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ACE2 Expression on the Keratinocytes and SARS-CoV-2 Percutaneous Transmission: Are they Related?

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TO THE EDITOR

Introduction

Human angiotensin-converting enzyme 2 (ACE2) is an important cell receptor for coronavirus entry into cell. ACE2 is ubiquitously expressed among human tissues. Previous studies have shown that ACE2 was highly expressed in the small intestine, testis, heart, and kidney; moderately in the lungs, colon, liver, and skin; and least expressed in the blood, spleen, and bone marrow (Li et al., 2020). The skin, the respiratory tract, and the digestive tract are the borders between the human body and the external environment, and they are vulnerable to the virus infection because of the expression of ACE2.

In the *Journal of Investigative Dermatology*, Xue et al. (2020) utilized single-cell RNA sequencing to examine the expression of ACE2 in skin tissues and confirmed that the ACE2 was mainly expressed in keratinocytes, which might provide possible routes for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to invade human cells. Their findings provide a novel insight into the potential transmission route through the skin.

A previous study showed that the virus can survive on the surface for several days (van Doremalen et al., 2020), and the viral RNA has been detected in stool and urine samples from patients who were diagnosed with severe acute respiratory syndrome and coronavirus disease 2019 (COVID-19) (Cheung et al., 2020). Besides, rising summer temperature means less clothing and an increased risk of skin exposure to the virus in the environment. These may increase the risk of skin contact with the virus and the virus invading the body through skin damage. However, whether there is a percutaneous transmission is still unknown.

COVID-19 skin manifestations were first reported in the study of Guan et al. (2020), in which 2 of 1099 patients diagnosed with COVID-19 showed a skin rash. Another Italian study reported that 20.4% of 88 diagnosed patients developed multiple types of cutaneous manifestations, including erythematous rashes, widespread urticaria, and chickenpox-like vesicles (Recalcati, 2020). However, SARS-CoV-2 PCR results were negative on skin lesion biopsies from diagnosed patients with skin manifestation (Ahouach et al., 2020). Likewise, ACE2 is also abundantly expressed in the testis (Li et al., 2020). What is more? Despite the presence of significant testicular parenchymal damage in male patients with COVID-19, no virus was detected in the testis and semen samples (Holtmann et al., 2020; Pan et al., 2020; Yang et al., 2020). These pieces of evidence suggest that direct infection of the virus is unlikely to be the cause of cutaneous and testicular manifestations in COVID-19; the pathologic changes in skin and testis are probably nonspecific reaction of COVID-19.

Skin barrier and immunity prevent virus infection

The skin barrier defends diverse external disturbances, and the human innate immune system protects the body from the invasion of pathologic microorganism (Handfield et al., 2018). Cutaneous innate immunity is the first line of immune defense, which restricts the virus from dispersing from the skin and activates the adaptive immune response. Meanwhile, intrinsic immunity provides an immediate and direct antiviral defense mediated by host intrinsic restriction factors. In contrast, host intrinsic immunity is immediately triggered and mediates antiviral defense action. To detect the invading viruses, skin cells express a variety of pattern-recognition receptors, such as toll-like receptors and C-type lectin receptors (Kawamura et al., 2014).

In the study of Xiao et al. (2017), they have found that the fomite transmission route of severe acute respiratory syndrome played a negligible role when working alone but had a much more effect when working in combination with the airborne transmission. Furthermore, there is no clinical evidence on skin-to-skin infection so far. These pieces of evidence imply that the coronavirus cannot infect the skin solely through skin contact and that skin immunity may play an important role in protecting our body from the coronavirus infection.

The invasion of coronavirus is not just about ACE2

The S protein on the SARS-CoV-2 surface is bound to the peptidase domain of ACE2, another protein TMPRSS2 primes the S protein–related viral entry, but the amino acid transporter B^0AT1

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

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(also known as SLC6A19) may act as a regulatory factor by blocking ACE2 cleavage to suppress SARS-CoV-2 infection (Yan et al., 2020). ACE2 expression is more widely distributed than that of B^0AT1 (Yan et al., 2020), which may explain why some of the ACE2 expressing organs, such as lung and heart, are attacked by SARS-CoV-2, whereas others are not.

Apart from ACE2, there may be another way for SARS-CoV-2 to infect host cells. ACE2 is scarcely present in immune cells. However, most patients with severe acute respiratory syndrome and patients with COVID-19 have lymphopenia; some patients may even have spleen and lymph nodes necrosis (Hamming et al., 2004). Similarly, ACE2 was absent in platelets, but SARS-CoV-2 was detected in platelets from patients with COVID-19 (Manne et al., 2020). These studies suggest that platelets and immune cells may take up SARS-CoV-2 mRNA independent of ACE2.

In summary, the work of Xue et al. (2020) provides a new perspective on the potential percutaneous transmission of COVID-19, but so far, from the clinical data we summarized, no definitive evidence had shown that there is a transmission of COVID-19 through the skin, especially owing to the difference of ACE2 expression. Anyhow, we should still attach importance to this potential transmission route owing to the fact that human coronavirus is an RNA virus with high mutation potential.

Data availability statement
No datasets were generated or analyzed during this study.

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CONFLICT OF INTEREST
The authors state no conflicts of interest.

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Intravenous Injection of Muse Cells as a Potential Therapeutic Approach for Epidermolysis Bullosa

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TO THE EDITOR
Multilineage-differentiating stress-enduring (Muse) cells, positive for stage-specific embryonic antigen-3, are endogenous pluripotent-like stem cells that reside in the bone marrow, peripheral blood, and connective tissue of organs and correspond to several percentages of cultured mesenchymal stem or stromal cells and fibroblasts (Kuroda et al., 2010). As shown by animal models of acute myocardial infarction, stroke, and chronic kidney disease, intravenously injected Muse cells specifically are home to damaged

Abbreviations: Col, collagen; EB, epidermolysis bullosa; hCOL, human collagen; KO, knockout; Muse, multilineage-differentiating stress-enduring

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