Molecular Phenotyping Small (Asian) versus Large (Western) Plaque Psoriasis Shows Common Activation of IL-17 Pathway Genes but Different Regulatory Gene Sets

Jaehwan Kim¹, Chil-Hwan Oh², Jiehyun Jeon², Yoosang Baek², Jaewoo Ahn², Dong Joo Kim¹,³, Hyun-Soo Lee³, Joel Correa da Rosa³, Mayte Suárez-Faríñas⁴,⁵, Michelle A. Lowes¹,⁶ and James G. Krueger¹

Psoriasis is present in all racial groups, but in varying frequencies and severity. Considering that small plaque psoriasis is specific to the Asian population and severe psoriasis is more predominant in the Western population, we defined Asian small and intermediate plaque psoriasis as psoriasis subtypes and compared their molecular signatures with the classic subtype of Western large plaque psoriasis. Two different characteristics of psoriatic spreading—vertical growth and radial expansion—were contrasted between subtypes, and genomic data were correlated to histologic and clinical measurements. Compared with Western large plaque psoriasis, Asian small plaque psoriasis revealed limited psoriasis spreading, but IL-17A and IL-17-regulated proinflammatory cytokines were highly expressed. Paradoxically, IL-17A and IL-17-regulated proinflammatory cytokines were lower in Western large plaque psoriasis, whereas T cells and dendritic cells in total psoriatic skin area were exponentially increased. Negative immune regulators, such as CD69 and FAS, were decreased in both Western large plaque psoriasis and psoriasis with accompanying arthritis or obesity, and their expression was correlated with psoriasis severity index. Based on the disease subtype comparisons, we propose that dysregulation of T-cell expansion enabled by downregulation of immune negative regulators is the main mechanism for development of large plaque psoriasis subtypes.

INTRODUCTION

Psoriasis is a common skin disease affecting 2% to 3% of the world population (Koo, 1996a; Stern et al., 2004; van de Kerkhof, 2008). It begins as a pinhead-sized papule on the skin that vertically grows to become a raised, red, scaly patch and radially expands to peripheral body surface area, progressing eventually to severe cutaneous disease in some individuals. Severe psoriasis is frequently associated with systemic inflammation and comorbidities, such as psoriatic arthritis, cardiovascular disease, diabetes, and depression.

Psoriasis is present in all racial groups, but in varying frequencies and severity. The prevalence is 2.5% in whites, 1.3% in African Americans, but significantly lower in Asians (0.8% in India, 0.4% in China, and 0.3% in Japan) (Campalani and Barker, 2005; Gelfand et al., 2005; Prashant, 2010). In Asians, less severe psoriasis is more predominant, and a distinct phenotype has been particularly reported, known as “small plaque psoriasis” (Lew et al., 2004; Youn, 2012). Small plaque psoriasis is the typical form of chronic
plaque psoriasis in adults living in Korea and other Asian countries. This form of psoriasis has some resemblance to guttate psoriasis but differs in that it is a chronic, stable form of psoriasis in adults across many years of disease persistence, and overall skin surface involvement is usually <10% body surface area (see Supplementary Table S1 online).

Considering that small plaque psoriasis is specific to the Asian population and severe psoriasis is more predominant in Western population, we compared plaque psoriasis subtypes between Asian and Western populations to explore possible disease progression mechanisms. We first subtyped Asian small and intermediate psoriasis based on the individual plaque size and the psoriasis area and severity index (PASI). Then, we confirmed Asian isoforms as true psoriasis subtypes by identifying a similar transcriptome and histology compared with moderate-to-severe Western large psoriasis. We next explored models of disease progression by contrasting different cellular and molecular signatures of the subtypes. The working models represented bidimensional features of disease progression by separating two different phases of psoriasis progression: vertical growth (epidermal hyperplasia) and radial expansion (the extension of overall psoriasis area and severity). By correlating the genomic data to the clinical and histologic measurements of disease progression, we propose that, rather than the increase in driver cytokines, dysregulation of T-cell expansion enabled by downregulation of negative regulators is the main mechanism of disease progression to large plaque psoriasis subtypes and overall disease severity.

