Pan-Cancer Analysis Reveals that the SARS-CoV-2 Receptor ACE2 is a Protective Factor for Cancer Progression

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Research

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Abstract

Background: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 13 million people and has caused more than 570,000 deaths worldwide as of July 13, 2020. The SARS-CoV-2 human cell receptor ACE2 has recently received *extensive attention for its role in* SARS-CoV-2 infection. Many studies have also explored the association between ACE2 and cancer. However, a systemic investigation into associations between ACE2 and oncogenic pathways, tumor progression, and clinical outcomes in pan-cancer remains lacking.

Methods: Using cancer genomics datasets from the Cancer Genome Atlas (TCGA) program, we performed computational analyses of associations between *ACE2* expression and antitumor immunity, immunotherapy response, oncogenic pathways, tumor progression phenotypes, and clinical outcomes in 12 cancer cohorts. We also identified co-expression networks of *ACE2* in cancer.

Results: *ACE2* upregulation was associated with increased antitumor immune signatures and *PD-L1* expression, and favorable anti-PD-1/PD-L1/CTLA-4 immunotherapy response. *ACE2* expression levels inversely correlated with the activity of cell cycle, mismatch repair, TGF-β, Wnt, VEGF, and Notch signaling pathways. Moreover, *ACE2* expression levels had significant inverse correlations with *tumor* proliferation, stemness, and *epithelial-mesenchymal transition (*EMT). *ACE2* upregulation was associated with favorable survival in pan-cancer and in multiple individual cancer types.

Conclusions: *ACE2* upregulation was associated with increased antitumor immunity and immunotherapy response, reduced tumor malignancy, and favorable survival in cancer, suggesting that ACE2 is a protective factor for cancer progression. Our data may provide potential clinical implications for treating cancer patients infected with SARS-CoV-2.

Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 13 million people and has caused more than 570,000 deaths worldwide as of July 13, 2020 (https://coronavirus.jhu.edu/map.html). SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) as a host cell receptor to infect humans [1, 2, 3, 4]. ACE2 plays an important role in regulating cardiovascular and renal function [5]. This protein has recently received extensive attention for its role in SARS-CoV-2 infection [1, 2, 4]. Our recent study revealed that ACE2 is expressed in various human tissues [6], suggesting that SARS-CoV-2 may invade various human organs besides the lungs. Also, many studies have investigated the association between ACE2 and cancer [7–13]. For example, Yu-Jun et al. analyzed ACE2 expression in various cancers and revealed a positive association between ACE2 expression and survival prognosis in liver cancer [7]. Cai et al. described the genetic alteration, mRNA expression, and DNA methylation of ACE2 in over 30 cancer types and revealed genetic and epigenetic variations of ACE2 in various cancers [8]. Several studies demonstrated that ACE2 had antitumor effects by inhibiting tumor angiogenesis [10, 11, 13]. A recent study [14] showed that *ACE2* expression was associated with

increased tumor immune infiltration and was a positive prognostic factor in uterine corpus endometrial and renal papillary cell cancers. Nevertheless, a systemic investigation into the association between ACE2 expression and antitumor immunity, oncogenic pathways, tumor progression phenotypes, and clinical outcomes in pan-cancer remains lacking.

In this study, we investigated associations between *ACE2* expression and antitumor immune signatures in 12 human cancer cohorts from the Cancer Genome Atlas (TCGA) program (https://cancergenome.nih.gov/). We also explored associations between *ACE2* expression and multiple tumor phenotypes, including cell proliferation, stemness, epithelial-mesenchymal transition (EMT), oncogenic signaling, and clinical outcomes in these cancer cohorts. We also investigated the association between *ACE2* expression and immunotherapy response in four cancer cohorts receiving the immune checkpoint blockade therapy. This study aimed to provide new insights into the association between ACE2 and cancer and the potential association between cancer and SARS-CoV-2 infection.

