



Irritated Skin Is Not Sensitive Skin

JID Innovations (2021);1:100031 doi:10.1016/j.xjidi.2021.100031

TO THE EDITOR

I was especially interested in the paper from [Harding et al. \(2021\)](#) on a genomic test on tissue-engineered skin equivalents for the determination of chemical irritation potential. The authors concluded that the expression of a seven-gene panel in human skin equivalents, based on immortalized keratinocytes, in combination with multivariate statistical approaches showed enhanced confidence in the discrimination of skin irritants from nonirritants. Such models are very interesting in the context of European Union directives prohibiting the use of animal testing for cosmetics or other ethic rules worldwide, which exclude the formerly used tests on animals.

However, there is a need to clearly distinguish skin irritation from skin sensitivity. Skin sensitivity is a fine-tuned response by the skin that is a known sensory organ. Sensitive skin, which should better be named reactive or hyperreactive or hypersensitive skin to avoid confusion, and irritated skin (orthoergic dermatoses) as well as sensitized (or allergic) skin are very different conditions in reaction to environmental factors ([Misery, 2007](#)). [Table 1](#) summarizes the differences. In the introduction of their paper, [Harding et al. \(2021\)](#) kindly cited four references—[Farage et al. \(2006\)](#), [Misery et al. \(2017\)](#), [Ständer et al. \(2009\)](#), and [Talagas and Misery \(2019\)](#)—about skin irritation or sensitivity with some ambiguity because these papers were rather related to sensitive skin.

Using the Delphi method, the special interest group on sensitive skin of the International Forum for the Study of Itch defined sensitive skin as follows: “a syndrome defined by the occurrence of unpleasant sensations (stinging, burning, pain, pruritus, and

Table 1. Different Types of Skin Reactions

Type	Irritated Skin	Allergic Skin	Sensitive Skin	Atopic Skin
Pathophysiology	Chemical reaction	Allergy	Neuropathic disorder	Atopy
Triggering factors	Irritant chemicals	Allergens	Physicochemical factors	Atopens, stress
Affected individuals	All	Allergic	Reactive	Atopic
Area	Area of application	Area of application and beyond	Area of application and beyond	Widespread
Objective symptoms	Erythema	Erythema, vesicles	Erythema	Erythema, vesicles
Subjective symptoms	Pain	Pruritus	Paresthesia	Pruritus
Epicutaneous tests	Irritative type	Eczema	Negative	Eczema
In vitro tests	Specific to irritants	Specific to allergens	Capsaicin, lactic acid	None

tingling sensations) in response to stimuli that normally should not provoke such sensations. These unpleasant sensations cannot be explained by lesions attributable to any skin disease. The skin can appear normal or be accompanied by erythema. Sensitive skin can affect all body locations, especially the face” ([Misery et al., 2017](#)). The same expert group published a second-position paper on the pathophysiology and management of sensitive skin ([Misery et al., 2020](#)). A multifactorial origin was suggested after a discussion of many putative mechanisms. However, it was concluded that sensitive skin is not an immunological disorder but is related to alterations of the skin nervous system and that skin barrier abnormalities are frequently associated but without any direct relationship. Growing evidence suggests that sensitive skin is a neuropathic disorder ([Huet and Misery, 2019](#)).

Sensitive skin is related to the characteristics of the subject’s skin, whereas skin irritation is related to the characteristics of a product. When a

chemical is applied, it will induce skin irritation on all subjects if this product is irritant, but it will induce paresthetic sensations only in patients with sensitive skin. An in vitro test for sensitive skin would test neurocutaneous interactions ([Sakka et al., 2018](#)), whereas an in vitro test for skin irritation would test the effects of chemicals on the skin itself, as shown in this study ([Harding et al., 2021](#)).

The authors recognized that the lack of a neuronal and immune component highlights the limitations of their elegant model ([Harding et al., 2021](#)). Consequently, [Harding et al. \(2021\)](#) did not find the same gene signatures as other authors who performed transcriptomic studies on skin biopsies from subjects with sensitive skin ([Bataille et al., 2019](#); [Harding et al., 2021](#); [Kim et al., 2015, 2014a](#); [Yang et al., 2017](#)). In these studies on sensitive skin, previous works found upregulations of genes involved in innate immunity, such as *IGHA1/2*, *CDH1*, *HLA-C*, toll-like receptor 1 gene *TLR1*, *S100A8*, and the noncoding gene *GATA3-AS1* ([Kim et al., 2014a](#); [Yang et al., 2017](#)), or a major role of adiponectin deficiency ([Kim et al., 2015](#)). Previous studies also found differentially expressed genes involved in the functions of Merkel cells and sensory neurons, such as *DOCK9* or *PIEZO2* ([Yang et al., 2017](#)). Regarding keratinocytes, studies on

Accepted manuscript published online 11 June 2021; corrected proof published online 20 July 2021

Cite this article as: JID Innovations 2021;1:100031

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sensitive skin mainly found upregulations of *CDH1* (encoding for E-cadherin), keratin 27 gene *K27*, *CLDN5*, *ANXA6* 217, and *ERBB4* (Kim et al., 2014a; Yang et al., 2017).

Harding et al. (2021) identified a putative seven-gene panel: *IL6*, *PTGS2*, *ATF3*, *TRPV3*, *MAP3K8*, *HMGB2*, and matrix metalloproteinase 3 gene *MMP3*. These markers were not found in transcriptomic studies on sensitive skin (Kim et al., 2014b; Yang et al., 2017), which supports that irritated skin is not sensitive skin. Further comparative studies for sensitive skin and irritation transcriptomes would be highly interesting to better understand the shared and/or distinct molecular players and pathways and what clinical results might be expected.

In practice, the determination of a chemical irritation potential of a substance using Harding's elegant technique (Harding et al., 2021) should discourage its use in topicals (or only in low concentrations), but it may not predict the skin reactivity of individuals with sensitive skin.

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CONFLICT OF INTEREST

LM states conflict of interest with BASF, Bayer, Beiersdorf, Bioderma, Clarins, Laboratories

Expanscience, Galderma, Gilbert, Pierre Fabre, La Roche-Posay, Solabia Group, and Uriage.

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