RESULTS

Clinical stratification of small and intermediate psoriasis in the Asian population

We studied 51 biopsy-confirmed psoriasis patients in Seoul, Korea, where small plaque psoriasis has been previously reported (Lew et al., 2004). Patients were clinically stratified into Asian small versus Asian intermediate psoriasis by considering individual plaque size and disease severity measured by PASI. Compared with Western large psoriasis, which has large individual plaque size and typical PASI > 12 (Feldman, 2004; Schmitt and Wozel, 2005), we defined Asian small and intermediate psoriasis as psoriasis subtypes with limited disease progression or “mild” disease (see Supplementary Figure S1 online). Forty-three percent of patients (22/51) had Asian small psoriasis, in which individual plaque size (<2 cm) and the extent of psoriasis area and severity (mean PASI 6.5 ± 0.64) were both limited (Supplementary Table S1) (Lew et al., 2004). Smaller plaque size was consistent with thinner epidermal thickness, representing less epidermal hyperplasia in disease progression (Figure 1a). Asian small psoriasis also revealed low PASI (Figure 1b), even when psoriatic plaques were widely distributed on the trunk and/or extremities (see Supplementary Figure S2 online).

Figure 1. Comparison of epidermal thickness, PASI, differentially expressed genes (DEGs), and meta-analysis-derived psoriasis transcriptome between Asian small, Asian intermediate, and Western large psoriasis. (a) Asian small psoriasis with limited epidermal thickness in comparison with Asian intermediate or Western large psoriasis. (b) Western large psoriasis with higher PASI in comparison with Asian small or intermediate psoriasis. (c) Area-proportional Venn diagram comparing DEGs; 27.7% of all DEGs were shared by the three comparison subtypes. (d) DEGs among meta-analysis-derived psoriasis transcriptome for Affymetrix Human Genome U133 Plus 2.0 Array (meta-analysis-derived transcriptome 3) (Suárez-Fariñas et al., 2012); 66.9% of the meta-analysis-derived psoriasis transcriptome was differentially expressed in all subtypes (more than twofold change and <0.05 false discovery rate).
Asian intermediate psoriasis comprised 57% (29/51), in which individual plaque size (>5 cm) was larger than Asian small psoriasis (<2 cm), but the extent of psoriasis area and severity (mean PASI 7.0 ± 0.93) was less than large psoriasis (PASI > 12). Psoriatic plaques were localized to the knees, elbows, scalp, and lower back/buttocks. Otherwise, the plaques were distributed to limited areas of the trunk or extremities. Overall, the clinical features of Asian intermediate psoriasis were similar to mild cases of psoriasis in the Western population. Clinical photos and immunohistochemical images of 10 representative Asian plaque psoriasis patients are presented in Supplementary Figure S3 (see online).

Genomic and histologic confirmation of Asian small and intermediate psoriasis as true psoriasis subtypes

We obtained gene expression profiles with the Affymetrix Human Genome U133 Plus 2.0 (Affymetrix, Santa Clara, CA) Array and established the psoriatic transcriptomes of Asian small, Asian intermediate, and Western large psoriasis by defining differentially expressed genes between lesional versus nonlesional skin within each subtype (more than twofold change, <0.05 false discovery rate). Among 9,637 differentially expressed genes, 2,674 (27.7%) were common to the three subtypes (Figure 1c). When the gene sets were narrowed down to a meta-analysis-derived transcriptome of Western large psoriasis for the identical array (Tian et al., 2012), there was 66.9% commonality in differentially expressed genes (Figure 1d).

We next validated if the dysregulation of established psoriasis gene sets (Bowcock et al., 2001; Gudjonsson et al., 2009; Jabbari et al., 2011; Suárez-Fariñas et al., 2010, 2012; Tian et al., 2012; Yao et al., 2008) was equivalently observed in Asian small and intermediate psoriasis in comparison with Western large psoriasis. We performed gene set variation analysis with the combined z-score method and generated pathway enrichment scores from the observed gene expression levels. The analysis revealed that the enrichment scores of Asian small and intermediate psoriasis were not different from, or were even higher than, the scores of Western large psoriasis (P < 0.01 and false discovery rate < 0.01; see Supplementary Figure S4 online).

