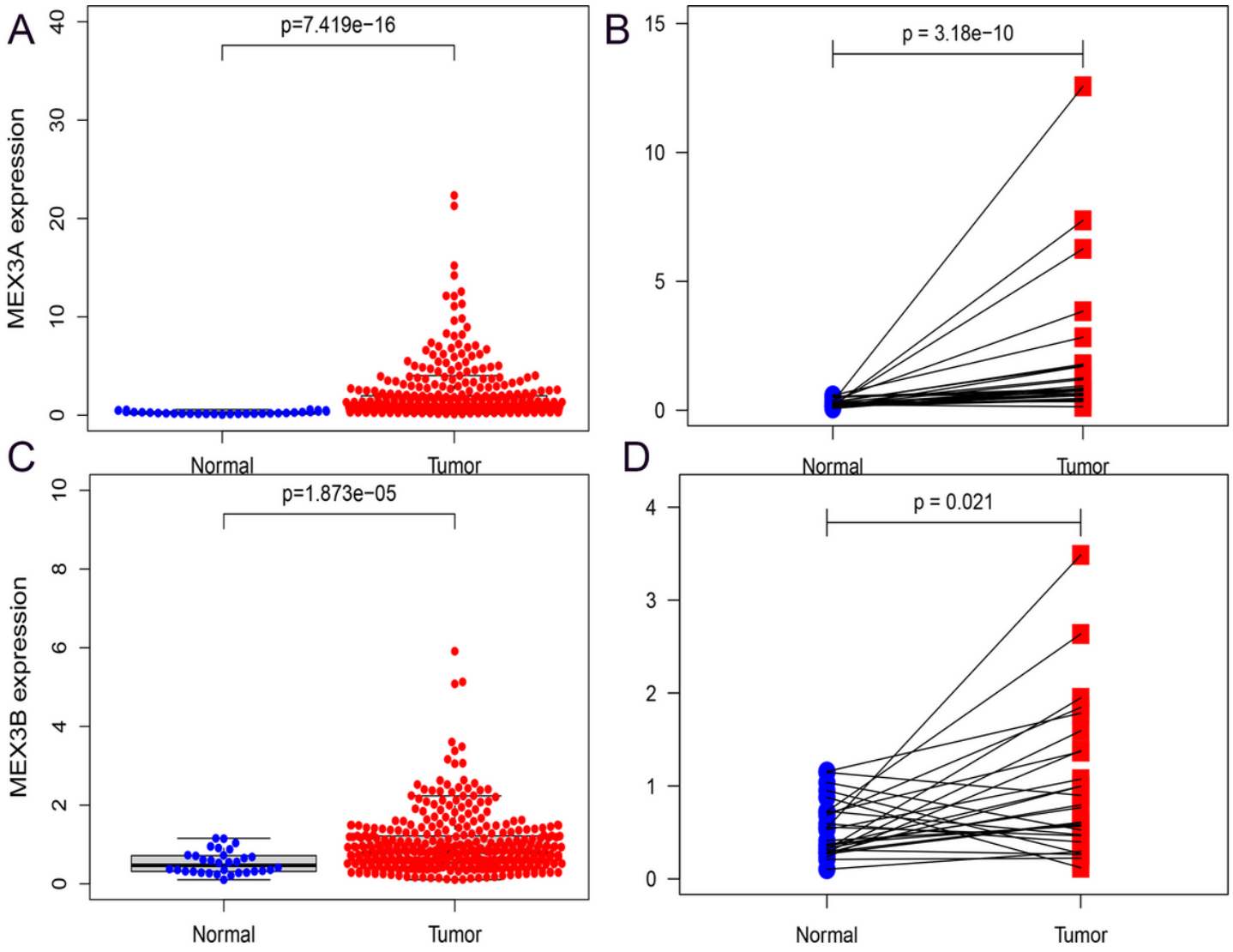

Figure 2

The MEX3A and MEX3B were expressed among the STAD. 2A: Expression of MEX3A had significance at a higher level among the tissues of cancers than among common ones. 2B: The expression of MEX3A had significance at a higher level among the tissues of gastric cancers than among the 27 paired noncancerous relevant ones. 2C: MEX3B expression was significantly higher in cancer tissues than in normal tissues. 2D: The expression of MEX3B had significance at a higher level among the tissues of gastric cancers than among the 27 paired noncancerous relevant ones.

