(see Fig E3, *A*). Similarly, mutant YFP-STIM1 (L74P) showed no response to thapsigargin but also appeared to form constitutive puncta, which was less distinct in appearance than that for the D76A mutant (see Fig E3).

We compared Ca^{2+} fluctuations in HEK293 cells transfected with ORAI-CFP and either wild-type YFP-STIM1, mutant YFP-STIM1 (D76A), or mutant YFP-STIM1 (L74P; see Fig E3, *B* and *C*). Both YFP-STIM1 (D76A) and YFP-STIM1 (L74P) transfected cells had increased basal Ca^{2+} concentrations compared with wild-type YFP-STIM1 and reduced peak and integral responses to CPA-induced SERCA inhibition (see Fig E3, *B* and *C*). However, in contrast to the EF-hand mutant YFP-STIM1 (D76A), YFP-STIM1 (L74P) did not demonstrate reduced SOCE after CPA washout and Ca^{2+} restoration, suggesting that the previously reported desensitization of SOCE observed with the YFP-STIM1 (D76A) mutant does not occur with the YFP-STIM1 (L74P) mutant form. Therefore the L74P mutation appears to result in a distinct molecular phenotype compared with the loss of function observed in immunodeficient patients and the constitutive activation observed in patients with myopathy.

This study is the first to report recessive *STIM1* mutations in patients presenting with AI and hypohidrosis without overt clinical immunodeficiency or myopathy. Clinical immunologic investigations were consistent with abnormal NK cell and T-lymphocyte function that might be expected to be associated with ongoing clinical immunodeficiency. However, despite severely abnormal SOCE, this was not the case in these patients. Missense mutations affecting the EF-hand can have very different clinical phenotypes with respect to the immune system, muscle, sweating, and enamel formation. This has important implications for clinical evaluation, as well as understanding the biological functions of STIM1.

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REFERENCES

1. Picard C, McCarl C-A, Papolos A, Khalil S, Lüthy K, Hivroz C, et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. N Engl J Med 2009;360:1971-80.
2. Fuchs S, Rensing-Ehl A, Speckmann C, Bengsch B, Schmitt-Graeff A, Bondzio I, et al. Antiviral and regulatory T cell immunity in a patient with stromal interaction molecule 1 deficiency. J Immunol 2012;188:1523-33.
3. Schaballie H, Rodriguez R, Martin E, Moens L, Frans G, Lenoir C, et al. A novel hypomorphic mutation in STIM1 results in a late-onset immunodeficiency. J Allergy Clin Immunol 2015;136:816-9.e4.
4. Zhang H, Clemens RA, Liu F, Hu Y, Baba Y, Theodore P, et al. STIM1 calcium sensor is required for activation of the phagocyte oxidase during inflammation and host defense. Blood 2014;123:2238-49.
5. Shaw PJ, Weidinger C, Vaeth M, Luethy K, Kaech SM, Feske S. $CD4^+$ and $CD8^+$ T cell-dependent antiviral immunity requires STIM1 and STIM2. J Clin Invest 2014;124:4549-63.
6. Böhm J, Chevessier F, Maues De Paula A, Koch C, Attarian S, Feger C, et al. Constitutive activation of the calcium sensor STIM1 causes tubular-aggregate myopathy. Am J Hum Genet 2013;92:271-8.
7. Liou J, Kim ML, Heo WD, Jones JT, Myers JW, Ferrell JE, et al. STIM is a Ca2+ sensor essential for Ca2+-store-depletion-triggered Ca2+ influx. Curr Biol 2005;15:1235-41.

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Antigen-presenting epithelial cells can play a pivotal role in airway allergy

To the Editor:

Professional antigen-presenting cells (APCs; ie, dendritic cells, macrophages, and B cells) react against exogenous antigens and initiate an adaptive immune response by presenting antigen peptides in the groove of the MHC class II molecules. During inflammation, ectopic expression of MHC class II has been reported on cells from multiple tissues, including the nasal mucosa, suggesting an antigen-presenting capacity of epithelial cells (ECs).[1-4] The present investigation was designed to examine the contribution of nasal epithelial cells (NECs) to the allergic inflammatory process. The abilities of NECs to take up antigen, express MHC class II and costimulatory molecules, and stimulate antigen-specific activation and proliferation of $CD4^+$ T cells were investigated by using a human mucosal specimen (see the Methods section in this article's Online Repository at www.jacionline.org).

First, the cell-surface expression of MHC class II and costimulatory molecules on human and mouse nasal epithelial cells (MNECs) was confirmed (see Figs E1 and E2 in this article's Online Repository at www.jacionline.org). Then the ability of MNECs to present the antigen ovalbumin (OVA) to naive T cells was demonstrated. MNECs from sensitized mice displayed an enhanced MHC class II expression on coculture

