Letters to the Editor

Response to Tembhre *et al.*: 'Enhanced expression of angiotensin-converting enzyme 2 in psoriatic skin and its upregulation in keratinocytes by interferon-γ: implication of inflammatory milieu in skin tropism of SARS-CoV-2'

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Linked Article: Tembhre *et al.* Br J Dermatol 2021; **184**:577–579.

Dear Editor, We recently read with great interest the research letter by Tembhre and colleagues[1] in which the authors describe that while expression patterns of angiotensin-converting enzyme 2 (ACE2) and other cofactors of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) have been characterized in the skin during homeostatic conditions, they have not been examined in the state of pathogenic inflammation. To follow up on the hypothesis that ACE2 is an interferon-stimulated gene (ISG), the authors evaluated psoriasis skin biopsies and performed *in vitro* experiments with cultured keratinocytes. The rationale for the experiments is reasonable, though we feel some additional commentary is warranted.

There is evidence suggesting that psoriasis may not be the most relevant inflammatory dermatosis in which to evaluate this hypothesis. While interferons type I (IFN-α/β) and type II (IFN-γ) have been proposed to play a role in psoriasis, a small study of a humanized anti-IFN-γ antibody showed disappointing efficacy in psoriasis.[2] The clinical success of interleukin (IL)-23 and IL-17 inhibitors points to their pivotal role in psoriasis pathogenesis. Moreover, recent studies have suggested that ACE2 is not an ISG.[3–5] Three new publications have identified a novel primate-conserved, truncated ACE2 isoform (dACE2) encoding the C-terminal amino acids (357–805) of full-length ACE2. This novel isoform is transcribed in response to interferon stimulation, while full-length ACE2 is not.

Notably, dACE2 lacks the domain that interacts with the SARS-CoV-2 spike protein and thus cannot mediate viral entry into a cell. In one study, the authors were unable to detect dACE2 protein via Western blotting with a polyclonal ACE2 antibody (ab15348; Abcam, Cambridge, UK) in transfection-based overexpression experiments in HEK293T, SCC-4 and SCC-25 cell lines,[3] suggesting that the novel isoform may be unstable at the protein level. However, the other two studies were able to detect dACE2 protein; one detected endogenous dACE2 in primary bronchial epithelial cells using the same C-terminal-targeted antibody (ab15348),[5] while the other required an overexpression system in the T24 human bladder cancer cell line.[4] These data indicate that stable expression of dACE2 protein may be cell-type dependent. The functional role of dACE2 is currently unclear.

Given the above, in order to fully interpret the studies reported by Tembhre and colleagues, additional information is required regarding the portion of the ACE2 mRNA detected by their quantitative reverse-transcriptase polymerase chain reaction (PCR) primers and the portion of ACE2 recognized by their antibody. We applaud the authors for their efforts and suggest there remains further need to study possible SARS-CoV-2 tropism to skin. Additionally, given the recent finding of this novel ACE2 isoform, all new publications in this area should include fundamental details on PCR primers and antibody reagents.

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References

1 Tembhre MK, Parihar AS, Sharma VK *et al.* Enhanced expression of angiotensin-converting enzyme 2 in psoriatic skin and its upregulation in keratinocytes by interferon-γ: implication of inflammatory milieu in skin tropism of SARS-CoV-2. Br J Dermatol 2021; **184**: 577–9.

2 Harden JL, Johnson-Huang LM, Chamian MF *et al.* Humanized anti-IFN-γ (HuZAF) in the treatment of psoriasis. J Allergy Clin Immunol 2015; **135**:553–6.

3 Ng KW, Attig J, Bolland W *et al.* Tissue-specific and interferon-inducible expression of nonfunctional ACE2 through endogenous retroelement co-option. Nat Genet 2020; **52**:1294–1302.

4 Onabajo OO, Banday AR, Stanifer ML *et al.* Interferons and viruses induce a novel truncated ACE2 isoform and not the full-length SARS-CoV-2 receptor. Nat Genet 2020; **52**:1283–93.

5 Blume C, Jackson CL, Spalluto CM *et al.* A novel isoform of ACE2 is expressed in human nasal and bronchial respiratory epithelia and is upregulated in response to RNA respiratory virus infection. bioRxiv 2020; https://doi.org/10.1101/2020.07.31.230870 (preprint).

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