Two Things About COVID-19 Might Need Attention

Xiaodong Jia[1#], Chengliang Yin[2, 3#], Shanshan Lu[1#], Yan Chen[1], Qingyan Liu[1], Junfan Bai[1], Yinying Lu[1,4,5*]

1 Comprehensive Liver Cancer Center, The Fifth Medical Center of PLA General Hospital, Beijing, 100039, China.

2 National Engineering Laboratory for Medical Big Data Application Technology, Chinese PLA General Hospital, Beijing,100853, China.

3 Medical Big Data Center, Chinese PLA General Hospital, Beijing,100853, China.

4 Center for Synthetic and Systems Biology (CSSB), Tsinghua University, Beijing, 100084, China.

5 Peking University, Beijing, 100871, China.

#These authors contributed equally to this article.

***Corresponding author:**

Yinying Lu

Comprehensive Liver Cancer Center, The Fifth Medical Center of PLA General Hospital

100 Xi-Si-Huan Middle Road, Beijing 100039, China

E-mial: luyinying1973@163.com

Keywords: COVID-19, Adipose tissue, Cancer, ACE2

Abstract

The spread of 2019 novel coronavirus disease (COVID-19) throughout the world has been a severe challenge for public health. The human angiotensin-converting enzyme 2 (ACE2) has a remarkably high affinity binding to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). By the search for network database and re-analysis of pubic data, we found the level of ACE2 expression in adipose tissue was higher than that in lung tissue, which indicated the

 doi:10.20944/preprints202002.0315.v1

adipose tissue might be vulnerable to SARS-CoV-2 as well; the levels of ACE2 expressed by adipocytes and adipose progenitor cells were similar between non-obese individuals and obese individuals, but obese individuals have more adiposes so as to increase the number of ACE2-expressing cells; the expression of ACE2 in tumor tissues posed by five different types of cancers increased significantly compared with that in adjacent tissues. Thus, we suggest that more attentions might be given to obese individuals and the five types of cancer patients during the outbreak of COVID-19.

Instruction

The COVID-19 that outbroke in Wuhan (Hubei province, China) in 2019 has become a public health emergency of international concern, and it was caused by the SARS-CoV-2[1]. As of 11:00 on February 21, 2020, there are 75,567 confirmed cases, 5,206 suspected cases, and 2,239 death cases in China.

The spike protein 3-D structure of SARS-CoV-2 is similar to that of SARS-CoV, and hence SARS-CoV-2 is also feasible to bind to ACE2[2]. The binding affinity between ACE2 and SARS-CoV-2 is approximately 10- to 20-fold higher than that between ACE2 and SARS-CoV[3]. Therefore, those ACE2-expressing cells and tissues, potentially act as targets of the novel coronavirus[4].

Two things in our research were explored to suppose some suggestions for prevention and treatment of COVID-19. First, is adipose potentially infected by SARS-CoV-2? It is reported that adipose tissues could be infected by some virus, like H5N1, HIV[5,6]. Furthermore, obesity could influence the mortality and transmission of influenza virus[7,8]. To date, no research has demonstrated that SARS-CoV-2 could infect adipose tissue. Moreover, there is still no evidence to show that obesity is associated with COVID-19. Second, although the COVID-19 patients with cancers have higher severe events[9], is the risk of different types of cancer patients facing with SARS-CoV-2 similar?

Materials and methods

Tissue ACE2 expression analysis

Four network databases, HCCDB[10] (http://lifeome.net/database/hccdb/home.html), HPA[11,12]

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2020 doi:10.20944/preprints202002.0315.v1

(https://www.proteinatlas.org/), UALCAN[13] (http://ualcan.path.uab.edu/analysis.html) and GEPIA2[14] (http://gepia.cancer-pku.cn/index.html), were used to search ACE2 gene. All data are available directly online.

