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Psoriatic lesional expression of SARS-CoV-2 receptor ACE2 is reduced by blockade of IL-17 signaling but not by other biologic treatments

To the Editor: Psoriatic skin was recently described as a potential host site for SARS-CoV-2, the cause of COVID-19, due to the high expression of angiotensin-converting enzyme 2 (*ACE2*), which is the main viral host receptor in the epidermis of lesional skin.[1,2] There are positive correlations between *ACE2* expression, Psoriasis Area Severity Index scores, and interleukin 17C (*IL-17C*) expression at baseline,[3] whereas treatment with an anti-IL-17 antibody reduces the risk of COVID-19 in psoriatic patients by downregulating *ACE2* expression in affected skin.[3,4] However, the effect of other molecule-targeted therapies on *ACE2* expression in psoriatic skin remains unknown.

To determine this effect, we collected microarray data (GSE13355, GSE14905, GSE30999, GSE34248, GSE41662, GSE47751, GSE50790, GSE53552, GSE57376, GSE78097, GSE106992, GSE117239, GSE136757, GSE31652, and GSE137218) from the Gene Expression Omnibus database. The samples included normal skin (n = 89), psoriatic nonlesional skin (n = 456), and lesional skin (n = 502) at baseline. Samples were also obtained from lesional skin after treatment with placebo (n = 23), with 140 mg, 350 mg, or 700 mg brodalumab (n = 4, 4 or 8), with LY2439821 (n = 6), with secukinumab (n = 14), with etanercept (n = 60), with 45 mg or 90 mg ustekinumab (n = 18 or 55), with tofacitinib (n = 8), or with 30 mg or 100 mg PF-06700841 (n = 7 or 5) at the end time point. The data were analyzed with the Transcriptome Analysis Console software 4.0 (Applied Biosystems, Thermo Fisher Scientific). The least square means by group and fold change were calculated. Hypotheses were tested using 1-way analysis of variance with Tukey's test. $P < .05$ was considered statistically significant.

At baseline, *ACE2* expression was significantly upregulated in psoriatic lesional skin compared to nonlesional or normal skin (Fig 1), which is consistent with previous studies.[1,2] Interestingly, after treatment with placebo or the different molecule-targeted treatments, only the IL-17 receptor A subunit inhibitor (brodalumab) and anti-IL-17A monoclonal antibodies (LY2439821 and secukinumab), but not the other treatments, such as the tumor nuclear factor-α inhibitor (etanercept), anti-IL-12/-23 antibody (ustekinumab), Janus kinase inhibitor (tofacitinib), or tyrosine kinase 2 inhibitor (PF-06700841), remarkably reduced *ACE2* expression in psoriatic skin. Notably, although no significant difference in *ACE2* expression was observed between lesional skin at baseline and lesional skin after being treated with lower concentrations of brodalumab, dose-dependent *ACE2* expression was observed in the brodalumab-treated groups (Fig 1).

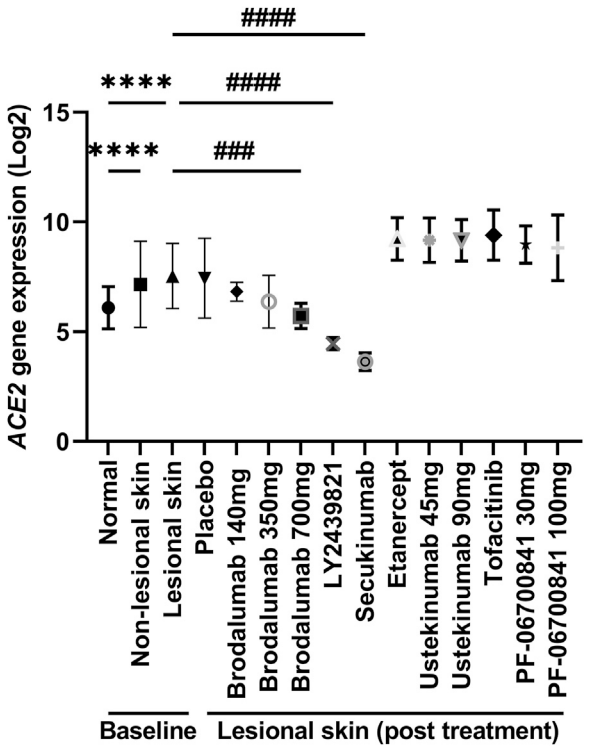

Fig 1. *ACE2* expression in normal, nonlesional, and lesional skin of patients with psoriasis before and after the indicated treatments. **** $P < .0001$, the fold change between the lesional and the nonlesional or the normal skin at baseline. ### $P < .001$, #### $P < .0001$, the fold change between the lesional skin at baseline and the lesional skin at the end time point.

