possibly contributing to the chronic, recurrent inflammation in these skin conditions (Wang, 2015). Thus, PG may be part of the autoinflammatory spectrum, together with HS and acne.

Genetic studies have identified 21 distinct mutations in *NCSTN*, most of them associated with HS/acne inversa (Li et al., 2011; Liu et al., 2011; Nomura et al., 2013; Pink et al., 2011; Wang et al., 2010; Zhang et al., 2013). To the best of our knowledge, the pathogenic variant identified in this study, c.1635C>G (p.Tyr545*) in *NCSTN*, is previously unreported, providing strong evidence for the critical functional role of *NCSTN* in the phenotype of our patients.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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IL-13 Signals Independent of IL-4 Receptor-Alpha Chain to Drive Ovalbumin-Induced Dermatitis

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TO THE EDITOR

Atopic dermatitis (AD) is an allergic skin condition that can result from intrinsic genetic factors or repetitive occupational damage. Disruption of the skin barrier leads to sensitization to allergens followed by local inflammation (Leung et al., 2004; Pigatto et al., 1992). Strong evidence has shown that the T helper-2 (Th2) cytokine, IL-13, is the dominant disease-causing factor in the pathogenesis of AD in mice (Nieuwenhuizen et al., 2009; Sivaprasad et al., 2010; Tazawa et al., 2004). Hence, it is possible that patients with AD would benefit from

Abbreviations: AD, atopic dermatitis; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; OVA, ovalbumin; PBS, phosphate buffered saline; Rα, receptor-alpha; Th2, T helper 2; TGF, transforming growth factor

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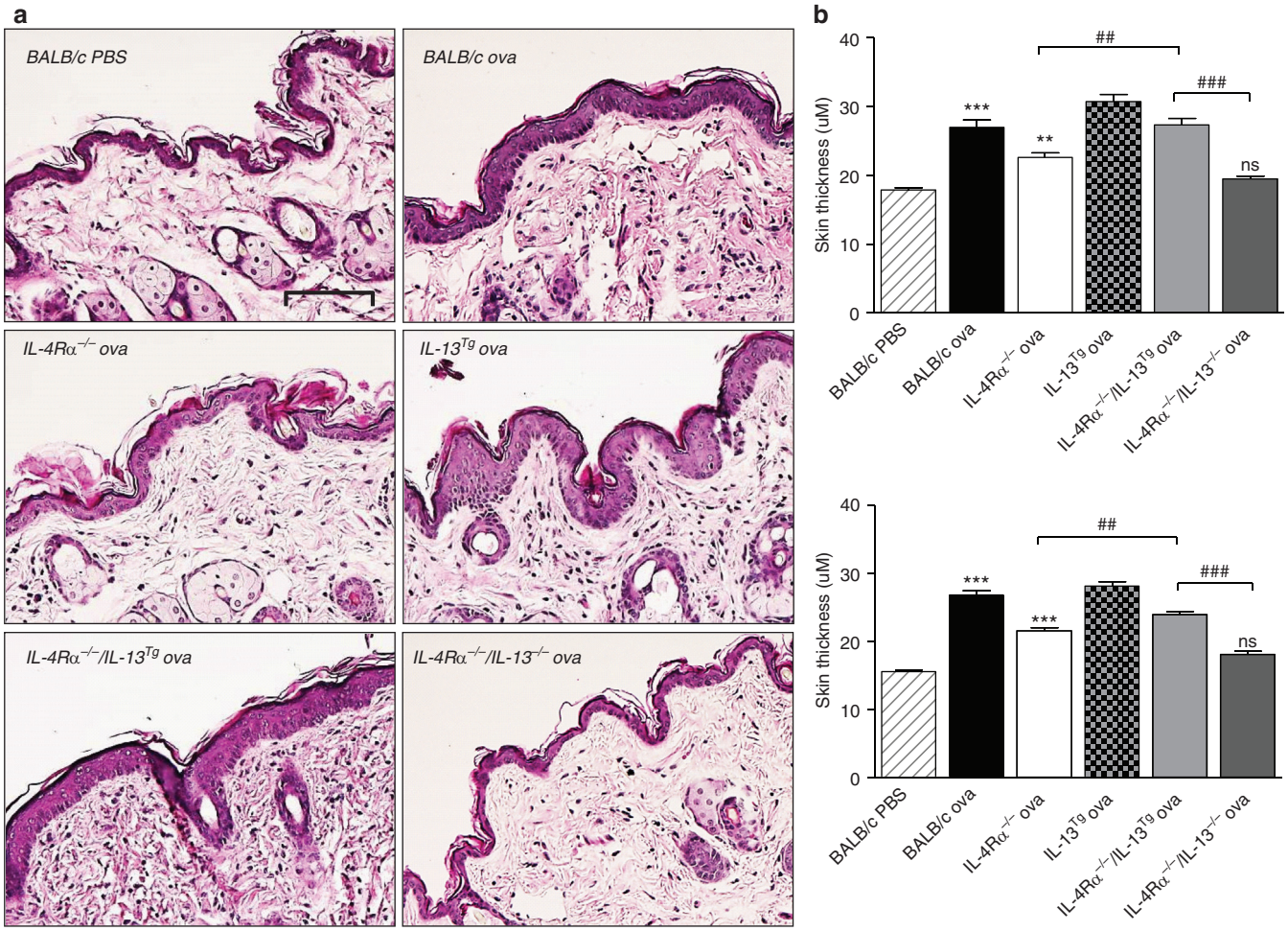

