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Letter to the Editor

Distinct kinetics of two pathologies induced in mice by topical treatment with imiquimod cream: Psoriasis-like inflammation and systemic autoimmunity

Perturbations of the immune system by a variety of microorganisms or endogenous molecules such as self-nucleic acids or antimicrobial peptides result in the activation of innate immunity through pattern recognition receptors (PRPs) and subsequent adaptive immunity to maintain the homeostasis of the body. However, abnormal responses of PRPs, including Toll-like receptors, can lead to the development of inflammatory diseases. It has been demonstrated that the TLR7 signaling pathway is involved in the pathogenesis of autoimmune diseases such as systemic lupus erythematosus (SLE) in humans as well as in mouse models [1–3].

Imiquimod (IMQ), an agonist of TLR7, has been used for the treatment of warts and actinic keratoses through the activation of dendritic cells, in particular plasmacytoid dendritic cells (pDCs), and the subsequent activation of natural killer (NK) cells and T lymphocytes, which produce interferon (IFN)-γ and/or IL-17 [4]. In contrast, it has been recognized that topical treatment with IMQ cream leads to the exacerbation of preexisting psoriasis or even to the *de novo* development of psoriasis [5]. Topical treatment of mice with IMQ cream leads to a psoriasis-like inflammation, providing a mouse model for psoriasis [6]. Recently, we demonstrated that repeated treatment with IMQ for more than 4 weeks leads to the development of a systemic autoimmune disease that resembles SLE, characterized by elevation of antinuclear antibodies, autoimmune hepatitis and glomerulonephritis [7]. Here, we report the different kinetics between the two distinct pathological conditions induced by topical IMQ cream. Topical treatment with 5% IMQ cream (Aldara) three times weekly onto the ears of C57BL/B6 mice gave rise to psoriasis-like inflammatory changes (Supplementary Fig. S1) in a week including epidermal hyperplasia (Fig. 1a). Indeed, epidermal proliferation detected by Ki67 staining reached a peak at 1 week, after which it gradually attenuated despite continued IMQ treatments (Figs. 1b, Fig. S1). Accordingly, scaly erythematous changes in the ear skin disappeared by 3–4 weeks of treatment. In contrast, the mice developed splenomegaly at 4 weeks onward (Fig. 1c) and the numbers of various subsets of splenocytes including T and B lymphocytes, macrophages, granulocytes, conventional dendritic cells (cDCs) increased but the number of pDCs was relatively stable over time (Fig. 1c). This might be explained by redistribution of pDCs to the skin where IMQ was applied at the early time point as we previously shown [7]. Disproportional increases in frequencies were found for granulocytes and cDCs at 6 weeks (5.5 and 4.9-fold of the baseline, respectively, compared with a 2.5-fold increase in splenocyte number). It has been demonstrated that epicutaneous IMQ treatment for longer than 4 weeks leads to immunological and hematological abnormalities, such as decreases of the marginal zone B cell population in the spleen, anemia and thrombocytopenia [7]. More strikingly, serum anti-dsDNA and anti-Sm autoantibodies, the hallmarks of lupus, were detected and increased over time (Fig. 1d). The mice developed a systemic lupus-like disease, including glomerulonephritis with proteinuria, autoimmune hepatitis and skin photosensitivity [7]. We found that the IMQ-induced autoimmunity was dependent on TLR7, since TLR7-knockout (KO) mice did not develop the disease [7]. Therefore, the disparity of the kinetics of the two pathological conditions induced by IMQ cream (Aldara) supports the findings of a previous study [8] demonstrating that the vehicle used in Aldara (isostearic acid) can directly induce skin inflammation via inflammasome activation that is largely independent of TLR7. Indeed, IMQ treatment of TLR7KO mice led to a considerable but mild skin thickening, keratinocyte proliferation as detected by Ki67 staining, and epidermal hyperplasia as compared with wild-type mice (Fig. 2a, b and Fig. S2a, b). IMQ-treated skin of TLR7KO mice exhibited upregulation of psoriasis-related genes, although some of them were less pronounced than in wild-type mice (Fig. 2c). This result suggests that both IMQ and vehicle are required for a full inflammatory response [8].

Notably, TLR7 deficiency protected splenomegaly (Fig. 2d) and emergence of autoantibodies (data not shown) induced by IMQ for 8 wk as previously reported [7]. In contrast, topical treatment with another TLR7 agonist resiquimod did not induce skin inflammation at any time point (Fig. 2e) but instead induced a severer autoimmune disease with elevation of higher titers of anti-dsDNA antibody than IMQ treatment (Fig. 2f) [7]. This observation implies that psoriasiform skin inflammation is not a prerequisite for the subsequent development of autoimmunity. Following topical treatment with IMQ cream, pDC mobilization in the skin was observed, but it was transient [7,8]. Furthermore, the *in vivo* deletion of pDCs abrogated both the psoriasiform skin inflammation and the autoimmunity [7,9]. Further study is required to fully understand the pathomechanism underlying the topical TLR7 agonist-mediated autoimmunity, which is dependent on pDCs. Although the IMQ model has been widely used in preclinical psoriasis studies, it requires careful consideration [10]. In conclusion, this model offers two distinct pathologies: an acute, transient psoriasiform skin inflammation largely through a TLR7-independent mechanism and a late-onset, systemic autoimmunity via the TLR7 signaling (Fig. S3).