Methods

Datasets

From the genomic data commons data portal (https://portal.gdc.cancer.gov/), we obtained RNA-Seq gene expression profiling datasets (level 3 and RSEM normalized) for 12 TCGA cancer cohorts. The 12 cancer cohorts included cervical squamous-cell carcinoma (CESC), colon adenocarcinoma (COAD), esophageal carcinoma (ESCA), head and neck squamous cell carcinoma (HNSC), kidney renal clear cell carcinoma (KIRC), kidney renal clear cell carcinoma (KIRP), lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), skin cutaneous melanoma (SKCM), thymoma (THYM), uterine corpus endometrial carcinoma (UCEC), and ovarian carcinoma (OV). We log2-transformed all RSEM-normalized gene expression values before further analyses. Besides, we obtained gene expression profiling and clinical data in four cancer cohorts receiving anti-PD-1/PD-L1/CTLA-4 immunotherapy from their related publications, including Nathanson (melanoma) [15], Topalian (melanoma) [16],Ascierto (renal cell carcinoma) [17], and Snyder (bladder cancer) cohorts [18]. A summary of these datasets is presented in Supplementary Table S1 (Additional file 1).

Evaluating the enrichment levels of immune signatures, pathways, and tumor phenotypes

We evaluated the enrichment level of a pathway or tumor phenotype in a tumor sample by the single-sample gene-set enrichment analysis (ssGSEA) score [19]. The gene set included all marker genes of a pathway or tumor phenotype. A total of six cancer-associated pathways (cell cycle, mismatch repair, TGF-β, Wnt, VEGF, and Notch signaling) and three tumor phenotypes (cell proliferation, stemness, and EMT) were analyzed. We presented the marker genes of these pathways and tumor phenotypes in Supplementary Table S2 (Additional file 2).

Gene-set enrichment analysis

We defined high-*ACE2*-expression-level (upper third) and low-*ACE2*-expression-level (bottom third) tumors in each cancer type based on *ACE2* expression profiles. We identified the KEGG [20] pathways highly enriched in both groups of tumors using GSEA [21] with a threshold of adjusted *p*-value < 0.05. Moreover, we used WGCNA [22] to detect the gene modules (gene ontology) differentially enriched between the high- and low-*ACE2*-expression-level tumors in pan-cancer. We identified the hub genes as the genes connected to at least 5 other genes with a connectedness weight greater than 0.25 in a gene module and built their co-expression network.

Statistical analysis

We used Spearman's correlation test to evaluate the correlation (ρ) of *ACE2* expression levels with the enrichment levels of pathways or tumor phenotypes, which were not normally distributed. We used Pearson's correlation test to evaluate the correlation (r) of *ACE2* expression levels with the ratios of immune signatures, which was the log2-transformed values of the ratios between the mean expression levels of all marker genes in immune signatures and was normally distributed. We used the Benjamini and Hochberg method [23] to calculate the FDR for adjusting for multiple tests. We compared overall survival (OS), disease-specific survival (DSS), progression-free interval (PFI), and disease-free interval (DFI) between the high- and low-*ACE2*-expression-level tumors. We utilized Kaplan-Meier curves to display survival time differences and the log-rank test to evaluate the significance of survival time differences. The R package "survival" was used to perform the survival analyses.

Results

Association of ACE2 expression with immune signatures and immunotherapy response in cancer

GSEA [21] identified many immune-related pathways highly enriched in the high-*ACE2*-expression-level tumors at least 5 cancer types. These pathways included cytokine-cytokine receptor interaction, hematopoietic cell lineage, viral myocarditis, natural killer cell-mediated cytotoxicity, chemokine signaling, Jak-STAT signaling, primary immunodeficiency, antigen processing and presentation, autoimmune thyroid disease, T cell receptor signaling, intestinal immune network for IgA production, B cell receptor signaling, systemic lupus erythematosus, Leishmania infection, NOD-like receptor signaling, and epithelial cell signaling in Helicobacter pylori infection (Fig. 1A). Moreover, we found that *ACE2* expression levels positively correlated with the pro-/anti-inflammatory ratios in pan-cancer (Pearson's correlation test, $r = 0.26$, $p = 3.31 \times 10^{-74}$) and in 11 individual cancer types (adjusted *p*-value (FDR) < 0.05) (Fig. 1B). This suggests that *ACE2* expression has a stronger positive association with the pro-inflammatory signature than the anti-inflammatory signature in these cancer types. Altogether, these results suggest a prominent positive association between *ACE2* expression and antitumor immune signatures in cancer. We found that *ACE2* had a positive expression correlation with *PD-L1* in pan-cancer and in 6 individual cancer types (FDR < 0.05) (Fig. 1C). We expected that the *ACE2* expression would have a positive association with the response to anti-PD-1/PD-L1/CTLA-4 immunotherapy. We confirmed the anticipation in four cancer cohorts receiving immune checkpoint blockade therapy. In these cohorts, the