Figure 1. IL-13 causes dermatitis in IL-4Rα—deficient mice. **(a)** Hematoxylin and eosin stained skin sections. Original magnification ×200. **(b)** Epidermal thickness from two individual experiments. Data represent at least 2 individual experiments (n = 5—6). $^{**}P < 0.01$, $^{***}P < 0.001$ versus BALB/c PBS-treated mice; $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ for IL-4Rα$^{-/-}$ OVA versus IL-4Rα$^{-/-}$/IL-13$^{-/-}$ or IL-4Rα$^{-/-}$/IL-13^{Tg} OVA mice or IL-4Rα$^{-/-}$/IL-13$^{-/-}$ versus IL-4Rα$^{-/-}$/IL-13^{Tg} mice. Scale bar = 100 μm. Values are given as mean ± standard error of the mean, and significant differences were determined using unpaired two-tailed Student *t* tests (GraphPad Prism version 4, GraphPad Software, San Diego, CA). $P < 0.05$ was considered significant. IL-4Rα, IL-4 receptor-alpha; ns, not significant; OVA, ovalbumin; PBS, phosphate buffered saline.

treatments specifically targeting IL-13 signaling pathways. However, current treatment strategies are limited to broader therapies, such as emollients, topical glucocorticoids, and calcineurin inhibitors (Beck et al., 2014; De Benedetto et al., 2012; Gittler et al., 2012). A recent study by Beck et al. (2014), which used the monoclonal antibody dupilumab to block IL-4 receptor-alpha (IL-4Rα) signaling, showed promise in targeting specific immunological pathways. Until recently, IL-13 was thought to signal only through the IL-4Rα/IL-13Rα1 complex; however, recent data suggest that IL-13 may also signal via IL-13Rα2, previously known as a decoy receptor. In AD, the signaling pathway of IL-13 remains to be defined. In this study we addressed this problem by using a combination of IL-4Rα—deficient mice that lacked or overexpressed IL-13 to determine if IL-13 can signal independently of the IL-4Rα chain to mediate AD. Our results may have potential implications for therapeutic strategies, such as using IL-4Rα—antagonists to treat the disease.