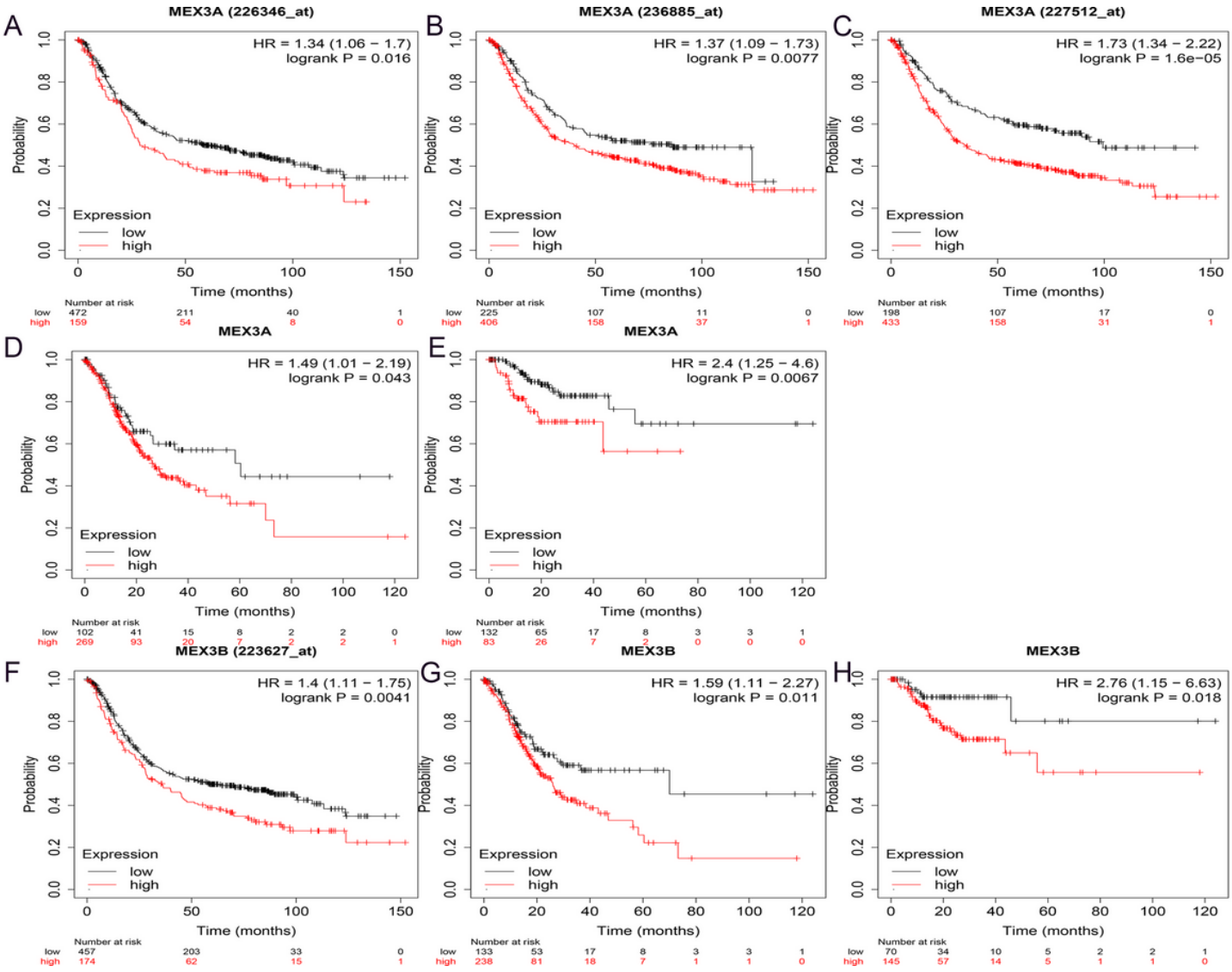

Figure 3

The prognostic value of MEX3A and MEX3B in STAD by using Kaplan Meier Plotter. 3A-3C: all of the probes associated with MEX3A were associated with poor OS in GEO database. 3D: MEX3A had expressions at a high level with a relationship with OS at a poor level in the database of TCGA. 3E: MEX3A had expression at a high level with a relationship with RFS at a poor level in the database of TCGA. 3F: the probe associated with MEX3B had correlations with OS at a poor level in the database of GEO. 3G: MEX3B had expression at a high level had relationships with OS at a poor level in the database of TCGA. 3H: MEX3B had expression at a high level had correlations with RFS at a poor level in the database of TCGA.