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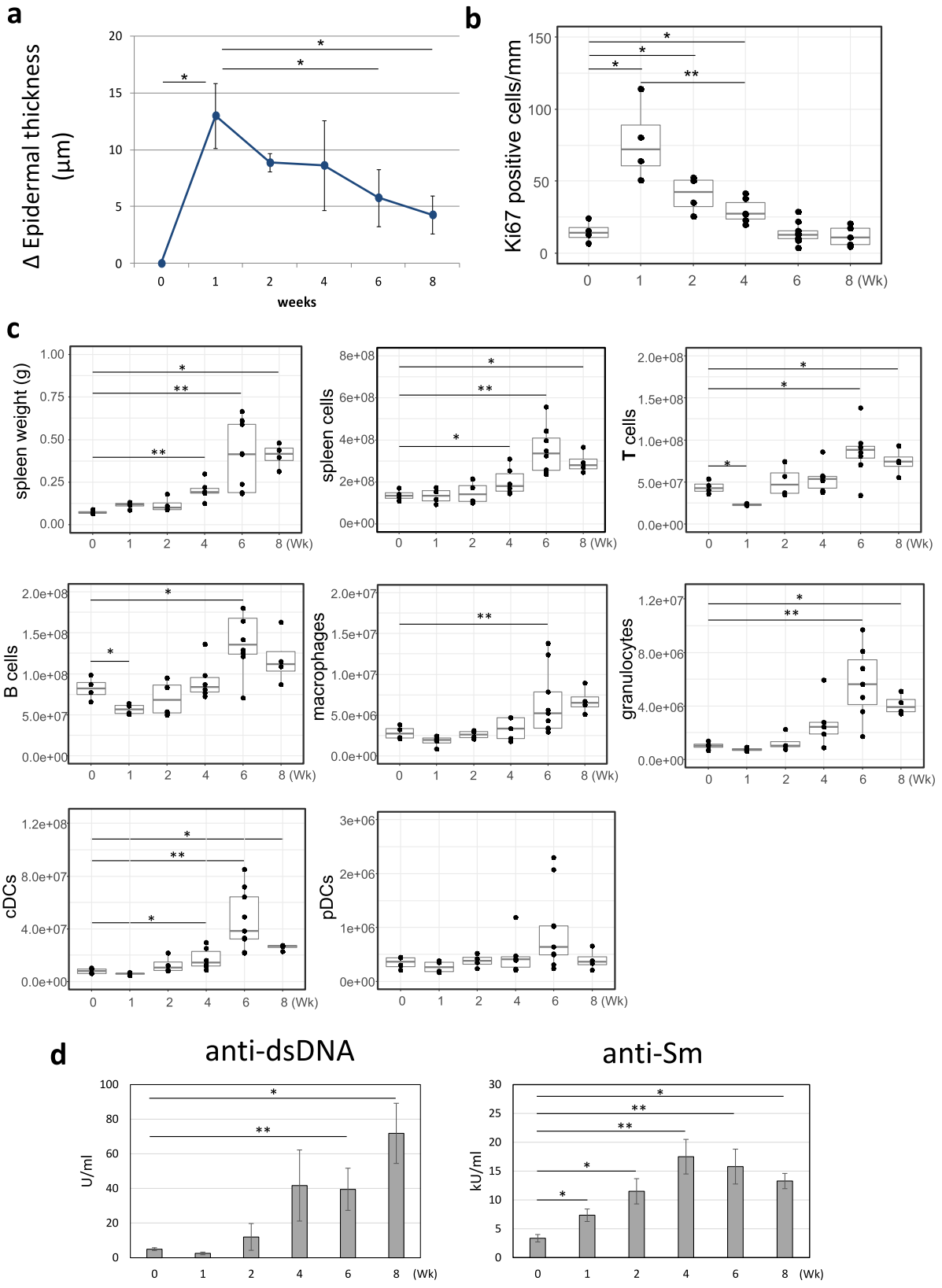

Fig. 1. Kinetics of epidermal and systemic immune responses to topical treatment with IMQ cream over time. (a) Increase of epidermal thickness (mean ± s.d., μm) from the baseline over time following IMQ treatment (weeks). n = 4-9 per group; *, $P < 0.05$, by the Mann-Whitney *U* test. (b) Number of Ki67$^+$ cells per mm in the epidermis at the indicated week of IMQ treatment. Horizontal lines of the box plot graph represent median values. n = 4–9; **, $P < 0.01$; *, $P < 0.05$, by the Mann-Whitney *U* test. (c) Spleen weight, total spleen cell number per head and the number of the indicated cells per spleen at the indicated week of IMQ treatment. Horizontal lines of the box plot graphs represent median values. n = 4–9; **, $P < 0.01$; *, $P < 0.05$, by the Mann-Whitney *U* test. (d) Serum titers (mean ± s.d.) of anti-double stranded (ds) DNA (U/mL, left panel) and Sm antibodies over time (kU/mL, right panel). n = 4-9. *, $P < 0.05$; **, $P = 0.01$, by the Mann-Whitney *U* test.

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