high-*ACE2*-expression-level (> median) tumors displayed a higher rate of immunotherapy response than the low-*ACE2*-expression-level (< median) tumors (67% versus 17%, 80% versus 40%, 40% versus 20%, and 46% versus 25% for Nathanson (melanoma), Topalian (melanoma), Ascierto (renal cell carcinoma), and Snyder (bladder cancer) cohorts, respectively) (Fig. 1D). As a result, the former had better overall survival (OS) than the latter in the Nathanson cohort, which had related data available (log-rank test, $p = 0.036$) (Fig. 1E). These results suggest that the *ACE2* expression is likely to be a positive predictor for anti-PD-1/PD-L1 immunotherapy.

Association of ACE2 expression with oncogenic pathways and tumor phenotypes in cancer

We quantified the activity of a pathway using the single-sample gene-set enrichment analysis (ssGSEA) [19] score of the set of genes included in the pathway. We found that *ACE2* expression levels inversely correlated with the activity of cell cycle, mismatch repair, TGF-β, Wnt, VEGF, and Notch signaling pathways in 9, 6, 9, 7, 6, and 7 individual cancer types, respectively (Spearman's correlation test, FDR < 0.05) (Fig. 2A). Moreover, we found that *ACE2* expression levels had a significant inverse correlation with the expression levels of *MKI67*, which is a tumor proliferation index marker, in pan-cancer and 8 individual cancer types (Pearson's correlation test, FDR < 0.05) (Fig. 2B). Tumor stemness represents a stem cell-like tumor phenotype associated with tumor progression, metastasis, immune evasion, and drug resistance. We found that *ACE2* expression levels showed a marked negative correlation with tumor stemness scores (ssGSEA scores) in pan-cancer and in 9 individual cancer types (FDR < 0.05) (Fig. 2C). EMT plays an outstanding role in facilitating malignant transformation, tumor progression, and metastasis. We observed a marked negative correlation between *ACE2* expression levels and EMT signature scores (ssGSEA scores) in 11 individual cancer types (FDR < 0.05) (Fig. 2D). Overall, these data indicate that ACE2 is a protective factor for cancer progression. Indeed, survival analyses showed that *ACE2* upregulation was associated with favorable survival in pan-cancer (log-rank test, $p < 0.001$ for OS, DSS, PFI, and DFI) and in KIRC, KIRP, LUSC, and OV (log-rank test, $p < 0.05$ for OS, DSS, PFI, and/or DFI) (Fig. 2E). Furthermore, we found that *ACE2* expression levels significantly increased with the tumor advancement in KIRC (two-sided Student's *t* test, $p < 0.01$, fold change > 1.5 for high-grade (G3-4) versus low-grade (G1-2), late-stage (stage III-IV) versus early-stage (stage I-II), large tumor size (T3-4) versus small tumor size (T1-2), without regional lymph nodes (N0) versus with lymph nodes (N1-3), and no metastasis (M0) versus metastasis (M1)) (Fig. 2F).

Identifying interaction networks of ACE2 in cancer

We identified 200 and 24 genes having marked positive and negative expression correlations with *ACE2* in pan-cancer, respectively ($|r| > 0.5$) (Fig. 3A). WGCNA [22] identified four gene modules (indicated in yellow, red, pink, and turquoise color, respectively) highly enriched in the high-*ACE2*-expression-level tumors and three gene modules (indicated in black, blue, and green color, respectively) highly enriched in the low-*ACE2*-expression-level tumors (Fig. 3B). The GO terms highly enriched in the high-*ACE2*-expression-level tumors mainly included immune response, induction of bacterial agglutination, regulation of microvillus length, and epidermal cell differentiation. In contrast, the GO terms highly

enriched in the low-*ACE2*-expression-level tumors mainly included cell cycle, nervous system process, and microtubule-based process (Fig. 3B). Again, these results indicate that *ACE2* expression has a significant positive association with antitumor immune response and a significant negative association with the cell cycle in cancer, suggesting the protective role of ACE2 from cancer progression.

From the yellow gene module, we identified 103 hub genes mainly associated with immune-related pathways. Among the 103 hub genes, three transcription factor (TF) genes, including *EOMES*, *IRF4*, and *TBX21*, were co-expressed with many other immune-related genes, such as *PDCD1*, *TIGIT*, *GZMK*, *IL21R*, and *IL2RG* (Fig. 3C). The association between these TFs and immune regulation has been well recognized, such as EOMES (Eomesodermin) mediating the $CD8^+$ T cell differentiation [24], IRF4 (interferon regulatory factor 4) regulating immune cell development [25], and TBX21 (T-bet) playing a pivotal role in regulating Th1 cell development [26].

