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., 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 Nrf2-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.

References


Helwa I, Choudhary V, Chen X, Kaddour-Djebbar I, and Bollag WB (2017) Anti-psoriatic drug monomethylfumarate increases nuclear factor erythroid 2-related factor 2-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.

References


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