In the present study, we investigated a potential influence of the HLA-DQB1 promoter polymorphisms on the development of NSV in the Korean population. One HLA-DQB1 SNP (rs9274552) demonstrated an association with NSV. In the haplotype analysis, the C-G and A-G haplotypes were significantly associated with NSV. To find whether these promoter SNPs affect transcription factors, the online program AliBaba 2.1 (http://www.gene-regulation.com/pub/programs/alibaba2) was used. At the rs9274552 SNP, the A-containing sequences bind with C/EBPa1p transcription factor, but C/EBPa1p disappears in the C-containing sequences. At the rs9274579 SNP site, the A-containing sequences interact with Oct-1, but Oct-1 transcription factor disappear in the G-containing sequences. Assuming the change of transcription factors according to variants of SNPs, these promoter SNPs may influence gene and protein expression of HLA-DQB1.

Our results indicate that the HLA-DQB1 promoter polymorphism (rs9274552) may increase susceptibility to NSV in Korean population along with genes previously confirmed to play a role in polygenic susceptibility to NSV. Further studies are needed to clarify the exact role of HLA-DQB1 on NSV pathogenesis.

Conflict of interest

The authors have no conflict of interest to declare.

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Immunosuppressive effect of adipose-derived stromal cells on imiquimod-induced psoriasis in mice

Letter to the Editor,

Psoriasis is one of the most common immune-mediated chronic, inflammatory skin diseases characterized by hyperproliferative keratinocytes and infiltration of T cells, dendritic cells, macrophages and neutrophils [1]. Especially, T helper 17 (Th17) cells and interleukin (IL)-17A, IL-22, and IL-23, known as Th17-related cytokines, play roles in the pathogenesis of psoriasis. Moreover, tumor necrosis factor (TNF) maintains an inflammatory loop in psoriatic lesions and promotes the increased expression of IL-17A, IL-21, and IL-22 in Th17 cells [2]. Imiquimod (IMQ)-induced psoriasis-like mice models feature lesions clinically and pathologically similar to human psoriasis lesion [3].

In 2001, Zuk et al. reported that stem cells could be isolated from human adipose tissue [4]. Many clinical studies have incorporated adipose-derived stromal cells (ASCs) for the potential therapeutic use in various diseases, although the exact mechanisms underlying their functions remain to be investigated. Herein, we focused on the regulatory and inhibitory effects of ASCs in the psoriatic skin and attempted to discover clues toward improving psoriasis.

We applied IMQ cream on the shaved dorsal skin for 5 consecutive days. On days 0, 2, and 4, either ASCs or PBS were injected into the intradermal dorsal areas (Fig. 1a). On day 6 (D6), we identified the location of surviving ASCs on the dorsal skin using in vivo imaging system (Fig. 1b). Three days after IMQ application, the dorsal skin treated with both IMQ and PBS began to display signs of erythema, scaling and thickening. These symptoms of inflammation increased in severity throughout the experiment (Fig. 1c). However, the dorsal skin co-treated with IMQ and ASCs exhibited only slight erythema, scaling and thickening on D6, indicating that the ASCs inhibited IMQ-induced inflammatory changes in murine skin. In hematoxylin and eosin staining, the cell cluster was located in the dermis of ASC-injected mice (Fig. 1d). Furthermore, we disclosed that these cells are consistent with fluorescence-labeled ASCs (Fig. 1d). A histological examination revealed epidermal hyperkeratosis and parakeratosis in the skin of mice treated with IMQ and PBS (Fig. 1e). On the other hand, the skin of ASC-injected mice exhibited no significant psoriatic findings. Moreover, ASC-injected mice had a significantly thinner epidermis, compared with PBS-injected mice (Fig. 1f). These

Abbreviations: ASC, adipose-derived stromal cell; IMQ, imiquimod; FBs, fibroblasts; MSC, mesenchymal stem cell; BM, bone marrow.