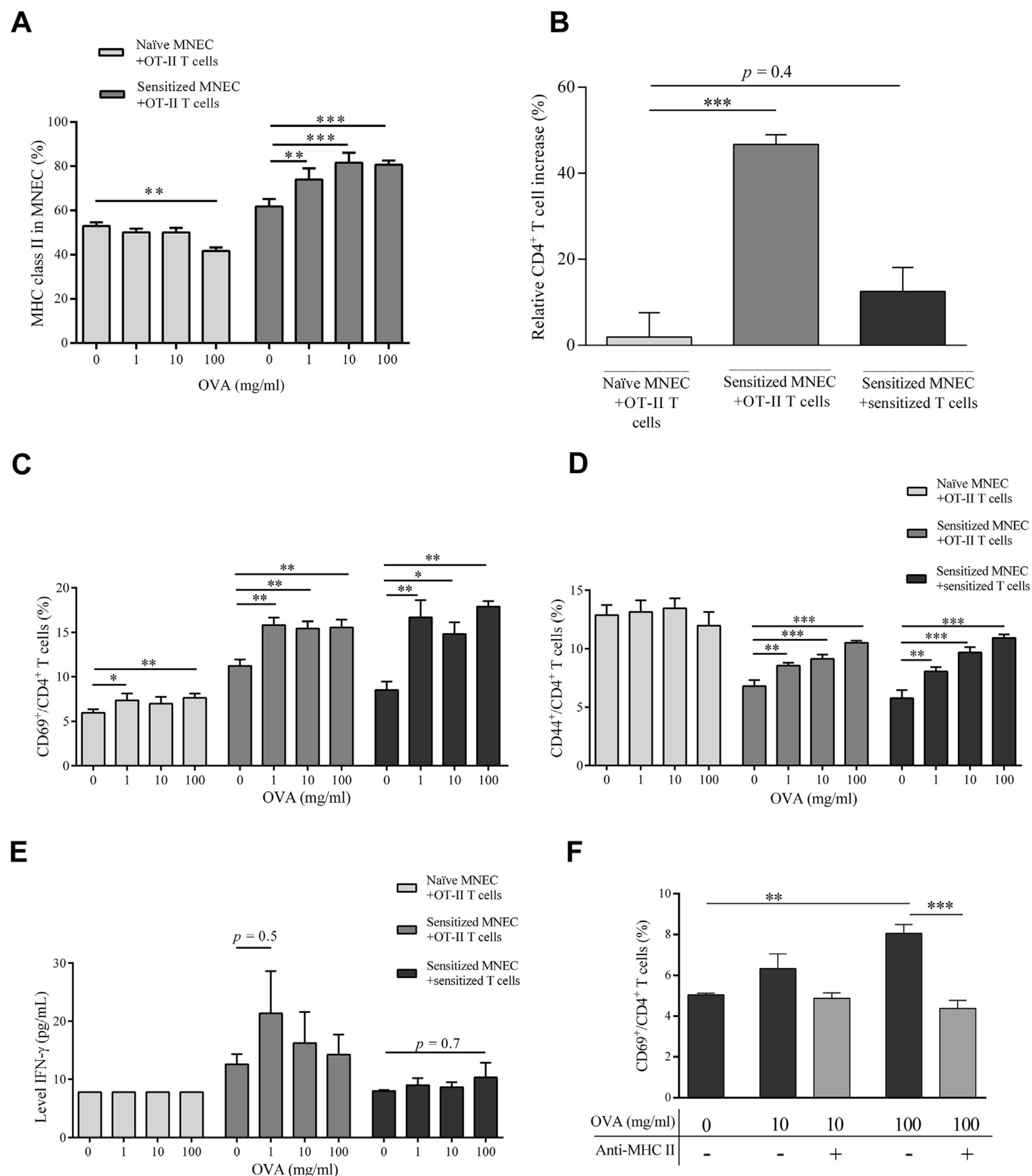

FIG 1. A, MHC class II expression on OVA-stimulated MNECs cocultured with T cells (4 hours). **B,** $CD4^+$ T-cell counts in cocultures with OVA-stimulated MNECs (24 hours). **C** and **D,** Fraction of $CD69^+/CD4^+$ (Fig 1, *C*) and $CD44^+/CD4^+$ (Fig 1, *D*) T cells after coculture with OVA-stimulated MNECs. **E,** INF-γ release in cocultures (24 hours). **F,** Cocultures with MNECs and T cells (both from sensitized mice) with anti–MHC class II antibodies *(anti-MHC II)*. $*P < .05$, $**P < .01$, and $***P < .001$.

with OT-II T cells compared with naive cells (Fig 1, *A*). The total number of OT-II $CD4^+$ T cells in the same cocultures was increased. A tendency toward an increase in $CD4^+$ T-cell counts was also seen when sensitized T cells were used as reporter cells (Fig 1, *B*). Analysis of T-cell activation revealed a pronounced increase in the total number (see Fig E3, *A*, in this article's Online Repository at www.jacionline.org) and fraction (Fig 1, *C*) of activated $CD69^+$ OT-II cells, as well as sensitized T cells, when using sensitized MNECs as APCs. Notably, sensitized MNECs exhibited significantly increased activating capacity, even without added OVA, which was supposedly partially due to the remaining OVA in the MNECs from the sensitization process. In line with this, MNECs from sensitized mice augmented the absolute number (see Fig E3, *B*) and fraction (Fig 1, *D*) of $CD44^+$ OT-II cells, as well as sensitized T cells, in a dose-dependent manner. A tendency toward an increased IFN-γ release was simultaneously seen when sensitized MNECs were used as APCs (Fig 1, *E*). