Original Article

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Angiotensin-Converting Enzyme 2 Gene Expression in Breast Tissue

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ABSTRACT

Objective: Binding to angiotensin-converting enzyme 2 (ACE2) receptor is a critical step for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to mediate its entry into target cells. ACE2 is expressed in many human tissues, including the lungs. However, no research has demonstrated that SARS-CoV-2 can infect human breast tissue. This study aimed to investigate *ACE2* gene expression in human breast tissue using a public database.

Materials and Methods: A search of a public gene expression database was performed to investigate *ACE2* gene expression in in human breast tissue.

Results: The gene expression profile demonstrated that *ACE2* gene expression was higher in human breast tissue than human lung tissue.

Conclusion: Our knowledge about coronavirus disease-2019 (COVID-19) is expanding rapidly. Clinicians are eager for vetted information regarding all aspects of this new illness, and this study demonstrates that the level of ACE2 expression in human breast tissue is higher than that in the lung tissue, a major target tissue affected by SARS-CoV-2 infection. This finding strongly suggests that SARS-CoV-2 infection causes breast pathology.

Keywords: Breast, angiotensin converting enzyme 2, gene expression, coronavirus, severe acute respiratory syndrome coronavirus 2, COVID-19

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Key Points

- SARS-CoV-2 binding to the ACE2 receptor is a critical step mediating viral entry into target cells.
- *ACE2* gene expression is higher in breast tissue than lung tissue.
- This critical discovery implies that breast tissue is directly susceptible to SARS-Cov-2 infection by the ACE2 receptor through hematogenous viral spreading following inoculation of the upper airways.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an enveloped, positive-sense, single-stranded RNA β-coronavirus (1). SARS-CoV-2, which causes the disease known as coronavirus disease-2019 (COVID-19), was first reported in late 2019 in Wuhan, China, and has rapidly developed into a pandemic and public health emergency (2-5). As of 5th October 2020, a total of 34,206,517 accumulated cases and 1,019,628 deaths have been reported worldwide, with an overall mortality rate of less than 1% (6). Researchers are integrating the rapidly emerging evidence into understanding the disease (3-9).

Angiotensin-converting enzyme 2 (ACE2) is expressed in many human tissues, including the lungs, and serves as a doorway by which the virus can enter and spread (10-12). During infection, ACE2-expressing tissues become direct targets, resulting in serious pathological changes and progressive multiple organ failure or even death in severe cases (13). Evidence has shown that, besides the respiratory injury, SARS-CoV-2 also damages the cardiac, renal, hepatic, and neurological systems (14). The influence of SARS-CoV-2 on the breast is limited and needs further investigation. This article aimed to search a gene expression database to find ACE2 expression in human breast tissue.

Materials and Methods

A search of the Gene Expression Profiling Interactive Analysis 2 (GEPIA2) database was performed to investigate ACE2 expression in human breast tissues (15). Ethical approval was not required as the study exclusively used publicly available data. The resource database from Genotype-

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Tissue Expression (version 8 data release) integrates the expression data of 11,688 normal tissue samples covering 54 tissue types to comprehensively annotate the expression patterns of each gene. Human samples are aligned against the *GRCh38* human reference genome. The GEPIA2 search of the Genotype-Tissue Expression data provided public RNA sequencing data of ACE2 expression. A differential expression analysis was performed on the selected ACE2 dataset to dynamically obtain differentially expressed genes in log2 (TPM + 1) transformed expression data. The transformed expression data from all tissue samples available were plotted using the box plots available from the GEPIA2 website with plots shown as median and 25th and 75th percentiles.

Results

The gene expression database included ACE2 expression profile. The gene expression profile demonstrated that *ACE2* gene expression was present in human breast tissue and was higher in breast tissue than in lung tissue (Figure 1).

Discussion and Conclusion

SARS-CoV-2 infection followed by COVID-19 is robust in cells expressing ACE2 receptor, a type I integral membrane protein, which controls cardiac and kidney functions by negatively regulating renin-angiotensin systems (10, 11). This study demonstrates that *ACE2* gene expression in human breast tissue is higher than in lung tissue, the major initial target tissue affected by SARS-CoV-2 infection. This is a critical discovery as these tissues may be susceptible to SARS-CoV-2 infection through the ACE2 receptor, which strongly suggests that SARS-CoV-2 infection may cause breast pathology. High ACE2 expression (e.g., in bronchial airway epithelium) may augment viral infection in patients with COVID-19 and has been demonstrated to contribute to COVID-19 morbidity and severity patterns, but studies have not looked at other tissues (9, 12, 16). Moreover, *ACE2* gene receptor expression is positively regulated in COVID-19 (16).

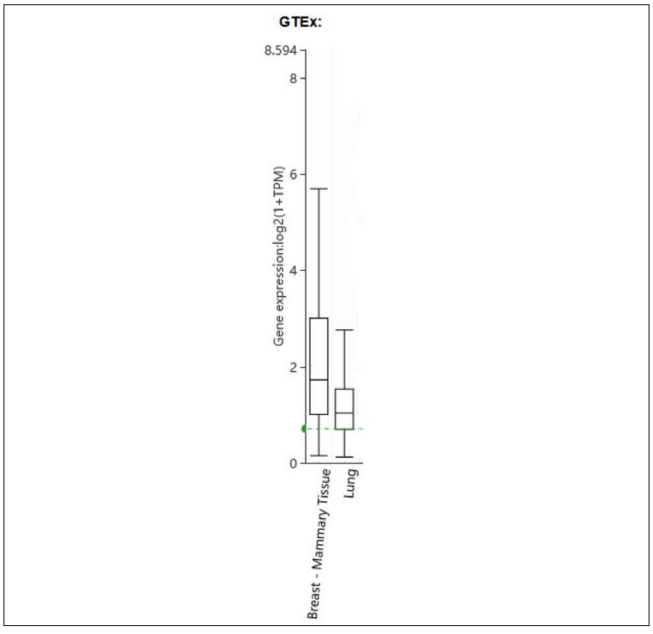

Figure 1. *ACE2* gene expression in human breast tissue and human lung tissue

ACE2: Angiotensin-converting enzyme 2; TPM: Transcripts per million

Most patients with COVID-19 present with extramammary-related manifestations of COVID-19, such as respiratory symptoms and pyrexia, and little is known about breast-related manifestations of the infection (13, 14). The outbreak of SARS-CoV-2 is still ongoing, and therefore the data on human breast tissue infected by SARS-CoV-2 are limited. At present, no certain direct impact of COVID-19 on the breast has been reported. Despite this, retrievable SARS-CoV-2 ribonucleic acid has been discovered in colostrum and breast milk using SARS-CoV-2 reverse transcriptase polymerase chain reaction examination up to four days postpartum (17-20). The implications of retrievable SARS-CoV-2 ribonucleic acid in human colostrum and breast milk remain unclear, regarding whether this translates to viable virus or degraded residual nucleic acid.

The local renin-angiotensin system importantly contributes to carcinoma micromilieu and influences carcinoma cell proliferation, infiltration, angiogenesis, and metastatic activities (21, 22). As a component of the renin-angiotensin system, ACE2 converts angiotensin II to angiotensin (1–7) (9). It is recognized that the renin-angiotensin system plays a strategic part in the adaptation of many physiological bodily functions (9). Emerging data suggest that the local renin-angiotensin system is an important component of the carcinoma micromilieu and plays a strategic part in the positive regulation of carcinoma cell proliferation, angiogenesis, metabolism, spread, and infiltration (21, 22). Meanwhile, the ACE2/angiotensin (1-7)/MAS axis plays a strategic part in positive regulation of exiguous, antiangiogenic, and antimetastatic actions (23).

The ACE2 protein expression levels in invasive breast carcinoma cells with lymphatic or distant metastasis spread and highly metastatic breast carcinoma cells are significantly lower than in neighboring breast cells, invasive ductal carcinoma cells, or low metastatic invasive breast carcinoma cells (23, 24). The staging and metastatic status of invasive breast, gallbladder, lung, pancreatic, and metastatic prostate carcinomas are negatively associated with ACE2 protein expression (23-29). Angiotensin (1-7) therapy or ACE2 protein overexpression decreases invasive carcinoma cell growth, local infiltration, and metastasis in breast invasive carcinoma, lung adenocarcinoma, and metastatic prostate carcinoma (23-29). Alternatively, invasive carcinoma cell growth, local infiltration, and metastasis of human breast adenocarcinoma are augmented in human breast adenocarcinoma cells with *ACE2* gene deactivation, but they are set free with angiotensin (1-7) therapy (23). Moreover, an angiotensin (1-7) receptor antagonist can block the effect of angiotensin (1-7) therapy or ACE2 overexpression (23). It is therefore evident that the ACE2/angiotensin (1-7)/Mas pathway acts to safeguard in a protective role, which counters both local infiltration and distant spread from invasive breast carcinoma (23, 24).

Although the precise system whereby the ACE2/angiotensin (1-7)/Mas pathway modifies invasive breast carcinoma growth, vascularity, infiltration, and metastasis is not fully known, store-operated calcium entry is crucial for the spread and infiltration of carcinoma cells by controlling cytoskeletal dynamics and organization and initiating the applicable signaling pathway for local infiltration and distant spread (30,31). Store-operated calcium entry is induced by AngII (32); ACE2 overexpression protein significantly reduces store-operated calcium entry activity (23).

Negative regulation of the ACE2/angiotensin (1-7)/Mas pathway promotes invasive breast carcinoma local infiltration and distant spread

through the activation of store-operated calcium entry pathways, which decreases E-cadherin expression (23, 24). As the *ACE2* receptor gene expression in lung tissue is dysregulated in COVID-19, it is possible that patients with invasive breast carcinoma that highly express ACE2 may have worse outcomes when infected by SARS-CoV-2 (15).

ACE2 gene expression is higher in the breast than in the lungs, and breast pathologies may ensue (33-36). This is a critical discovery as SARS-CoV-2 infection may directly and indirectly affect the breast in addition to the lungs by the ACE2 receptor.

Ethics Committee Approval: Ethical approval was not required as the study exclusively used publicly available data.

Informed Consent: This study exclusively used publicly available data.

Peer-review: Externally peer-reviewed.

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