Histologic findings in Asian small and intermediate psoriasis also revealed hallmarks of histologic findings in Western large psoriasis. In the psoriatic lesional skin of both Asian small and intermediate psoriasis, the epidermis revealed hyperplasia with focal parakeratosis (Supplementary Figure S3, immunohistochemical images). Key cellular subsets of psoriasis immunopathogenesis, CD3+ T cells, and CD11c+ myeloid dendritic cells accumulated in both subtypes. Numbers of CD3+ T cells and CD11c+ dendritic cells in Asian small psoriasis were not different from Western large psoriasis in slide sections of lesional skin (see Supplementary Figure S5 online). The number of CD3+ T cells in Asian intermediate psoriasis was also not different from Western large psoriasis, whereas CD11c+ dendritic cells were more abundant in Asian intermediate psoriasis compared with Western large psoriasis. Taken together, Asian small and intermediate psoriasis phenotypes were validated as psoriasis variants, sharing a common psoriasis transcriptome and histologic findings with Western large psoriasis (psoriasis vulgaris).

Models of disease progression emerge from subtype comparisons

We next explored models of disease progression by correlating two different phases of disease progression: vertical growth (epidermal hyperplasia) measured by epidermal thickness of lesional skin and radial expansion (the extension of overall psoriasis area and severity) measured by PASI (Figure 2). Because Asian small psoriasis was limited in both epidermal thickness and PASI, we considered it as a model of the initial stage of disease progression.

To explore mechanisms of vertical growth, we compared Asian small and intermediate psoriasis, because epidermal thickness was significantly different between the two subtypes, without a difference in PASI (Figure 2a). In this model, CD3+ T cell and CD11c+ dendritic cell infiltrates within the epidermis and dermal papillary area were significantly different (see Supplementary Figure S6 online). In addition, CD3+ T cells and CD11c+ dendritic cells within the epidermis and dermal papillary area were linearly correlated with the epidermal thickness (Figure 2b and d; see Supplementary Table S2 online).

To explore mechanisms of radial expansion, we compared Asian intermediate and Western large psoriasis, because PASI was significantly different between the two subtypes, without a difference in epidermal thickness (Figure 2a). In this model, the accumulated T-cell and dendritic cell numbers in total psoriasis body surface area of Western large psoriasis (CD3+ T cells: 6.24 × 109 ± 4.68 × 109; CD11c+ dendritic cells: 5.13 × 109 ± 4.74 × 109) were exponentially higher than the numbers for Asian intermediate psoriasis (CD3+ T cells: 1.18 × 109 ± 9.76 × 108; CD11c+ dendritic cells: 1.45 × 109 ± 1.43 × 109) (Supplementary Figure S5). In addition, CD3+ T cells and CD11c+ dendritic cells in total psoriasis body surface area were highly correlated to PASI (Figure 2c and d; Supplementary Table S2).

Genomic exploration of disease progression models

To explore molecular correlates of disease progression, we simultaneously measured expression levels of 35 genes in both lesional and nonlesional skin of Asian small (n = 16), Asian intermediate (n = 21), and Western large (n = 20) psoriasis by reverse transcriptase (RT) PCR (Figure 3; see Supplementary Figure S7 online). In the model of the initial stage of disease progression, IL-17A and IL-17-regulated proinflammatory cytokines (IL-1B and IL-8) were highly expressed even before vertical growth and radial expansion. The expression levels of IL-17A, IL-1B, and IL-8 in RT-PCR were highest in lesional skin of Asian small psoriasis and were significantly higher than in Western large psoriasis (Figure 3a).