Discussion

We investigated the association of *ACE2* expression with immune signatures, oncogenic pathways, and tumor phenotypes in diverse cancer cohorts. Our results indicate that ACE2 is a protective factor for cancer progression. In particular, the ACE2 downregulation correlates with worse survival and tumor advancement in KIRC, also known as clear cell renal cell carcinoma (ccRCC). Previous studies demonstrated that ACE2 exerts antitumor effects by inhibiting tumor angiogenesis [10] and promoting tumor immune infiltration [14]. Our results are consistent with these previous findings. Besides, we found that ACE2 upregulation was associated with reduced cell proliferation, stemness, and EMT, as well as the downregulation of oncogenic pathways, such as cell cycle, mismatch repair, TGF-β, Wnt, and Notch signaling. Moreover, we found that ACE2 had a negative expression correlation with PD-L1, an immunosuppressive molecule, and a predictive marker for an active response to immune checkpoint inhibitors. As a result, ACE2 upregulation correlates with a favorable response to anti-PD-1/PD-L1/CTLA-4 immunotherapy.

ACE2 also plays a protective role in hypertension and heart disease [27]. Moreover, ACE2 deficiency may exacerbate outcomes in patients with SARS-CoV-2 infection [27]. Indeed, a recent study showed that ACE2 was downregulated in virus-infected lung tissue [14], indicating a potential protective role of ACE2 in patients with SARS-CoV-2 infection. Thus, using ACE2 inhibitors for preventing and treating SARS-CoV-2 infections may not be an advisable strategy for individuals with hypertension, heart disease, or cancers.

Conclusions

ACE2 upregulation was associated with increased antitumor immunity and immunotherapy response, reduced tumor malignancy, and favorable survival in cancer, suggesting that ACE2 is a protective factor for cancer progression. Our data may provide potential clinical implications for treating cancer patients infected with SARS-CoV-2.

Abbreviations

ACE2
angiotensin-converting enzyme 2; **DFI**:disease-free interval; **DSS**:disease-specific survival; **EMT**:epithelial-mesenchymal transition; **FDR**:false discovery rate; **GO**:gene ontology; **GSEA**:gene set enrichment analysis; **OS**:overall survival; **PFI**:progression-free interval; **SARS-CoV-2**:severe acute respiratory syndrome coronavirus 2; **TCGA**:The Cancer Genome Atlas; **TF**:transcription factor; **WGCNA**:weighted gene co-expression network analysis; **CESC**:cervical squamous-cell carcinoma; **COAD**:colon adenocarcinoma; **ESCA**:esophageal carcinoma; **HNSC**:head and neck squamous cell carcinoma; **KIRC**:kidney renal clear cell carcinoma; **KIRP**:kidney renal papillary cell carcinoma; **LUAD**:lung adenocarcinoma; **LUSC**:lung squamous cell carcinoma; **OV**:ovarian carcinoma; **SKCM**:skin cutaneous melanoma; **THYM**:thymoma; **UCEC**:uterine corpus endometrial carcinoma

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and material

From the genomic data commons data portal (https://portal.gdc.cancer.gov/), we obtained RNA-Seq gene expression profiling datasets (level 3 and RSEM normalized) and clinical data for 12 TCGA cancer cohorts. We performed all the computational and statistical analyses using R programming (https://www.r-project.org/).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ZZ performed data analyses and helped in manuscript preparation. LL performed data analyses and helped in manuscript preparation. ML performed data analyses and helped in manuscript preparation. XW conceived the study, designed analysis strategies, and wrote the manuscript. All the authors read and approved the final version of the manuscript.

Acknowledgments

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Figures

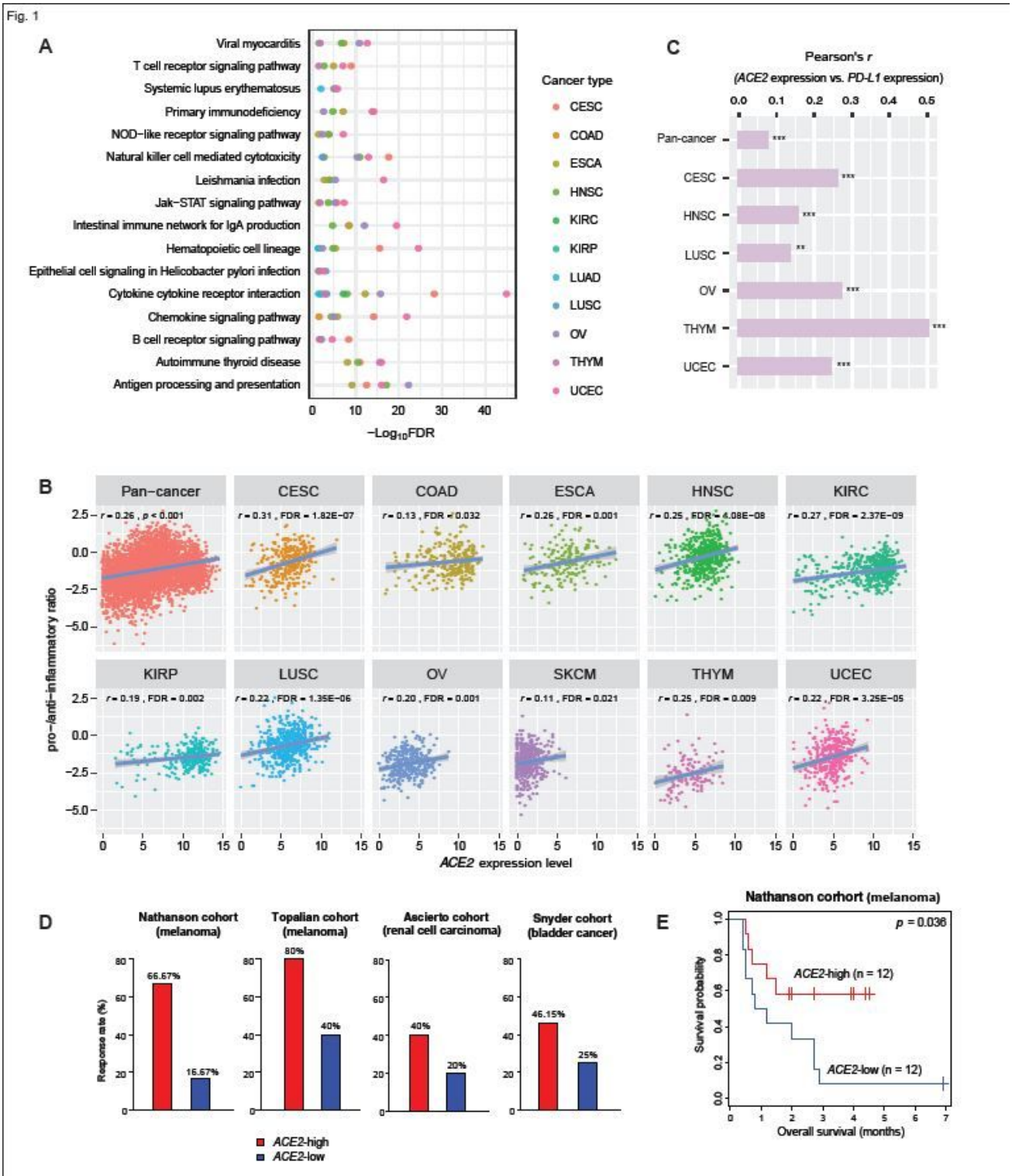

Figure 1

Association of ACE2 expression with immune signatures and immunotherapy response in cancer. A. Immune-related pathways upregulated in high- (upper third) versus low-ACE2-expression-level (bottom third) tumors in at least 5 cancer types identified by GSEA [21] (adjusted p-value (FDR) < 0.05). B. Significant positive correlations of ACE2 expression levels with the ratios of pro−/anti−inflammatory cytokines in pan-cancer and in 11 individual cancer types. The Pearson correlation coefficient (r) and p- or FDR-value are shown. C. The positive expression correlation between ACE2 and PD-L1 in pan-cancer and in 6 individual cancer types. D. Higher rate of immunotherapy response in the high-ACE2-expression-level (> median) than in the low-ACE2-expression-level (< median) tumors in four cancer cohorts receiving immune checkpoint blockade therapy. E. Kaplan-Meier survival curves showing better survival in high-ACE2-expression-level (> median) than in low-ACE2-expression-level (< median) cancer patients with immune checkpoint blockade therapy. The log-rank test p-value is shown. FDR: false discovery rate. * FDR < 0.05; ** FDR < 0.01; *** FDR < 0.001. They also apply to the following figures.

