

LETTER TO THE EDITOR

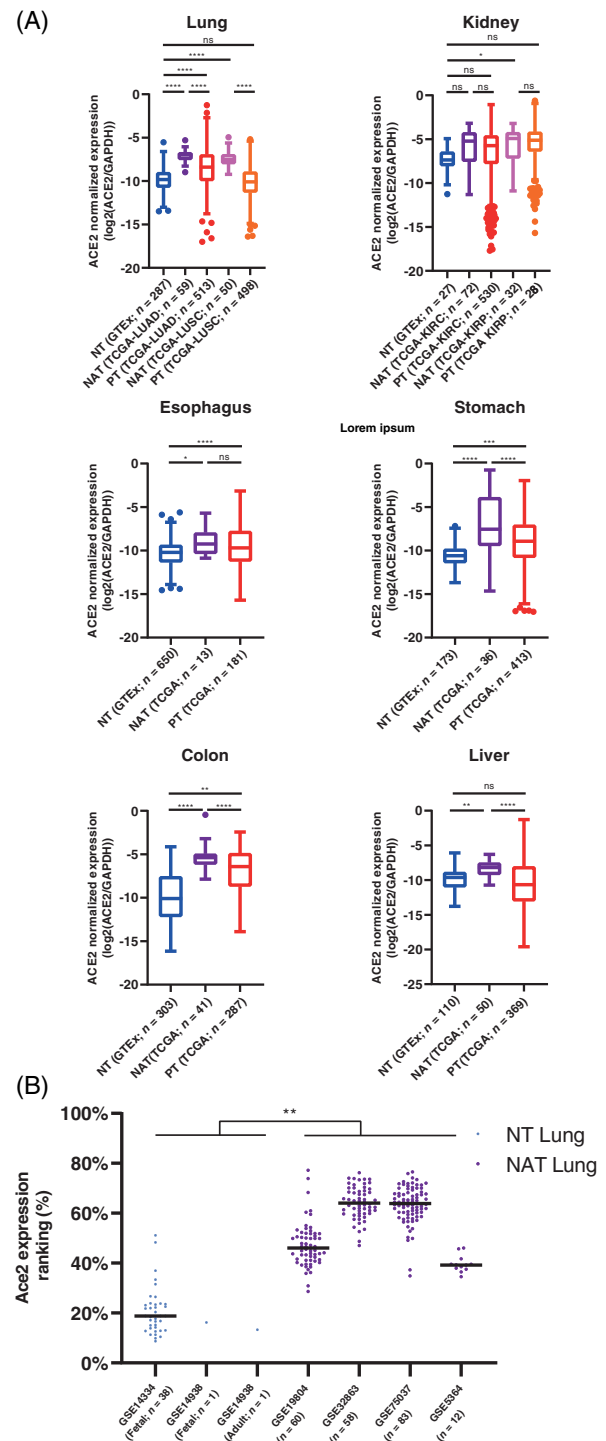
Elevated expression of ACE2 in tumor-adjacent normal tissues of cancer patients

Dear editor,

The recent outbreak of a novel betacoronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has raised the concern that cancer patients might be particularly susceptible to infection by this virus.¹⁻³ Importantly, the guidelines for cancer patients during the COVID-19 pandemic focus on lung cancer patients who are undergoing active chemotherapy or radical radiotherapy, and on patients with blood cancers.¹ Intentional postponing of adjuvant chemotherapy or elective surgery for stable cancer has even been proposed to alleviate the risk.² However, it is currently unknown whether patients with other epithelial solid tumors, or cancer patients not currently undergoing chemotherapy, are also more susceptible to COVID-19.

SARS-CoV-2 requires the angiotensin-converting enzyme 2 (ACE2) to enter human cells.^{4,5} Moreover, ACE2 gene expression levels in epithelial tissues corresponded to survival after SARS-CoV infection in transgenic mice⁶ and soluble human ACE2 inhibited SARS-CoV-2 infections in engineered human tissues.⁷ ACE2 mRNA levels are particularly high in the human kidney, testis, heart and intestinal tract.^{8,9} Albeit not highly expressed in most cells of the normal lungs, ACE2 expression levels in the airway epithelia increase due to chronic exposure to cigarette smoke,^{8,10} which was associated with infection susceptibility.¹¹ ACE2 expression levels have also been suggested to underlie the increased susceptibility of patients with hypertension and diabetes to SARS-CoV-2 infection,¹² and to be increased in patients with comorbidities associated with severe COVID-19.¹³ Therefore, ACE2 expression in epithelial tissues, and in particular in the airway epithelia, seem to have considerable effect on COVID-19 morbidity and mortality.