In our disease progression model of the vertical growth phase (Asian small vs. Asian intermediate psoriasis), epidermal hyperplasia was confirmed by high lesional expression of keratin 16 in RT-PCR (Figure 3b) and Ki67 in microarray data (3.9-fold change, P < 0.05, and false discovery rate < 0.05). IL-20, a key molecule for epidermal hyperplasia response, was expressed higher in Asian intermediate psoriasis in nonlesional skin (Figure 3b). In the multiple linear regression model predicting epidermal thickness from the RT-PCR expression levels of 35 psoriatic...
Figure 2. Exploratory models of disease progression. (a) Vertical growth and radial expansion models emerged from contrasting epidermal thickness and PASI between Asian small, Asian intermediate, and Western large psoriasis. (b) In the model of vertical growth phase, epidermal thickness was correlated with the numbers of CD3$^+$ T cells and CD11c$^+$ dendritic cells within the epidermis and dermal papillae (method of counting cells in epidermis and dermal papillae: Supplementary Figure S6). (c) In the model of radial expansion phase, PASI was correlated with CD3$^+$ T cells and CD11c$^+$ dendritic cells in total psoriasis body surface area. (d) Summary of exploratory models ($r$ = Pearson correlation, $P < 0.0001$). Number of inflammatory cells in total psoriasis body surface area = cell count in the slide section × body surface area × proportion of psoriasis involvement.
genes in lesional and nonlesional skin (expressions of Asian small and intermediate psoriasis in Figure 3 and Supplementary Figure S7), epidermal thickness of lesional skin increased in accordance with IL-17A expression in nonlesional skin (epidermal thickness\_Lesional = 230.6 + 34.8 \times \text{defensin-\textbeta}103B\_\text{Lesional} + 12.4 \times \text{IL-17A}\_\text{Nonlesional} + 11.7 \times \text{IFN-\gamma}\_\text{Lesional} - 35.9 \times \text{Fas}\_\text{Lesional}, R^2 = 0.47, adjusted R^2 = 0.40).

In our disease progression model of the radial expansion phase (Asian intermediate versus Western large psoriasis), we observed an increase in CD3^+ T cells (Figure 2c) and a paradoxic decrease in driver cytokines (IL-17A, IL-1B, IL-8, and IL-20) (Figure 3a and b) in psoriatic lesional skin. We hypothesized that rather than the increase in driver cytokines, dysregulation of T-cell expansion is the main mechanism of the radial expansion phase. To explore this hypothesis, we...
first identified significant downregulation of negative regulator signaling in Western large psoriasis in comparison with Asian intermediate psoriasis (Figure 4a). Among the immune molecules whose function as a negative regulator have been described (Abrams et al., 1999; Bovenschen et al., 2011; Chen et al., 2008; Cortes et al., 2014; Gorbachev and Fairchild, 2010; Kagen et al., 2006; Sancho et al., 2005; Stranges et al., 2007; Sugiyama et al., 2005), downregulation of CD69, Fas, cytotoxic T lymphocyte-associated protein 4 (CTLA4), programmed death-ligand 1, and forkhead box P3 (FoxP3) was confirmed by RT-PCR in lesional skin of Western large psoriasis in comparison with Asian small or intermediate psoriasis (Figure 3c). In addition, the expressions of CD69 (lesional and nonlesional), Fas (lesional and nonlesional), and CTLA4 (lesional) were negatively correlated with PASI (Figure 5 and Supplementary Table S2).

Using a multiple regression model to predict PASI from the RT-PCR expression levels of 35 psoriatic genes in lesional and nonlesional skin (expressions of Asian intermediate and Western large psoriasis in Figure 3 and Supplementary Figure S7), PASI increased in accordance with the reduction of CD69 expression in nonlesional skin (PASI = -18.2 + 5.5 × tumor necrosis factor [TNF]-α Nonlesional + 3.3 × defensin-β103B Nonlesional - 4.1 × CD69Nonlesional - 1.2 × IL-9Lesional; $R^2 = 0.67$, adjusted $R^2 = 0.63$).

**DISCUSSION**

Recent transethnic genome-wide meta-analysis of Asian and Western psoriasis populations observed the population-specific effects of the AA positions 114 and 144 of HLA-A as well as another 10 non-major histocompatibility complex psoriasis susceptibility loci (Yin et al., 2015). These population-specific risk factors might lead to ethnically different expression patterns of psoriasis-associated transcripts, resulting in different psoriasis prevalence and clinical phenotypes. In this study, we compared psoriasis transcriptomes of clinically different Asian and Western psoriasis cohorts by two independent measures of clinical phenotyping: epidermal thickness (vertical growth) and PASI (radial expansion). To understand functional disease status by molecular characterization, quantitative expression analysis of RT-PCR (Figure 3 and Supplementary Figure S7) and pathway analysis of microarray (Figure 4) were combined to compare against the mRNA transcriptome that has been established in previous studies (Jabbari et al., 2011; Loscalzo, 2007; Perera et al., 2014; Suárez-Fariñas et al., 2010, 2012). Serving as a reference list of genes for the core pathogenesis of psoriasis, we used a meta-analysis-derived transcriptome built on the same microarray platform (Figure 1d) (Tian et al., 2012). This approach revealed that IL-17A and IL-17-regulated proinflammatory cytokines drive disease progression from the early stage of psoriatic plaque development, particularly as IL-17 expression was highest in Asian small psoriasis (Figure 3a). Currently, IL-17-targeted therapies that neutralize IL-17 (i.e., secukinumab and ixekizumab) have been studied in phase I to III clinical trials and receive U.S. Food and Drug Administration approval only for “moderate-to-severe” psoriasis (typical PASI > 12) (Chiricuzzi and Krueger, 2013). However, Asian forms of psoriasis, which are classified as “mild” disease (mean PASI < 7) in spite of significant disease extent, might also benefit from anti-IL-17 agents.