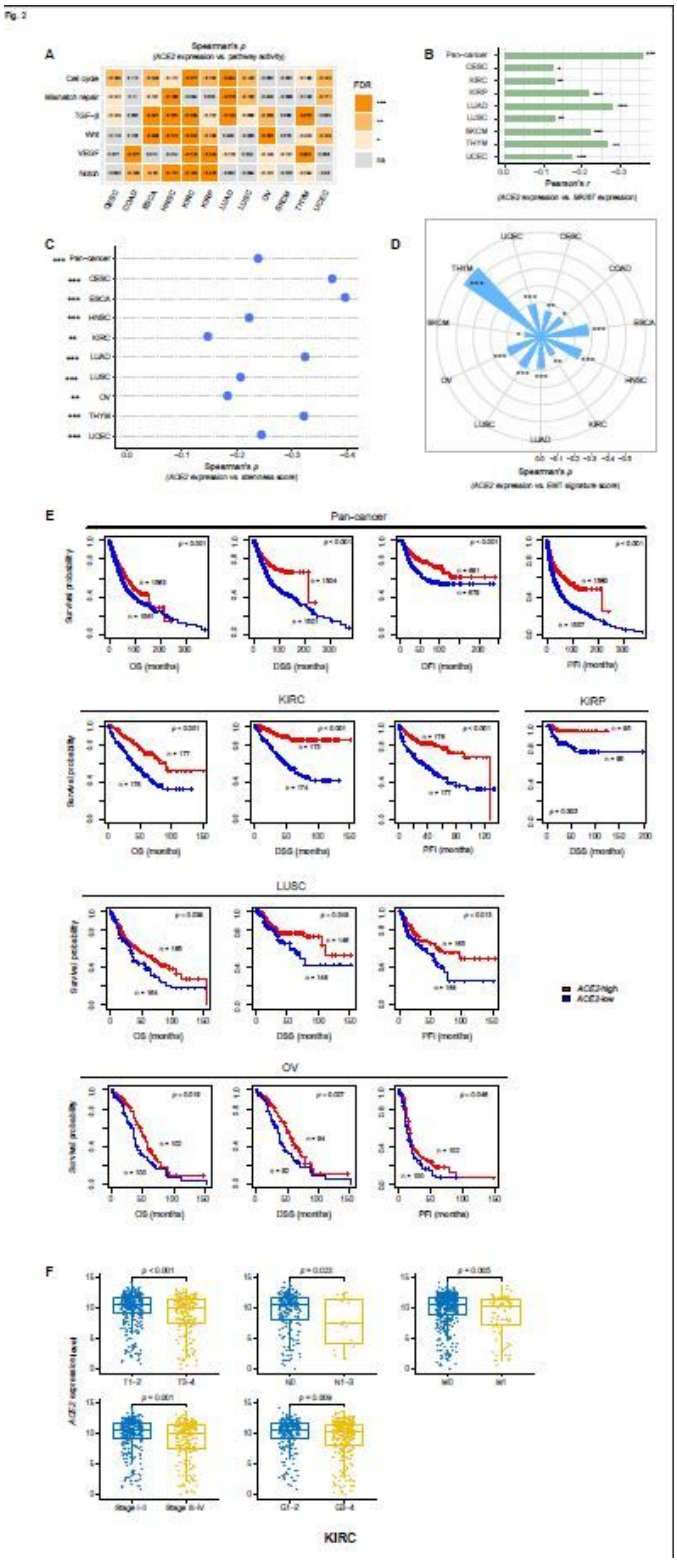

Figure 2

Association of ACE2 expression with oncogenic pathways and tumor phenotypes in cancer. ACE2 expression levels are likely to inversely correlate with the activity of oncogenic pathways (A), MKI67 expression levels (B), stemness scores (C), and EMT signature scores (D) in cancer. Kaplan-Meier survival curves showing that ACE2 upregulation is associated with favorable survival in pan-cancer and multiple individual cancer types. Log-rank test p-values are shown. EMT: epithelial-mesenchymal transition; OS:

overall survival; DSS: disease-specific survival; PFI: progression-free interval; DFI: disease-free interval. E. ACE2 expression levels significantly increase with tumor advancement in KIRC. KIRC: kidney renal clear cell carcinoma.