Ovalbumin (OVA)-induced dermatitis is a classic murine model of AD in which repeated epicutaneous application of OVA results in local skin inflammation and systemic sensitization. This reflects what is seen in human disease, where levels of associated Th2 cytokines are increased, specifically IL-4, IL-13, and IL-5 (Brandt and Sivaprasad, 2011; Jin et al., 2009). In mice IL-13 mediates local skin pathology (Nieuwenhuizen et al., 2009), and in humans IL-13 mRNA is increased and associated with AD (Hamid et al., 1996; Tazawa et al., 2004). Differences in responses driven by IL-4 or IL-13 can be attributed to differing signaling pathways. Both IL-4 and IL-13 can signal via the IL-4Rα chain, which can associate either with the common gamma chain (type I) to form IL-4 receptor type 1, through which only IL-4 can signal, or with the IL-13Rα1 (type II) subunit to form the IL-13 receptor type 1 chain, through which both IL-4 and IL-13 can signal (Nelms et al., 1999). In a previous study we found that IL-13 was responsible for the induction of skin pathology in *Anisakis* species-induced dermatitis, because IL-13$^{-/-}$ but not IL-4$^{-/-}$ mice were protected from disease (Nieuwenhuizen et al., 2009).

Furthermore, abrogation of IL-4Rα signaling significantly reduced epidermal

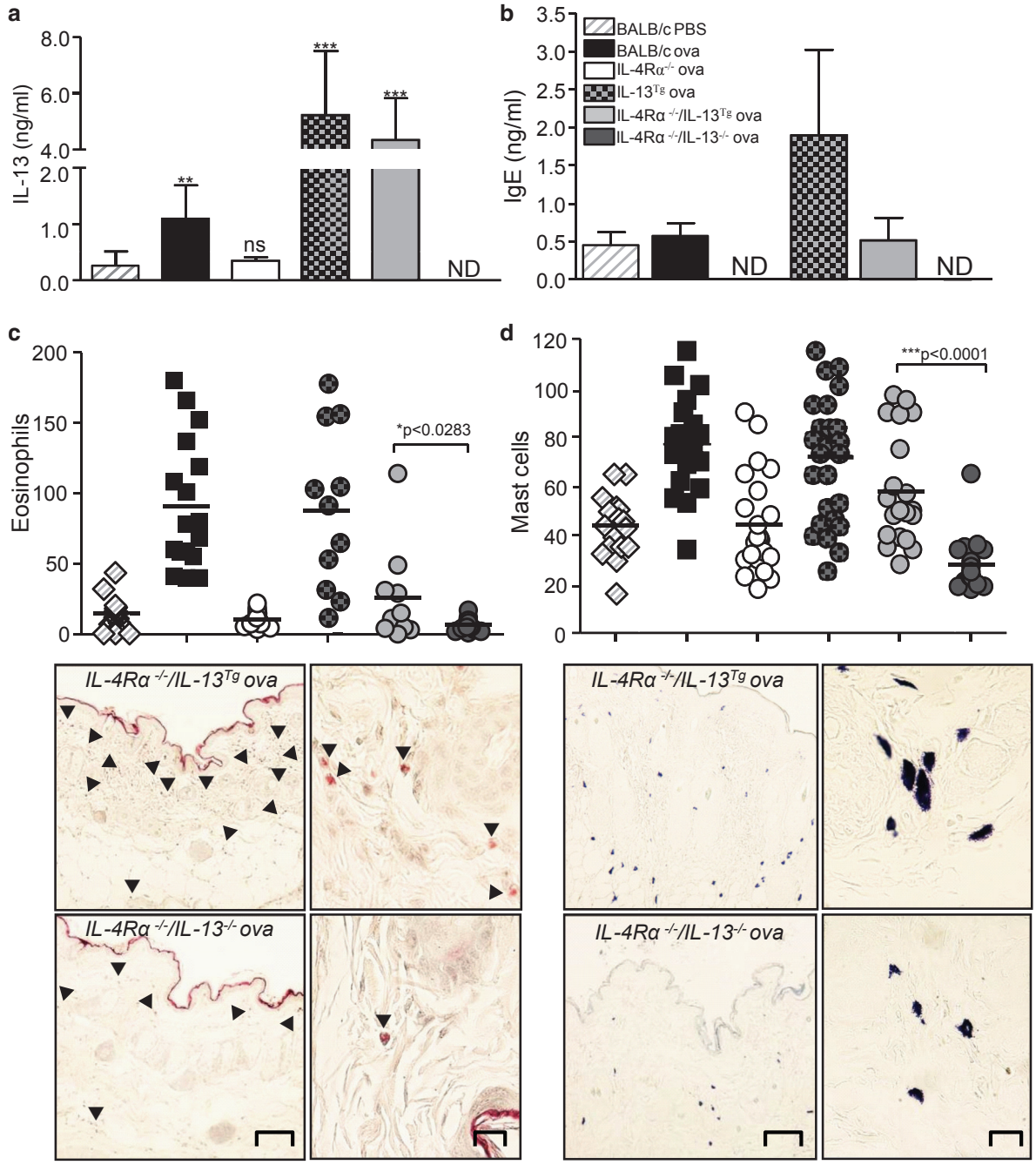

Figure 2. IL-13 is important in inducing the allergic phenotype during dermatitis. **(a)** IL-13 production in lymph nodes. **(b)** Total serum IgE level. Cell infiltration into the skin showing **(c)** eosinophils and **(d)** mast cells (including histology). Data represent 2 or more individual experiments (n = 5–6). $^{**}P < 0.01$ and $^{***}P < 0.001$ versus BALB/c PBS-treated mice. **(c)** and **(d)** represent pooled data from 2 independent experiments, * and *** represent IL-4Rα$^{-/-}$/IL-13$^{-/-}$ vs. IL-4Rα$^{-/-}$/IL-13^{Tg}. Scale bar left panel = 100 μm and scale bar right panel = 20 μm. Values are given as mean ± standard error of the mean, and significant differences were determined using unpaired two-tailed Student *t* tests (GraphPad Prism version 4, GraphPad Software, San Diego, CA). Values of $p < 0.05$ were considered significant. IL-4Rα, IL-4 receptor-alpha; ND, not determined; ns, not significant; ova, ovalbumin; PBS, phosphate buffered saline.

hyperplasia and skin inflammation compared with wild type mice (Nieuwenhuizen et al., 2009). An important role for IL-4Rα in AD was recently confirmed in a clinical study, in which treatment with the anti–IL-4Rα antibody dupilumab significantly improved signs and symptoms of AD (Beck et al., 2014). Because recent evidence suggests that IL-13 could signal independently of IL-4Rα (Brunner et al., 2013; Fichtner-Feigl et al., 2006), which could have important implications for therapeutic intervention, we aimed to determine whether IL-4Rα–independent IL-13 signaling is important in AD. Using a genetic loss or gain strategy, we compared double-deficient IL-4Rα$^{-/-}$/IL-13$^{-/-}$ mice with IL-R4α–deficient, IL-13–overexpressing (IL-4Rα$^{-/-}$/IL-13^{Tg}) mice on a BALB/c background. This allowed us to detect the role of IL-13 in the presence or absence of the IL-4Rα chain during OVA-induced AD. All mice were housed in specific pathogen-free conditions at the University of Cape Town, South Africa, and experiments

were approved by the University's Animal Ethics Committee.