Our study also revealed that nonlesional skin around the psoriatic plaques is not normal but actively reflects disease progression status: the epidermal thickness and PASI increase in accordance with IL-17 and TNF-α in nonlesional skin, respectively. Also, there was a strong and significant correlation between PASI and negative immune regulatory gene expressions (CD69 and FAS) in nonlesional skin (Figure 5 and Supplementary Table S2). Given that excessive immune activation may be present in nonlesional skin, the expression of negative immune regulatory pathways may be important in restraining activation to below-thresholds of producing clinically detectable disease.

The function of negative regulators within lesional and nonlesional skin is likely important in preventing the disease progression of psoriasis. In accordance with PASI, CD3+ T cells were increased in psoriasis body surface area (Figure 2c
Figure 4. Psoriasis pathway enrichment scores. (a) The enrichment of pivotal immune pathways of IL-17 and IFN-γ signaling was not different between Asian small, Asian intermediate, and Western large psoriasis. Negative regulator signaling in Western large psoriasis was downregulated compared with Asian intermediate psoriasis (*P < 0.01 and false discovery rate < 0.01). (b) Pathways involved in psoriasis comorbidities (psoriatic arthritis, cardiovascular disease, and atherosclerosis) were significantly enriched only in Western large psoriasis (P < 0.001 and false discovery rate < 0.001). The scores were generated by gene set variation analysis with the combined z-score method. Gene sets for pathway analysis were curated from published papers (Belasco et al., 2015; Chiricozzi et al., 2014), molecular signatures database (http://www.broadinstitute.org/gsea/msigdb), and gene ontology consortium (http://geneontology.org).
and Supplementary Table S2), whereas the expression of negative regulators decreased proportionally (Figure 5 and Supplementary Table S2). Therefore, we hypothesized that the lack of negative regulator signals may allow for extensive expansion of disease-related T-cell clones. In our study, the expression of FoxP3 in nonlesional skin increased as PASI increased, but the correlation was not linear (Figure 5 and Supplementary Table S2). However, the expression of CTLA4, the inhibitory coreceptor of regulatory T cells (Tregs), revealed significant linear correlation with PASI in lesional skin. The expression of the Fas receptor, which is a component of the Fas-Fas ligand interactions used by CD4+ CD25+ Tregs to restrict CD8+ T-cell-mediated immune response in the skin (Gorbachev and Fairchild, 2010; Stranges et al., 2007), also revealed significant correlation with PASI in both lesional and nonlesional skin. Fas is an important regulator of migratory dendritic cell function and was recently identified as central to human skin dendritic cell programming (Anandasabapathy et al., 2014; Baratin et al., 2015). Potentially, negative immune regulators such as CTLA4 and Fas could be more important than classic Tregs in regulating T-cell expression in psoriasis.

C-type lectin receptor, CD69, exerts a proinflammatory function in vitro, but recent in vivo studies revealed its function as an immunoregulatory molecule induced after activation (Sancho et al., 2005). Because CD69 induction can block sphingosine 1-phosphate receptor-1-mediated T-cell egress from lymphoid tissues through interaction with membrane helix 4, CD69 is demonstrated to be a critical determinant of prolonged T-cell retention (Bankovich et al., 2010; Mackay et al., 2015; Shiow et al., 2006). In this context, downregulation of CD69 in Western large psoriasis despite an exponentially higher number of CD3+ T cells in total psoriasis body surface area may represent how T-cell