Cell ACE2 expression analysis

The cohort of obese and non-obese individuals was derived from public datasets (GEO: GSE80654), including RNA expression profiling by microarray of major white adipose tissue cell types (adipocytes from 7 non-obese and 7 obese human adipose tissue, progenitor cells from 10 non-obese and 9 obese human adipose tissue). Gene expression data was extracted and analyzed in R 3.4.4 statistical software.

Results

One: Adipose tissue might be infected by SARS-Cov-2.

We have employed two databases, HCCDB and HPA, to search the SARS-Cov-2 receptor ACE2 in normal tissues. In terms of RNA level, it shows that the expression of ACE2 in heart, kidney, testis, intestine and bladder is higher than that in lung, which is consistent with the previous report by Zin Zhou *et al*[4]. Moreover, we found the expression of ACE2 in gallbladder and adipose tissue (including subcutaneous and visceral) is significantly higher than that in lung (Figure 1). In addition, we have explored whether obesity could affect the expression of ACE2. On account of data deficiency, it is impossible to test ACE2 expression in the whole adipose tissue. Nevertheless, the level of ACE2 expression in adipocytes and adipocyte progenitor cells isolated from adipose tissues of non-obese and obese individuals was compared by re-analysis of public data from Anna Ehrlund *et al*[15]. The results of ACE2 expression levels between two kinds of cells from obese and non-obese individuals are similar (Figure 2).

Two: Five types of cancer patients facing with COVID-19 might require more medical attentions.

The ACE2 expression level in cancers was analyzed by three databases, HCCDB, UALCAN and GEPIA2. We found tumor tissues of five types of cancers including CESC (Cervical squamous cell carcinoma and endocervical adenocarcinoma), PAAD (Pancreatic adenocarcinoma), READ (Rectum adenocarcinoma), KIRP (Kidney renal papillary cell carcinoma) and KIRC (Kidney renal clear cell carcinoma) expressed more ACE2 than adjacent

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2020 doi:10.20944/preprints202002.0315.v1

tissues, especially the former three cancers (Figure 3). The expression level of ACE2 in tumor tissue of CESC was closed to that in lung tissue, whereas the expression level of ACE2 in tumor tissue of PAAD got higher than that in lung tissue. In conclusion, the risk that these cancer sites infected by SARS-Cov-2 might increase.

Discussion

Some organs (kidney, liver, bladder, testis *et al*.) were demonstrated to have the potential risk of SARS-Cov-2 infection by characterizing the expression patterns of ACE2[16,17]. However, it has not been reported whether the adipose tissue might be vulnerable to the novel virus. We used the public database to analyze the ACE2 expression in adipose tissue, and found a higher RNA level than lung tissue. It was reported that adipose tissue could serve as a reservoir for human adenovirus Ad-36, influenza A virus, HIV, cytomegalovirus *Trypanosoma gondii*, and *Mycobacterium tuberculosis*[18]. Certainly, it's further required to be determined whether SARS-Cov-2 could infect adipose tissue through nucleic acid detection and pathological diagnosis for adipose tissue.

We found obesity didn't affect ACE2 expressions in adipocytes and adipocyte progenitor cells in human adipose tissues. In adipose tissues, the expression level of ACE2 in other cells (monocytes, macrophages, leukocytes and NK cells *et al*) was unknown. Thales de Almeida Pinheiro *et al.* reported that there was no difference in ACE2 expression between adipose tissues of eutrophic patients and obese patients[19]. However, epididymal adipose tissues of rats with HFD-induced nonalcoholic steatohepatitis and HFD-induced mice upregulated ACE2 expression[20,21]. Obesity was reported to increase vulnerability to infection[22]. Obesity is an independent risk factor for hospitalization and death to H1N1 influenza virus, and HFD-induced and genetic-induced obese mice exhibited greater H1N1 mortality[7]. Symptomatic obese adults were shown to shed influenza A virus 42% longer than non-obese adults. Obesity increases the duration of influenza A virus shedding in adults, which suggests obesity may play an important role in influenza transmission[8]. Even though obesity really has no effect on ACE2 expression, the obese individuals have more adipose to increase the quantities of ACE2 proteins. Therefore, the role of obesity in SARS-Cov-2 infection shouldn't be ignored.

Wenhua Liang *et al*. analyzed the risk for COVID-19 in patients with cancer for the first

 doi:10.20944/preprints202002.0315.v1

time, and they found cancer patients had more severe events[9]. As limited number of COVID-19 patients with cancer, they couldn't compare the severe events between different types of cancers. We found five types of cancers (CESC, PAAD, READ, KIRP and KIRC) increased the ACE2 expression at the original organs, which might worsen the COVID-19. It's also required more clinical data to further verify this find.

Finally, we proposed two suggestions at this critical period of epidemic. First, the above cancer patients and obese individuals should pay great attention to protection from SARS-Cov-2 infection. Second, the more intensive surveillance or treatment should be delivered to the above cancer patients and obese individuals in the early stages of COVID-19.

Acknowledgements

This work was funded by National Science Foundation of China (81902495), National Science and Technology Major Project (2018ZX10723204) and Medical Big Data and AI R & D Project of General Hospital (2019MBD-025).

Reference

1. Liu J, Li S, Liu J, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. 2020: 2020.02.16.20023671.

2. Zhou P, Yang X-L, Wang X-G, et al. Discovery of a novel coronavirus associated with the recent pneumonia outbreak in humans and its potential bat origin. 2020: 2020.01.22.914952.

3. Wrapp D, Wang N, Corbett KS, et al. Cryo-EM Structure of the 2019-nCoV Spike in the Prefusion Conformation. 2020: 2020.02.11.944462.

4. Xin Zou KC, Jiawei Zou, Peiyi Han, Jie Hao, Zeguang Han. The single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to Wuhan 2019-nCoV infection. 0-.

5. Couturier J, Suliburk JW, Brown JM, et al. Human adipose tissue as a reservoir for memory CD4+ T cells and HIV. *AIDS (London, England)* 2015; **29**(6): 667-74.

6. Nishimura H, Itamura S, Iwasaki T, Kurata T, Tashiro M. Characterization of human influenza A (H5N1) virus infection in mice: neuro-, pneumo- and adipotropic infection. *The Journal of general virology* 2000; **81**(Pt 10): 2503-10.

7. Milner JJ, Rebeles J, Dhungana S, et al. Obesity Increases Mortality and Modulates the Lung Metabolome during Pandemic H1N1 Influenza Virus Infection in Mice. *J Immunol* 2015; **194**(10): 4846-59.

8. Maier HE, Lopez R, Sanchez N, et al. Obesity Increases the Duration of Influenza A Virus Shedding in Adults. *J Infect Dis* 2018; **218**(9): 1378-82.

9. Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *The Lancet Oncology* 2020.

10. Lian Q, Wang S, Zhang G, et al. HCCDB: a database of hepatocellular carcinoma expression atlas. 2018; **16**(4): 269-75.

11. Uhlen M, Oksvold P, Fagerberg L, et al. Towards a knowledge-based Human Protein Atlas. *Nature biotechnology* 2010; **28**(12): 1248-50.

12. Uhlen M, Fagerberg L, Hallstrom BM, et al. Proteomics. Tissue-based map of the human proteome. *Science (New York, NY)* 2015; **347**(6220): 1260419.

13. Chandrashekar DS, Bashel B, Balasubramanya SAH, et al. UALCAN: A Portal for Facilitating Tumor Subgroup Gene Expression and Survival Analyses. *Neoplasia (New York, NY)* 2017; **19**(8): 649-58.

14. 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 research* 2019; **47**(W1): W556-w60.

15. Ehrlund A, Acosta JR, Bjork C, et al. The cell-type specific transcriptome in human adipose tissue and influence of obesity on adipocyte progenitors. *Scientific data* 2017; **4**: 170164.

16. Chai X, Hu L, Zhang Y, et al. Specific ACE2 Expression in Cholangiocytes May Cause Liver Damage After 2019-nCoV Infection. 2020: 2020.02.03.931766.