Our results showed that although mice deficient in IL-4Rα still showed significant epidermal hyperplasia compared with phosphate buffered saline (PBS)-treated control mice, IL-4Rα$^{-/-}$/IL-13$^{-/-}$ mice were completely protected (Figure 1a and b), indicating that IL-13 was responsible for the partial protection of IL-4Rα$^{-/-}$ mice. This was confirmed by the fact that overexpressing IL-13 in IL-4Rα$^{-/-}$ mice (IL-4Rα$^{-/-}$/IL-13^{Tg}) resulted in more severe dermatitis, with increased epidermal hyperplasia and dermal inflammation, compared with IL-4Rα$^{-/-}$ mice (Figure 1a and b). In the absence of IL-4Rα, IL-13 levels were low but still present, and IgE levels were not detectable (Figure 2a and b). However, IL-4Rα$^{-/-}$/IL-13^{Tg} mice had significantly raised levels of IL-13, which were accompanied by an increase in IgE, compared with IL-4Rα$^{-/-}$ mice. Although eosinophil infiltration appeared to be controlled by IL-4Rα (Figure 2c), IL-13 appeared to partially regulate mast cell infiltration, because significantly more mast cells were recruited in IL-4Rα$^{-/-}$/IL-13^{Tg} mice than in IL-4Rα$^{-/-}$/IL-13$^{-/-}$ mice (Figure 2d). PBS-treated controls of all genetically altered mouse strains showed no difference in cell infiltration or epidermal thickening compared with wild type PBS-treated mice (data not shown). These results strongly suggest that IL-13 is responsible for OVA-induced dermatitis independent of the IL-4Rα chain, which may mediate dermatitis partially by regulating levels of Th2 cytokines, including IL-13.

Alternative signaling pathways for IL-13 remain to be elucidated in dermatitis and could include signaling via IL-13Rα2, previously believed to be only a decoy receptor for IL-13. Despite conflicting reports regarding the functions of IL-13Rα2, increasing evidence suggests that IL-13Rα2 may be a signaling receptor for IL-13, because an independent IL-13/IL-13Rα2 signaling pathway was found that can control activation of activator protein-1 (AP-1) to induce transforming growth factor-β secretion (Brunner et al., 2013; Fichtner-Feigl et al., 2006). It has further been shown that IL-13 binding to IL-13Rα2 mediates initiation of mitogen-activated protein kinase (MAPK) (extracellular signal-regulated kinase [ERK]) signaling (Mandal and Levine, 2010). Sustained ERK phosphorylation was observed in the sensory neurons of mice with allergic contact dermatitis (Zhao et al., 2013). In the chronic itch model described in this study, inhibition of BRAF (a serine/threonine kinase that activates ERK) signaling attenuated itch sensations, suggesting Raf—MAPK/ERK kinase—ERK signaling as a key regulator in initiating and maintaining chronic itch. Our preliminary data showed significantly increased ERK1 and ERK2 phosphorylation in the skin of OVA-treated IL-4Rα$^{-/-}$/IL-13^{Tg} mice compared with IL-4Rα$^{-/-}$/IL-13$^{-/-}$ mice (see Supplementary Figure S1 online). This is consistent with the previously described role of IL-13Rα in MAPK signaling (Mandal and Levine, 2010), but further evidence is required before conclusions can be drawn about the mechanisms of IL-4Rα—independent IL-13 signaling. Currently we are generating IL-13Rα2 floxed mice to investigate the contribution of IL-13/IL-13Rα2 signaling to dermatitis pathology.

In summary, we showed that IL-13 is able to signal independent of the IL-4Rα chain in AD, which may lead to the identification of molecular pathways downstream of IL-13 signaling that could be targeted in future therapies for AD. IL-13 overexpression in the absence of IL-4Rα reconstituted the disease phenotype and resulted in phosphorylation of ERK1 and ERK2. The role of IL-4Rα—independent signaling of IL-13 is an important consideration for therapies that neutralize IL-4Rα in the treatment of allergic diseases, because it is possible that combined neutralization of IL-4Rα and IL-13 may be more effective.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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SUPPLEMENTARY MATERIAL

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The Alarmin IL-33 Derived from HSV-2-Infected Keratinocytes Triggers Mast Cell-Mediated Antiviral Innate Immunity

