Dear Editor

With great interest we read the recent publication from Vinter and colleagues describing the role of TNFα in the Aldara model. Through the use of scoring skin inflammation, RT-PCR, and histology, they showed that TNFα-deficient mice showed less erythema, scaling, epidermal hyperplasia, Ki67, CD3+ T cells staining and splenomegaly. The authors continued by quantifying several mediating cytokines, such as IL-17A, IL-22, IL-12p40, and IL-23p19; which were significantly reduced in TNFα-knockouts. They also quantified interferon regulatory factor (IRF) -7, which on day 1 was clearly elevated in response to Aldara. Similar dynamics and levels were observed in TNFα-knockouts. Therefore, the authors conclude that TNFα does not affect the early type I interferon response. However, we believe this statement is not sufficiently supported by their study and kindly refer the authors to our previous study with TNFR1-knockout mice, which showed a sustained type I interferon response within hours after application. First, we found that IFNα levels in the skin decreased in response to repetitive Aldara treatment. In contrast, TNFR1-knockouts showed steady levels instead. Measurement of IFNα and IFNβ in wild type serum revealed a peak at 3 hours after Aldara, whereas the levels kept increasing in the absence of TNFR1. A similar trend was found in the expression levels of Cxcl10, Ifit2, and Usp18; interferon-responsive genes. We attribute these results to the TNF/TNFR1 pathway negatively regulating type I interferon production in response to Aldara.

Since TNFα may act through two different receptors, TNFR1 and TNFR2, it is difficult to interpret results obtained with TNFα-knockout mice only. Yet, similar to the findings of Vinter and coworkers, TNFR1-deficient mice in our study showed reduced IL-12p40 and S100A8 levels.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/bjd.14453

This article is protected by copyright. All rights reserved.
Consequently, we believe that the sole measurement of IRF7 after 24 hours of application, does not capture sufficient evidence to state that TNFα is dispensable for early type I interferons in the Aldara model. Nevertheless, the findings of Vinter et al. are still relevant as they reaffirm the use of the Aldara model in mice since loss of TNFα leads to amelioration of inflammatory parameters, similarly to what is observed in patients treated with TNFα-inhibitors.

The authors declare no conflict of interest.

References