17. Lin W, Hu L, Zhang Y, et al. Single-cell Analysis of ACE2 Expression in Human Kidneys and Bladders Reveals a Potential Route of 2019-nCoV Infection. 2020: 2020.02.08.939892.

18. Bourgeois C, Gorwood J, Barrail-Tran A, et al. Specific Biological Features of Adipose Tissue, and Their Impact on HIV Persistence. *Frontiers in microbiology* 2019; **10**: 2837.

19. Pinheiro TA, Barcala-Jorge AS, Andrade JMO, et al. Obesity and malnutrition similarly alter the renin-angiotensin system and inflammation in mice and human adipose. *J Nutr Biochem* 2017; **48**: 74-82.

20. Zhang W, Xu YZ, Liu B, et al. Pioglitazone upregulates angiotensin converting enzyme 2

 doi:10.20944/preprints202002.0315.v1

expression in insulin-sensitive tissues in rats with high-fat diet-induced nonalcoholic steatohepatitis. *ScientificWorldJournal* 2014; **2014**: 603409.

21. Gupte M, Boustany-Kari CM, Bharadwaj K, et al. ACE2 is expressed in mouse adipocytes and regulated by a high-fat diet. *Am J Physiol Regul Integr Comp Physiol* 2008; **295**(3): R781-8.

22. Misumi I, Starmer J, Uchimura T, Beck MA, Magnuson T, Whitmire JK. Obesity Expands a Distinct Population of T Cells in Adipose Tissue and Increases Vulnerability to Infection. *Cell reports* 2019; **27**(2): 514-24 e5.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2020 doi:10.20944/preprints202002.0315.v1