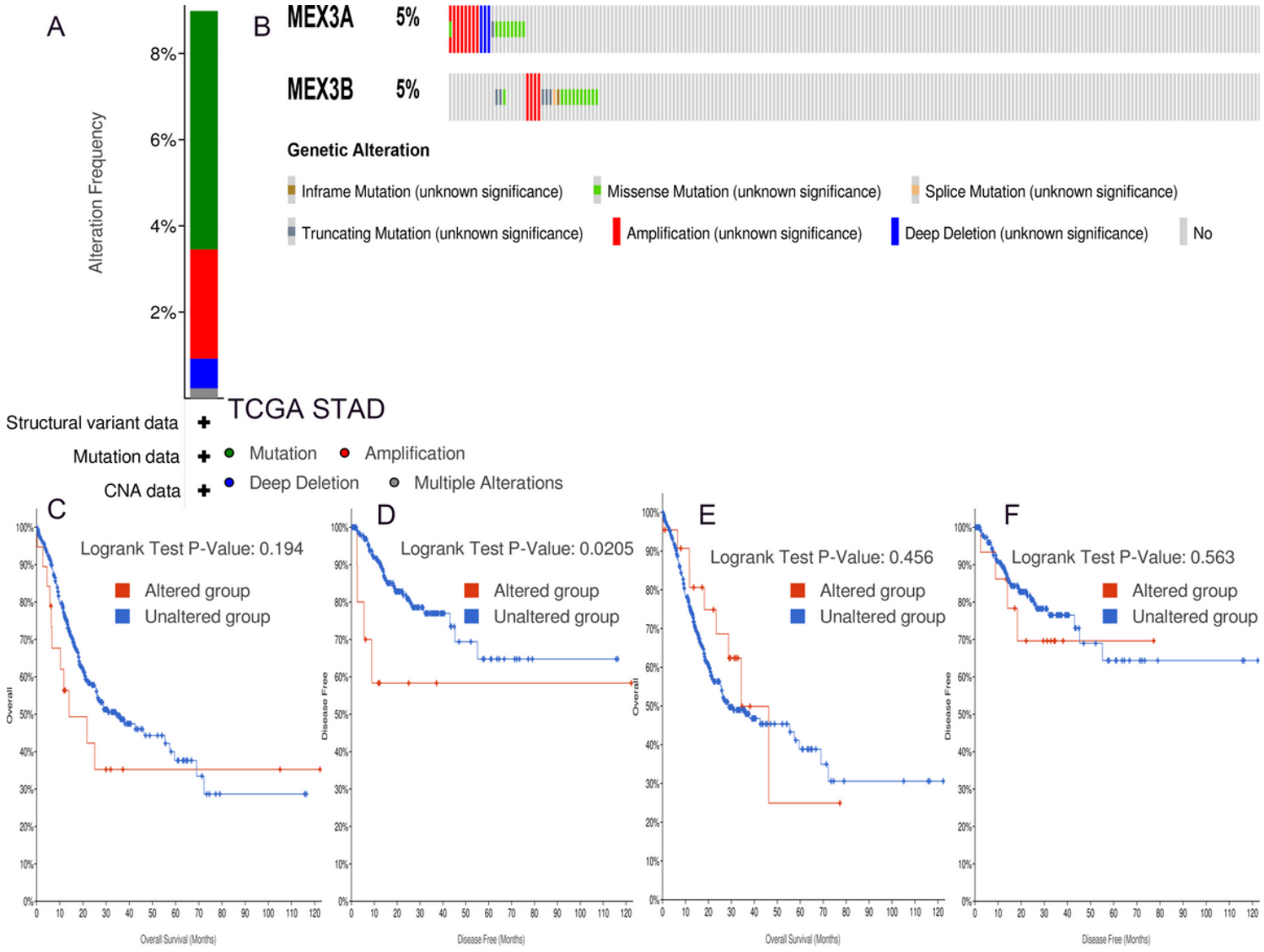

Figure 4

Genetic alterations and MEX3A prognostic functions and MEX3B among the STAD (cBioPortal). 4A-4B: graphic alteration conclusion following the interrogations regarding MEX3A and MEX3B. 4C: relationships of the alteration of genes of MEX3A with the OS in the cancer of gastric. 4D: relationships of the alteration of genes of MEX3A with the DFS in the cancer of gastric. 4E: relationships of the alteration of genes of MEX3B with the OS in the cancer of gastric. 4F: relationships of the alteration of genes of MEX3B with the DFS in the cancer of gastric.