Our report, together with previous studies,[3,4] suggests that the *ACE2* levels in psoriatic lesional skin are reduced by IL-17 blockade and that perhaps psoriatic patients who become COVID-19 infected may benefit from IL-17–targeted treatment. Although there is no evidence that COVID-19 spreads through skin contact, if future studies suggest that *ACE2* expression in psoriatic lesional skin correlates with COVID-19 susceptibility or severity, then perhaps IL-17–targeted therapies may be preferred in psoriasis patients at risk for COVID-19. This is worth confirming by further investigation.

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Funding sources: None.

IRB approval status: Not applicable.

Key words: ACE2; COVID-19; IL-17; molecule-targeted therapy; psoriasis; SARS-CoV-2.

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Conflicts of interest

None disclosed.

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Association of psoriasis with risk of COVID-19: A 2-sample Mendelian randomization study

To the Editor: With the growing pandemic of COVID-19, psoriasis has been reported to be linked with COVID-19 from genetic and epidemiological perspectives, especially in patients receiving systemic treatments.[1-3] However, traditional epidemiology is inevitably affected by confounding bias. Mendelian randomization (MR) is an approach based on genome-wide association studies to construct instrumental variables (IVs) and can effectively control the confounding bias of observational studies. IVs refer to variables that only affect the outcome through risk factors, and MR uses single-nucleotide polymorphisms as IVs to identify risk factors. MR draws on the experiences of randomized trials and uses the Mendelian law of heredity that parental alleles are randomly assigned to the offspring to simulate the causal relationships between exposures and outcomes. Here, we performed a 2-sample MR, in which genetic associations with exposures and outcomes are estimated in different sets of individuals, to investigate the association of psoriasis with COVID-19.

We downloaded the summary data from open-access genome-wide association studies data sets at https://gwas.mrcieu.ac.uk/. We used R 4.0.4 and package "TwoSampleMR," and statistical methods can be found in the guidelines (https://mrcieu.github.io/TwoSampleMR). We used the inverse variance weighted (IVW) method as the primary approach and other algorithms as the supplementary methods. We then tested pleiotropy using MR-Egger regression because valid MR estimations require IVs to be independent of outcomes. Finally, reverse MR and sensitivity analysis were used to test the unidirectionality and robustness of the results, respectively. A P value of $<.05$ was considered statistically significant.

For psoriasis, we extracted the results from the studies by the Neale laboratory, with 3871 cases and 333,288 controls, to generate the IVs (https://gwas.mrcieu.ac.uk/datasets/ukb-a-100/). For COVID-19, the data from the COVID-19 Host Genetics Initiative with 14,134 cases and 1,284,876 controls were gathered as the outcome variables (https://gwas.mrcieu.ac.uk/datasets/ebi-a-GCST010776/).[4] After removing linkage disequilibrium, 28 single-nucleotide polymorphisms were selected from the exposure datasheet and incorporated into the outcome datasheet. The IVW method, in conjunction with other methods (Fig 1), suggested that the genetic risk of psoriasis was associated with increased susceptibility to COVID-19 ($\beta_{IVW} = 2.94$, $P = .01$). The MR-Egger regression identified no significant horizontal pleiotropy ($P = .74$). The reverse MR analysis treating COVID-19 as the exposure and psoriasis as the outcome demonstrated an insignificant association ($P = .94$), indicating the unidirectionality of the relationship. The leave-one-out sensitivity analysis that removed 1 SNP at a time showed stable results, except for rs13196409 (Fig 2).

Our study revealed a unidirectional effect of psoriasis on COVID-19. By constructing IVs, the associations estimated by the MR analysis have