We compared ACE2 mRNA levels between normal tissues (NT), primary tumors (PT) and normal tissues adjacent to tumors (NAT), using data from The Cancer Genome Atlas (TCGA) and GTEx¹⁴ (Supporting Information). Across multiple tissues, ACE2 mRNA levels in PT were significantly higher than in NT of the respective tissue (Figures 1A and S1). Surprisingly, ACE2 expression levels in NAT were also significantly higher than in NT across tissues, and in all cases were



Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; FANTOM5, Functional Annotation of the Mammalian Genome; GTEx, genotype-tissue expression; HPA, Human Protein Atlas; NAT, normal tissue adjacent to tumor; NT, normal tissue; PT, primary tumor; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TCGA, The Cancer Genome Atlas.

at least as high as in the respective PT (Figures 1A and S1). This result suggests that the NAT of cancer patients would likely be more susceptible to SARS-CoV-2 infection than the corresponding tissues of healthy individuals.

Focusing on the lung due to its relevance in the disease etiology, we next queried the mRNA expression levels of *ACE2* in two additional datasets of normal human tissues, the Human Protein Atlas¹⁵ and FANTOM5.¹⁶ In concordance with the GTEx data, the expression levels of *ACE2* in whole-lung tissues from healthy donors were negligible (median of 0.7pTPM, 1.8pTPM and 2.6 scaled tags per million, in GTEx, HPA and FANTOM5, respectively). Next, we compared the relative expression levels of *ACE2* between healthy and tumor-adjacent lung tissues, using six published gene expression microarray datasets¹⁷⁻²⁰ (Supporting Information Methods). *ACE2* expression levels in the tumor-adjacent normal lung samples were detected at discernible levels, and were significantly higher than those in the healthy normal lung samples (Figure 1B). This analysis confirmed that the mRNA levels of *ACE2* are elevated in tumor-adjacent lung tissues of lung cancer patients.

This observation raises the possibility that lung cancer patients may have an increased risk to SARS-CoV-2 infection, regardless of chemotherapy-induced immune suppression. Furthermore, patients with other types of cancer, such as renal or gastrointestinal cancers, may also have elevated infection risk. However, to determine whether this is indeed the case, two questions require urgent attention: (a) Is *ACE2* expression level in non-lung epithelia associated with SARS-CoV-2 infection risk?; and (b) Is *ACE2* upregulation limited to the tissue adjacent to the tumor (presumably due to the tumor microenvironment), or are *ACE2* levels systemically elevated in cancer patients? In addition, although *ACE2* mRNA levels are upregulated in NAT and PT compared to NT, we cannot rule out the possibility that *ACE2* protein levels are not significantly different due to post-transcriptional regulation mechanisms. Until these questions are resolved, we propose that the discussion of cancer guidelines during the COVID-19 pandemic should expand beyond patients with treatment-induced immune suppression.

FIGURE 1 Elevated expression of *ACE2* in tumor-adjacent normal tissues of cancer patients. A, mRNA levels of *ACE2* (normalized to GAPDH) in normal tissues (NT), Normal tissues adjacent to tumors (NAT) and primary tumors (PT) across eight tumor types representing six distinct tissues. KIRC, Kidney renal clear cell carcinoma; KIRP, kidney renal papillary cell carcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma. Bar, median; box, 25th and 75th percentiles; whiskers, 1.5 × IQR of lower and upper quartile. **P* < .05; ***P* < .01; ****P* < .001; *****P* < .0001; One-way ANOVA with Tukey's test. B, Relative mRNA levels of *ACE2* in normal lung tissues (NT) and normal tissues adjacent to tumors (NAT), calculated based on six gene expression microarray datasets. Bar, median. ***P* = .0045; two-tailed Student's *t* test for a comparison between the median values of the datasets in each group [Color figure can be viewed at wileyonlinelibrary.com]

KEYWORDS

ACE2, COVID-19, NAT, SARS-CoV-2

ACKNOWLEDGEMENTS


Research in the Ben-David lab is supported by the Azrieli Foundation, the Richard Eimert Research Fund on Solid Tumors, the Tel-Aviv University Cancer Biology Research Center and the Israel Cancer Association (grant #20200111).

CONFLICT OF INTEREST

We declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of our study are available in Xena at <https://xena.ucsc.edu/>, in the Human Protein Atlas at <https://www.proteinatlas.org/>, and in GEO at <https://www.ncbi.nlm.nih.gov/geo/> (accession numbers GSE14334, GSE14938, GSE5364, GSE19804, GSE32863 and GSE75037).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.