Fig. 3

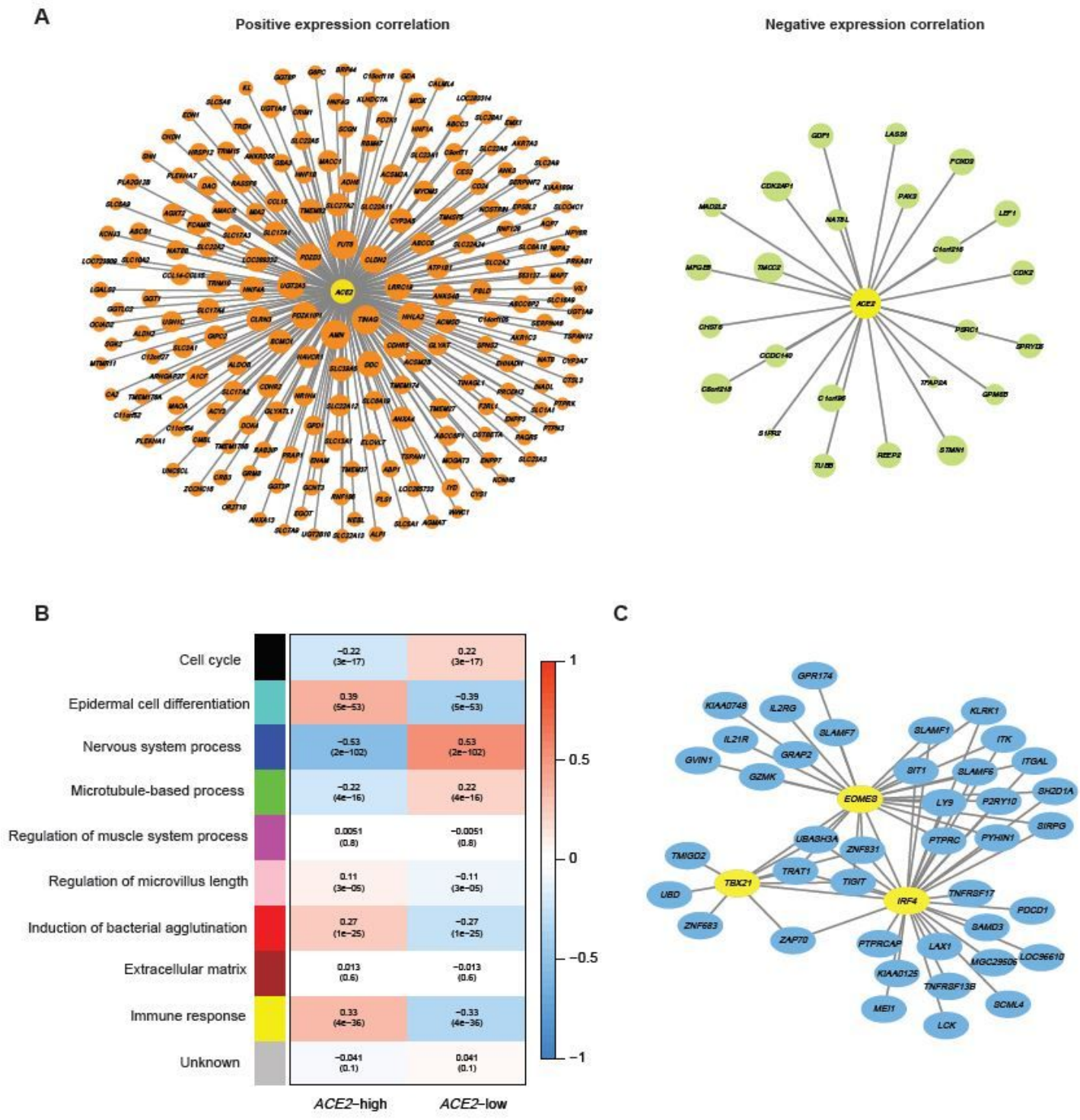

Figure 3

Interaction networks of ACE2 in cancer. A. 200 and 24 genes having marked positive and negative expression correlations with ACE2 in pan-cancer, respectively (|r| > 0.5). B. Gene modules (gene ontology)

enriched in high-ACE2-expression-level and low-ACE2-expression-level pan-cancer. C. Co-expression subnetwork of the immune response module enriched in high-ACE2-expression-level pan-cancer centered on three transcription factor genes (in yellow).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarytables.xlsx