Figure legends

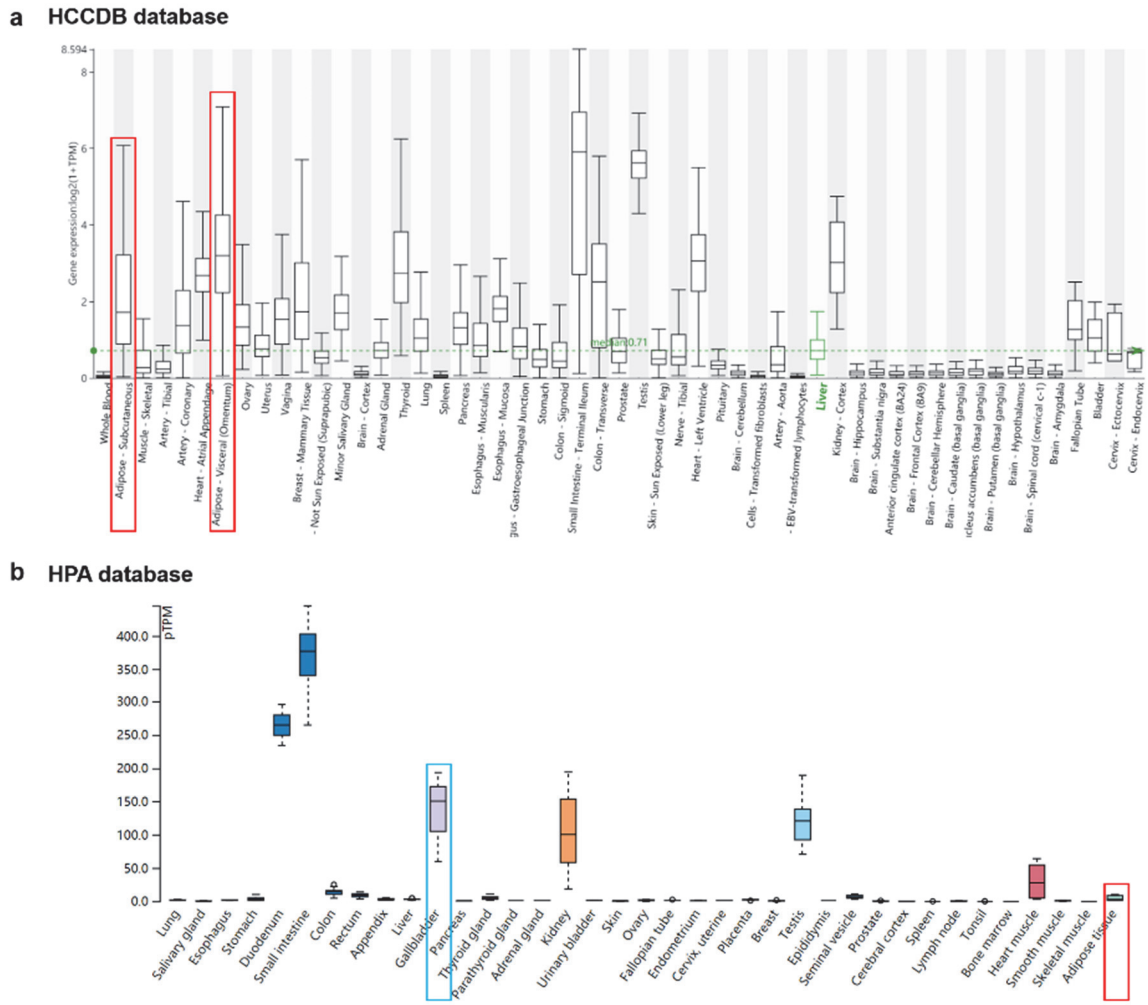

Figure 1. ACE2 expressions of different normal tissues were analyzed using two databases, HCCDB (a) and HPA (b). The red box indicates adipose tissue, and the blue box indicates gallbladder.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2020 doi:10.20944/preprints202002.0315.v1

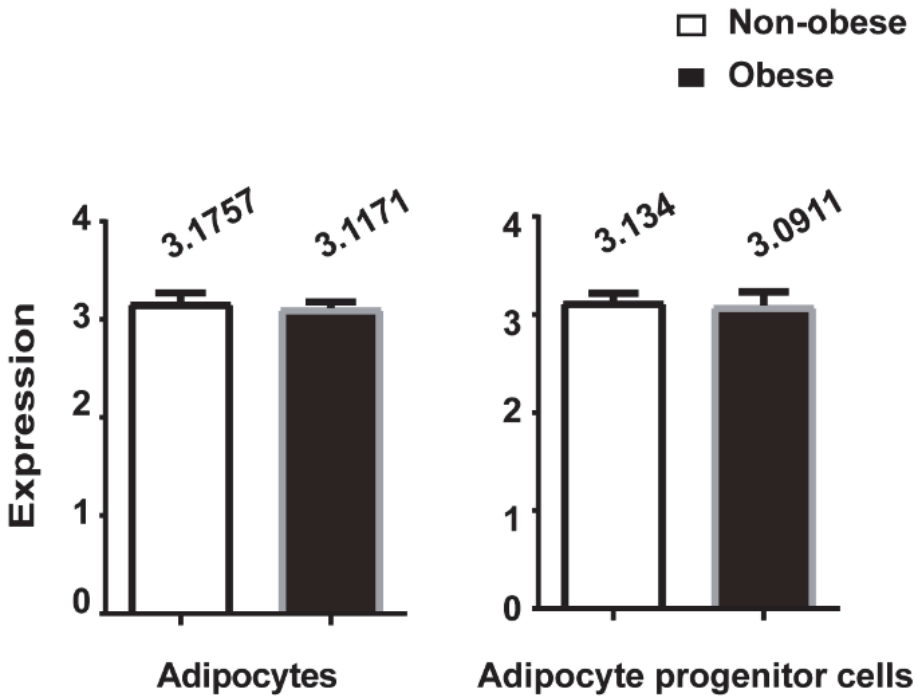

Figure 2. ACE2 expressions of adipocytes and progenitor cells isolated from adipose tissues of non-obese and obese individuals were shown.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 23 February 2020 doi:10.20944/preprints202002.0315.v1