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TO THE EDITOR

IL-33, a member of the IL-1 family, is a nuclear-associated multifunctional cytokine that acts as damage-associated molecular patterns, so-called "alarmins," following external insults to induce innate immunity, inflammation, and allergy (Cayrol and Girard, 2014; Molofsky et al., 2015). IL-33 interacts with the IL-1 family receptor ST2, which is expressed on mast cells (MCs), eosinophils, basophils, natural killer cells, group 2 innate lymphoid cells, and T cells (Cayrol and Girard, 2014). Although IL-33 is most frequently characterized as an epithelial cytokine that promotes T helper type 2-mediated immune responses, recent studies have extended its biology to include roles in basal tissue regulation, organ-specific injury and repair, T helper type 1-, T helper type 17-, or cytotoxic T lymphocyte-mediated immune responses, and immune tolerance by affecting regulatory T cells (Gajardo Carrasco et al., 2015; Molofsky et al., 2015). Moreover, IL-33/ST2 signaling has been recently found to be involved in the response to viral infections (Rostan et al., 2015), such as airway infection with influenza virus or parainfluenza virus (Byers et al., 2013; Chang et al., 2011; Monticelli et al., 2011), splenic infection with lymphocytic choriomeningitis virus (Baumann et al., 2015; Bonilla et al., 2012), and intraperitoneal infection with mouse cytomegalovirus (Nabekura et al., 2015). Some of these studies have highlighted the new role of IL-33 as an "alarmin" in host defense against viral infections; however, its role against cutaneous viral infections remains to be defined.

Herpes simplex virus type 2 (HSV-2) is a sexually transmitted pathogen that infects more than 500 million people worldwide and causes most cases of genital herpes (Looker et al., 2008). Although adaptive immune responses mediated by HSV-specific cytotoxic T lymphocytes are known to play a central role in controlling primary and recurrent HSV infections, the importance of innate immune effectors, including plasmacytoid dendritic cells, natural killer cells, and γδ T lymphocytes, has been recently re-emphasized, either in direct immune control or via modulation of adaptive immune responses (Chew et al., 2009; Kawamura et al., 2014). In addition to these innate immune cells, we have recently demonstrated that MCs are critically involved in host defense at HSV-infected sites through tumor necrosis factor-α and IL-6 production (Aoki et al., 2013). Our study also demonstrated that IL-33 expression was upregulated by HSV-infected Pam-212 keratinocytes in vitro, suggesting the significance of IL-33 as a trigger for the host anti-HSV innate immunity.

To further explore cutaneous IL-33 expression after HSV-2 infection in vivo, we examined the tissue levels of IL-33 in an HSV-2 cutaneous infection model, whereby HSV-2 was intradermally injected into wild-type (WT) mice. As expected, significant IL-33 production was observed at the skin sites of infection, which peaked at 1 day after infection, and importantly, paralleled the kinetics of HSV-2 titer in the skin (Figure 1a, Detailed methods; see Supplementary Materials online), suggesting that productive viral replication promotes IL-33 release in the murine skin. Immunohistochemical staining for IL-33 in HSV-2-infected skin at 1 day after infection revealed that IL-33 was dominantly expressed in the nucleus of epidermal keratinocytes (Figure 1b). Importantly, we could confirm a significant increase in IL-33 expression and production by HSV-2-infected human HaCaT keratinocytes and normal human epidermal keratinocytes (Supplementary Figures S1 and S2 online). We found that increased IL-33 expression was selectively detected on damaged or degenerating HaCaT cells and normal human epidermal keratinocytes 24 hours after HSV-2 exposure, and the frequency of IL-33-expressing cells was increased in a multiplicity of infection-dependent manner. In line with these findings, we could detect abundant IL-33 expression in degenerating keratinocytes in lesional blister roof of HSV-infected patients (Supplementary Figure S3 online). All patients provided written informed consent to participate in the study, which was

Abbreviations: BMMC, bone marrow-derived mast cell; HSV-2, herpes simplex virus-2; MC, mast cell; WT, wild-type

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