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Letters to the Editor

A Comment on "Anti-Psoriatic Drug Monomethylfumarate Increases Nuclear Factor Erythroid 2-Related Factor 2 Levels and Induces Aquaporin-3 mRNA and Protein Expression"

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In their article, Helwa et al. (2017) show the effect of monomethylfumarate (MMF) in the treatment of psoriasis through enhancing the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and aquaporin-3 (AQP3). In our opinion, however, there are some doubts about the results of their study that puzzle us.

First, the mechanism of MMF for psoriasis remains uncertain. Although oxidative stress is associated with an attack of psoriasis, it is not an etiological factor but a promoting one. Psoriasis, a T cell–mediated disease, mainly involves genetic, environmental, and immunologic factors, i.e., in particular, T cell abnormality (Raychaudhuri, 2013). T cell imbalance and inflammatory reaction benefit keratinocyte hyperproliferation and angiogenesis (Karczewski et al., 2016), which ultimately lead to the typical histopathologic features of psoriasis, presented as epidermal hyperplasia (hyperkeratosis, parakeratosis, and hypogranulosis), angiogenesis of dermal papillae, and sustained infiltration of lymphocytes and neutrophils (Beek and van Reede, 1977). Thus, it appears inadequate only to investigate the mechanism of MMF against oxidative stress in keratinocytes. Second, Helwa et al. (2017) found that higher doses of (200 or 300 μM) MMF increased Nrf2 and its target gene expression in keratinocytes, further indicating that the mechanism of MMF in keratinocytes was Nrf2 dependent and MMF worked on psoriasis via enhancement or activation of Nrf2. However, many reports have demonstrated that Nrf2 promotes cell proliferation (Kurinna et al., 2016). Yang et al. (2017) not only found that the epidermis of psoriasis exhibited increased Nrf2 expression but they also revealed that Nrf2 enhanced the proliferation of primary keratinocytes and HaCaT cells; conversely, Nrf2-targeted siRNA mitigated epidermal hyperplasia in the imiquimod-induced psoriasis-like mouse model. Third, in the Helwa et al. (2017) study, it was shown that AQP3 expression also increased when accompanied with MMF treatment. It is confirmed that AQP3 enhances K10 promoter activity (Bollag et al., 2007). Nevertheless, K10 is one of hyperproliferation-associated keratins (including K6, K14, K16, and K17,), and is closely correlated with the severity and activity of psoriasis (Mommers et al., 2000; Ramot et al., 2013; Elango et al., 2015). Furthermore, K6, K16, and K17 could be induced by interleukin 17 and 22 stimuli via upregulation of Nrf2 expression in vitro (Yang et al., 2017). Also, Nrf2 overexpression in HaCaT cells could increase K16 gene expression and contribute to epidermal hyperkeratosis (Endo et al., 2008). Based on the aforementioned points, reaching the conclusion that MMF would increase keratinocyte proliferation and promote epidermal hyperplasia if the action of MMF is dependent on the Nrf-mediated pathway is somewhat confusing. It should be noted that their results, in part, may be contradictory to their previous findings that MMF could inhibit the proliferation of keratinocytes (Helwa et al., 2015). Therefore, it is important for us to clarify the mechanism of MMF in the treatment of psoriasis and the roles of Nrf2, AQP3, and keratins in psoriasis.

This Letter to the Editor is in response to "Anti-psoriatic drug monomethylfumarate increases nuclear factor erythroid 2-related factor 2 levels and induces aquaporin-3 mRNA and protein expression" by Helwa I, Choudhary V, Chen X, Kaddour-Djebbar I, and Bollag WB, found in *J Pharmacol Exp Ther* 2017, **362**:243–253.
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References

Beek CH and van Reede EC (1977) The nature and frequency of the histological changes found in psoriasis vulgaris. *Arch Dermatol Res* **257**:255–264.
Bollag WB, Xie D, Zheng X, and Zhong X (2007) A potential role for the phospholipase D2-aquaporin-3 signaling module in early keratinocyte differentiation: production of a phosphatidylglycerol signaling lipid. *J Invest Dermatol* **127**:2823–2831.
Elango T, Thirupathi A, Subramanian S, Dayalan H, and Gnanaraj P (2015) Methotrexate normalized keratinocyte activation cycle by overturning abnormal keratins as well as deregulated inflammatory mediators in psoriatic patients. *Clin Chim Acta* **451**:329–337.
Endo H, Sugioka Y, Nakagi Y, Saijo Y, and Yoshida T (2008) A novel role of the NRF2 transcription factor in the regulation of arsenite-mediated keratin 16 gene expression in human keratinocytes. *Environ Health Perspect* **116**:873–879.
Helwa I, Choudhary V, Chen X, Kaddour-Djebbar I, and Bollag WB (2017) Anti-psoriatic drug monomethylfumarate increases nuclear factor erythroid 2-related

ABBREVIATIONS: AQP3, aquaporin-3; MMF, monomethylfumarate; Nrf2, nuclear factor erythroid 2-related factor 2.

factor 2 levels and induces aquaporin-3 mRNA and protein expression. *J Pharmacol Exp Ther* **362**:243–253.
Helwa I, Patel R, Karempelis P, Kaddour-Djebbar I, Choudhary V, and Bollag WB (2015) The antipsoriatic agent monomethylfumarate has antiproliferative, pro-differentiative, and anti-inflammatory effects on keratinocytes. *J Pharmacol Exp Ther* **352**:90–97.
Karczewski J, Dobrowolska A, Rychlewska-Hańczewska A, and Adamski Z (2016) New insights into the role of T cells in pathogenesis of psoriasis and psoriatic arthritis. *Autoimmunity* **49**:435–450.
Kurinna S, Muzumdar S, Köhler UA, Kockmann T, Auf dem Keller U, Schäfer M, and Werner S (2016) Autocrine and paracrine regulation of keratinocyte proliferation through a novel Nrf2-IL-36γ pathway. *J Immunol* **196**:4663–4670.
Mommers JM, van Rossum MM, van Erp PE, and van De Kerkhof PC (2000) Changes in keratin 6 and keratin 10 (co-)expression in lesional and symptomless skin of spreading psoriasis. *Dermatology* **201**:15–20.Ramot Y, Sugawara K, Zákány N, Tóth BI, Bíró T, and Paus R (2013) A novel control of human keratin expression: cannabinoid receptor 1-mediated signaling down-regulates the expression of keratins K6 and K16 in human keratinocytes in vitro and in situ. *PeerJ* **1**:e40 .
Raychaudhuri SP (2013) A cutting edge overview: psoriatic disease. *Clin Rev Allergy Immunol* **44**:109–113.
Yang L, Fan X, Cui T, Dang E, and Wang G (2017) Nrf2 promotes keratinocyte proliferation in psoriasis through up-regulation of keratin 6, keratin 16, and keratin 17. *J Invest Dermatol* **137**:2168–2176.

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