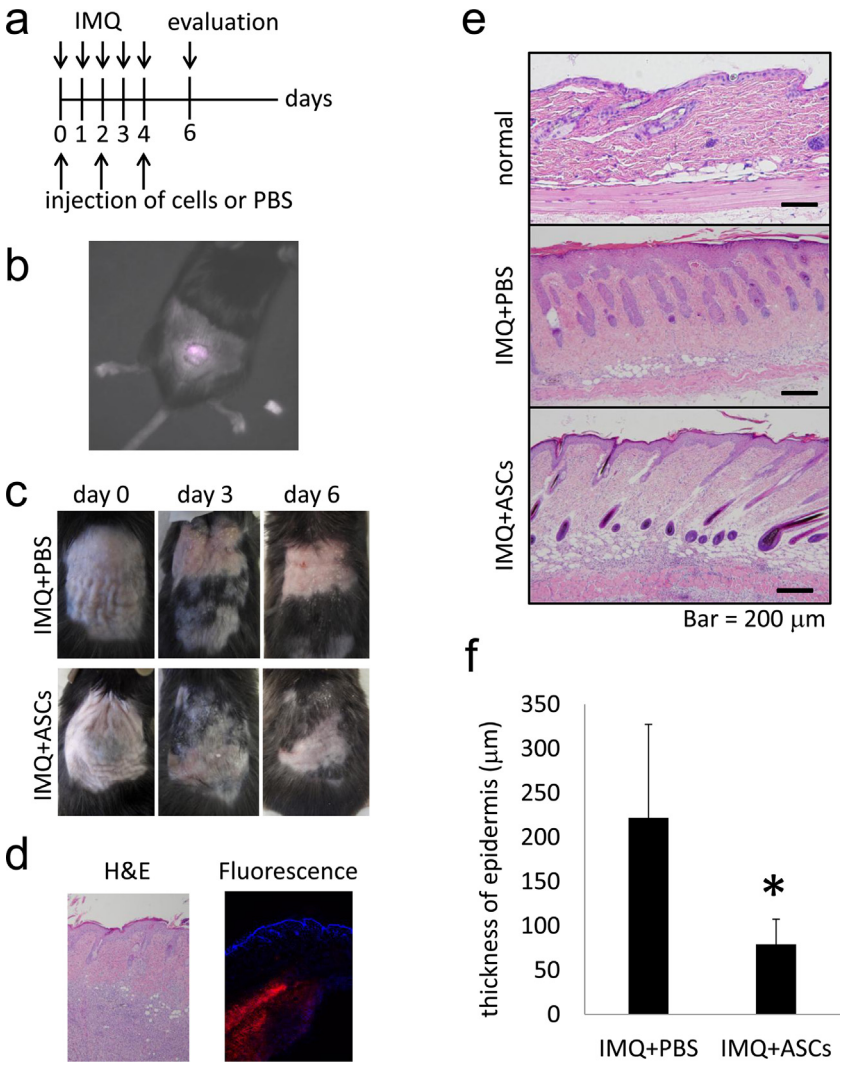

Fig. 1. The immunosuppressive effect of murine adipose-derived stromal cells (ASCs) on imiquimod (IMQ)-induced psoriatic inflammation. (a) IMQ was applied to shaved dorsal skin of mice for 5 consecutive days. On days 0, 2, and 4, either 1×10^6 cells or PBS was intradermally injected into the IMQ-treated skin. On D6, mice were sacrificed for skin and blood sample collection. (b) In vivo imaging of injected living ASCs (Fig. 1b). (c) Consecutive IMQ application clearly induced severe erythema and scaling, similar to that observed in psoriatic skin. In contrast, skin co-treated with IMQ and ASCs exhibited only slight scaling and erythema. (d and e) Samples of IMQ-treated dorsal skin were taken on D6 and were observed by microscope. Each representative section is shown ($100 \times$ magnification, scale bar = 200 μm). (f) Comparison of the epidermal thickness in murine dorsal skin samples following co-treatment with IMQ and either ASCs or PBS. The ASC-injected epidermis was significantly thinner than the PBS-injected epidermis. Data are presented as mean ± standard deviations ($n = 5$/group, $^*p < 0.05$).

findings suggested that ASCs could strongly inhibit not only the inflammation but also psoriatic scaling and erythema.

To elucidate the immunosuppressive effects of intradermally injected ASCs in IMQ-induced psoriatic mice, spleens were harvested and measured on D6. In addition to the mice treated with PBS or ASCs, another group of mice received intradermal injections of FBs, which are similar to ASCs in morphology and appearance, into the IMQ-treated areas of skin. All IMQ-treated mice exhibited splenomegaly, compared with normal mice (Fig. 2a and b). However, intradermal ASC injection had a tendency to reduce the weights and sizes of spleens in IMQ-applied mice.

To examine the systemic effects of ASCs in IMQ-induced psoriatic mice, we analyzed the levels of the IL-17A, TNF-α, IL-23, and IL-6 using ELISA. The serum levels of these cytokines were significantly lower in ASCs-injected mice than in PBS-injected mice ($p < 0.01$; Fig. 2c). This indicates that the direct administration of ASCs to the intradermal skin inhibits systemic IMQ-induced inflammation. Furthermore, we quantified IL-17A and TNF-α mRNA expression in skin lesions and spleens from IMQ-applied mice co-treated with either type of cells or PBS. The splenic levels of IL-17A mRNA were significantly lower in ASC-injected mice than in FB-injected mice ($p < 0.01$), although there was no difference when compared with PBS-injected mice (Fig. 2d). We also did not find significant differences in TNF-α mRNA expression among the groups. Conversely, IL-17A and TNF-α were significantly upregulated in the skin lesions of PBS- and FB-treated mice, compared with ASC-injected mice ($p < 0.01$)(Fig. 2d). These results indicate that ASCs inhibit the production of Th17-associated cytokines, such as IL-17A and TNF-α, and minimize the psoriatic skin changes induced by IMQ. These results demonstrate the potential of ASCs as strong immunosuppressive mediators in psoriasis.

Mesenchymal stem cells (MSCs) are immunoregulatory and multipotent progenitor cells that can be easily isolated and expanded from the bone marrow (BM), umbilical cord, and other tissues. MSCs and ASCs are thought to possess similar characteristics in terms of cell proliferation, anti-inflammatory effects, and regeneration-promoting factor secretion. In our study, IMQ-induced skin lesions treated with murine ASCs had normal levels of IL-17A and TNF-α mRNA, in contrast to untreated IMQ-induced skin lesions, suggesting that murine ASCs could locally inhibit the