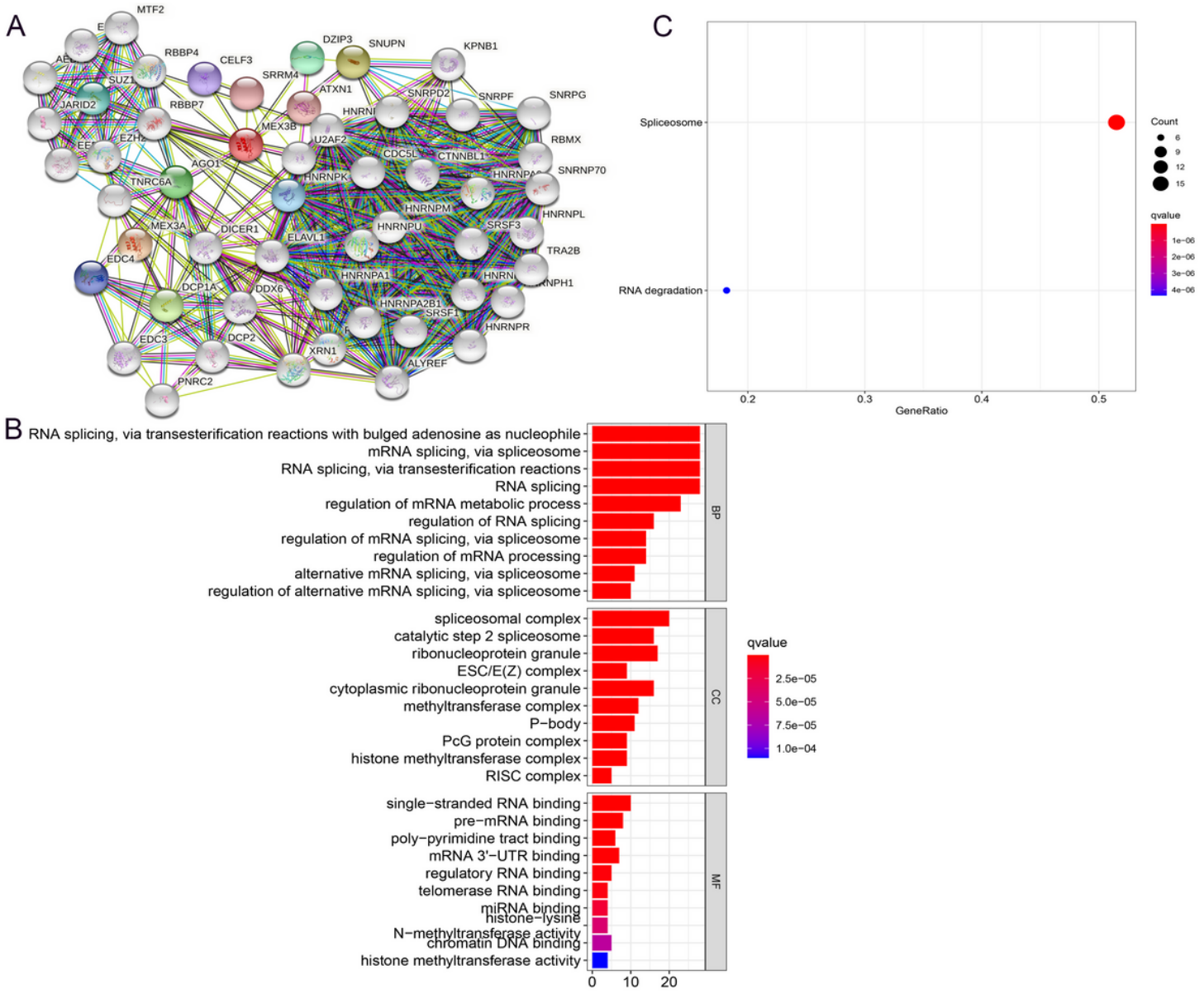

Figure 5

MEX3A and MEX3B-related genes enrichment analysis. 5A: we first use the String tool to obtain the proteins associated with Mex3A and Mex3B. 5B: GO analysis of the MEX3A and MEX3B-related genes. 5C: Based on the MEX3A and MEX3B-related genes, KEGG pathway analysis was performed.