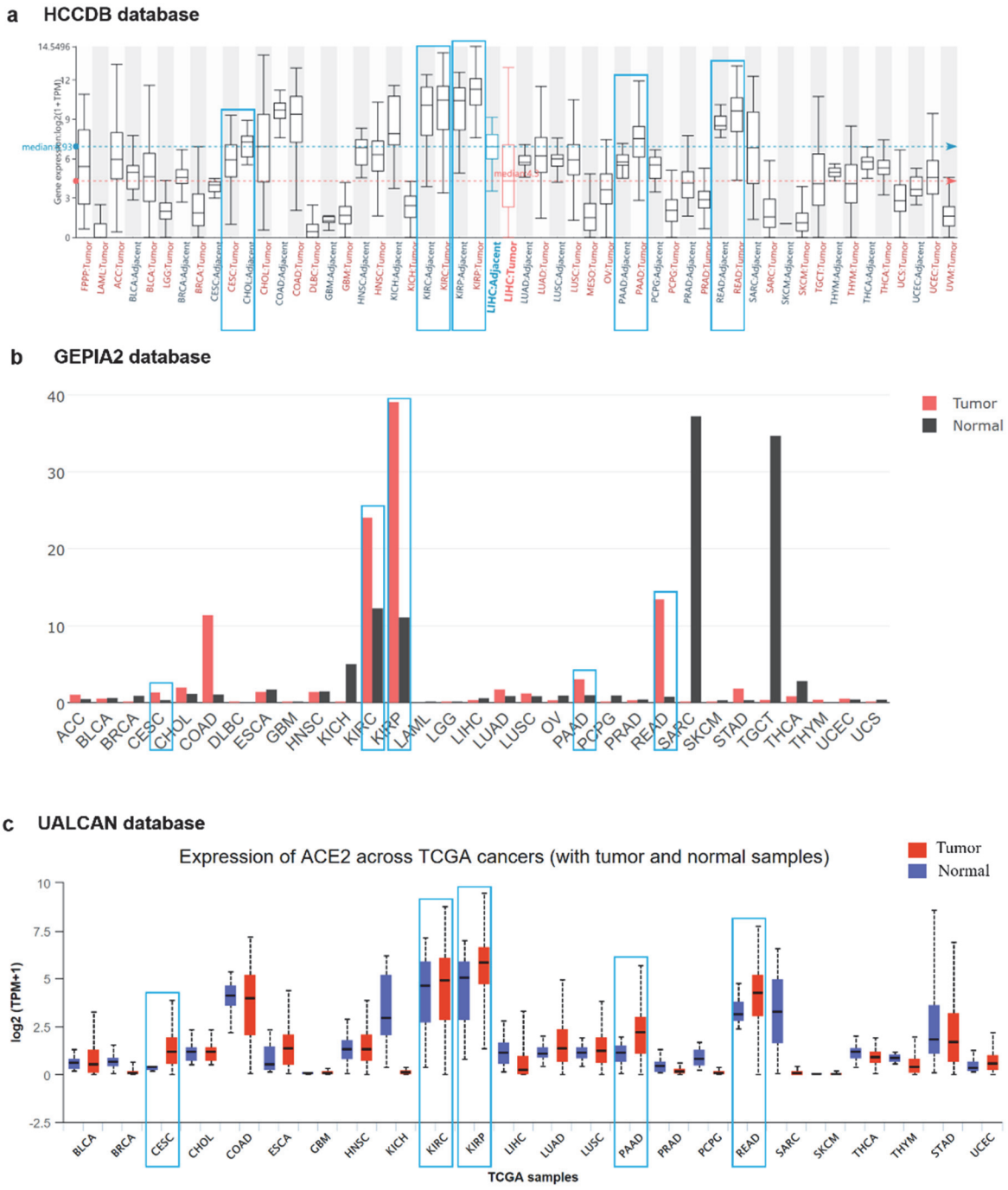

Figure 3. ACE2 expressions of different kinds of cancers were analyzed using three databases, HCCDB (a), GEPIA2 (b) and UALCAN (c). The blue box indicates that ACE2 expresses higher in tumor tissue than the normal tissue, i.e. adjacent tissue.