Figure 5. Correlation between PASI and expression levels of negative regulators in lesional and nonlesional skin. Overlay scatter-plot to display the correlation between PASI and expression levels of negative regulators (CD69, FAS, CTLA4, programmed death-ligand 1 [PD-L1], and FoxP3) in lesional (red) and nonlesional (blue) skin. The expression of TNF-α in lesional and nonlesional skin is presented as a control. Gene expression: Log2 conversion of mRNA expression normalized to human acidic ribosomal protein (HARP).
expansion is dysregulated in psoriasis. Also, it is feasible that CD69 could be persistently expressed by a subset of regulatory T cells (Sancho et al., 2005). Although CD69\(^+\) and CD69\(^-\) FoxP3\(^+\) Tregs exist in homeostasis, only CD69-expressing Tregs express high levels of CTLA4 and have potent suppressor activity secreting high amounts of transforming growth factor-\(\beta\) (Cortes et al., 2014). Considering that transforming growth factor participates in the differentiation of both Tregs and T helper 17 cells and that Tregs in psoriasis patients can easily differentiate into IL-17A-producing cells, CD69 might be the key determinant of disease progression in psoriasis (Bettelli et al., 2006; Bovenschen et al., 2011; Cortes et al., 2014; Veldhoen et al., 2006). In our study, the expression of CD69 in both lesional and nonlesional skin was highly correlated with PASI in a negative direction (Figure 5 and Supplementary Table S2).

Figure 6. Downregulation of negative regulators and upregulation of driver cytokines in the skin of psoriasis patients with psoriatic arthritis (a) or obesity (b). Overlay scatter-plot to display different expression levels of negative regulators (CD69, FAS, and FoxP3) and driver cytokines (tumor necrosis factor [TNF]-\(\alpha\), IL-1B, and IL-17A) in lesional (red) and non-lesional (blue) skin between psoriasis without (No) and with (Yes) comorbidities. The data include total study population of Asian small, Asian intermediate, and Western large psoriasis. Gene expression: Log\(_2\) conversion of mRNA expression normalized to human acidic ribosomal protein.
Taken together, we showed the utility of disease subtype comparisons with detailed cellular and molecular signatures to advance new hypothesis generation and future testing of concepts in clinical trials (Figure 7). A limitation of study is comparing subtypes between distinct ethnic populations under the assumption that psoriasis transcriptome profiles represent functional disease status regardless of ethnicity. Ethnicity may confound the correlation between RNA expression of genes involved in psoriasis pathogenesis and clinical phenotypes that might be influenced by other factors, such as genetic/environmental differences. To overcome this limitation, the concepts should be further tested in different subtyping strategies and ultimately in clinical trials blocking driver cytokines and/or boosting negative regulators in an attempt to prevent disease progression.

MATERIALS AND METHODS
A detailed Materials and Methods description is available in Supplementary Materials and Methods (see online).

Study design
This study was designed to conduct ex vivo human observations with human skin biopsy tissues for the purpose of subtype comparisons (see Supplementary Figure S6 online). Psoriasis lesional and nonlesional skin biopsy tissues were obtained in accordance with the Helsinki Declaration and approved by the Institutional Review Board of Korea University Guro Hospital, Seoul, South Korea, and the Rockefeller University, New York, New York, USA. Written informed consent was obtained from all patients. Fifty-nine psoriasis patients were enrolled at Korea University Guro Hospital, and 21 patients were enrolled at the Rockefeller University Hospital (ClinicalTrials.gov; NCT01920906). Eight patients enrolled in Korea were excluded because the pathology report from independent dermatopathologists did not support the diagnosis of psoriasis. Asian population (2004). We thank psoriasis patients attending Korea University Guro Hospital, Seoul, Korea, and the Rockefeller University Hospital, New York, New York, USA, for donating tissue. Korea University Guro Hospital Biobank facilitated international collaboration between Korea University Guro Hospital and the Rockefeller University Hospital. We thank research support from the Translational Technology Core Laboratory (Clinical Translational Science Award, Rockefeller University Center for Clinical and Translational Science, grant no. UL1 TR000043) from the National Center for Advancing Translational Sciences (grant no. UL1 TR000043) from the National Center for Advancing Translational Sciences (grant no. UL1 TR000043) from the National Center for Advancing Translational Sciences (National Institutes of Health).

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SUPPLEMENTARY MATERIAL
Supplementary material is linked to the online version of the paper at www.jidonline.org, and at http://dx.doi.org/10.1038/jid.2015.378.
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