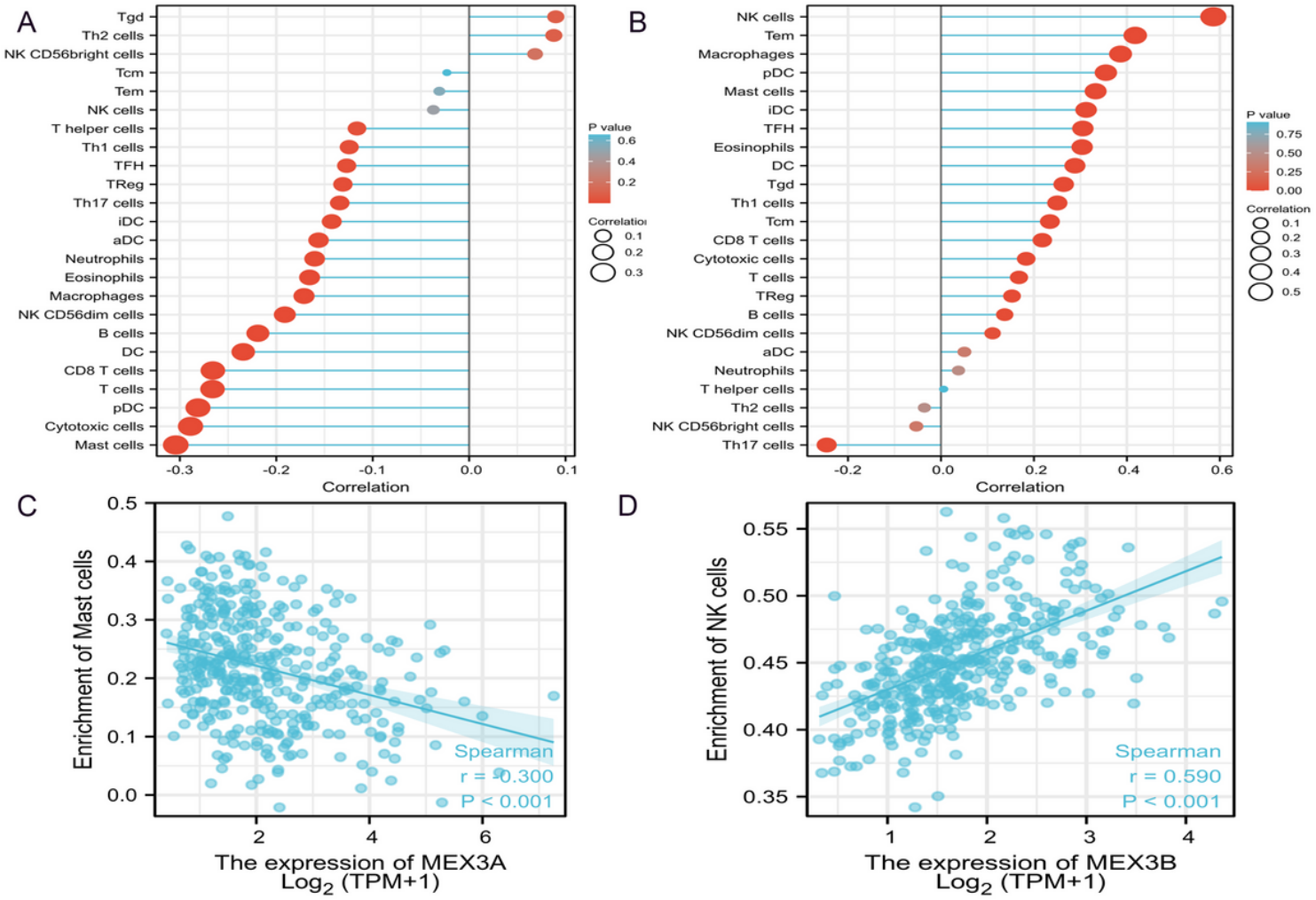

Figure 6

Correlation analysis between how MEX3A and MEX3B were expressed and infiltrating the immunity among the STAD. 6A: analyzing the relationships of expressing MEX3A and infiltrating the immunity. 6B: analyzing the relationships of expressing MEX3B and infiltrating the immunity. 6C: scatter diagrams of MEX3A and mast cells. 6D: scatter diagrams of MEX3B and NK cells.