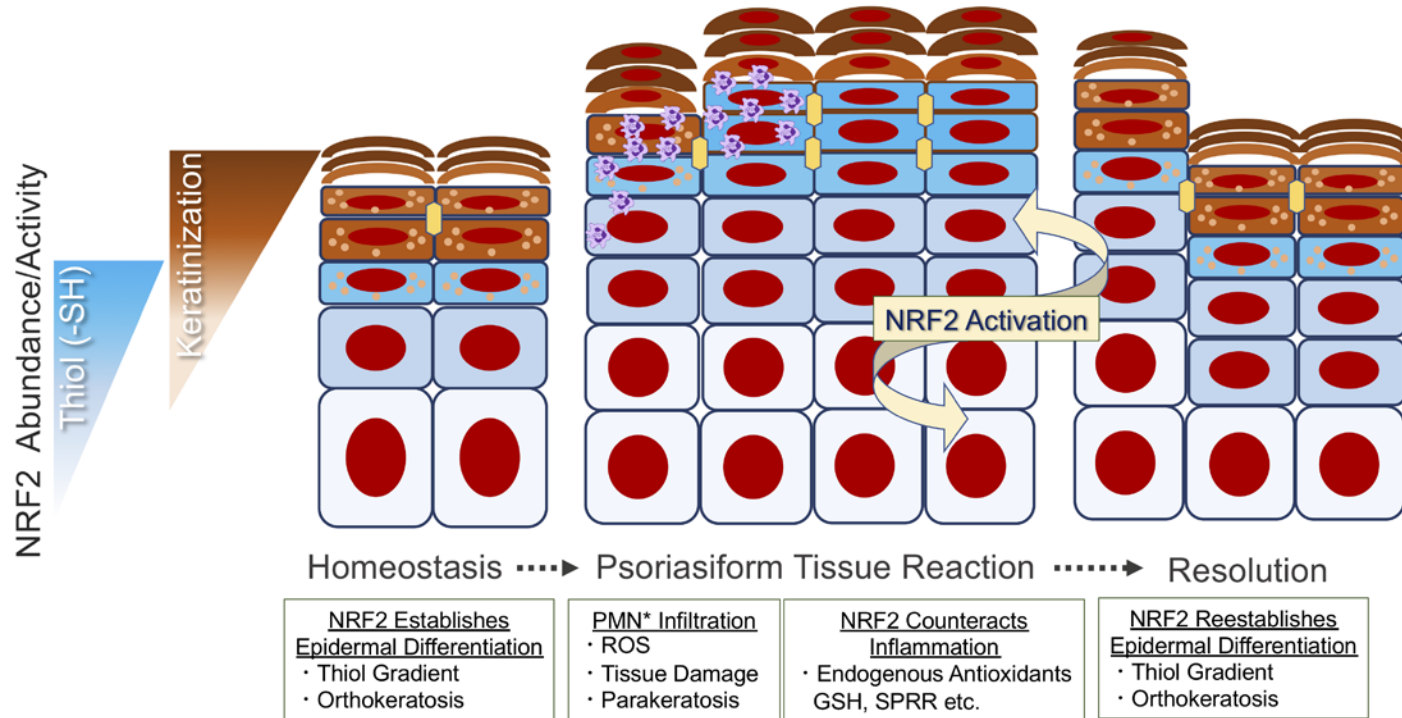


Nrf2 regulates epidermal keratinization under psoriatic skin inflammation



Psoriasis is an autoinflammatory/autoimmune skin disease and the epitome of exaggerated primary inflammatory response in the surface barrier tissue. Despite the efficacy of dimethyl fumarate (DMF), an electrophilic drug for psoriasis management, there is a paucity of mechanistic evidence *in vivo*. In response to electrophiles, the KEAP1/NRF2 system mediates a myriad of cytoprotective mechanisms, including the regulation of excessive inflammatory response and epidermal differentiation. Since the psoriasiform tissue reaction comprises neutrophil infiltration and parakeratotic scaling, we hypothesized that Nrf2 not only regulates inflammatory responses but is also required for the maintenance of epidermal differentiation, a hallmark of epidermal homeostasis. By utilizing the imiquimod-induced cutaneous inflammation model, we showed an exaggerated inflammatory response and impaired epidermal differentiation in Nrf2^{-/-} mice. DMF treatment in Nrf2^{+/+} mice attenuated psoriasiform tissue reaction and rescued epidermal differentiation, which was not observed in Nrf2^{-/-} mice. In accordance with the fact that psoriasis plaques form well-demarcated parakeratotic lesions in association with the psoriasiform tissue reaction, the lesional skin exhibited reduced expression levels of NRF2 and its downstream target genes compared with non-lesional skin. In conclusion, our results suggest that Nrf2 attenuates psoriasiform tissue reaction and underscore the mechanistic legitimacy of the electrophile-based approach for the management of psoriasis.

References: Ogawa *et al.*, Am J Pathol. 2020: S0002-9440(20)30002-
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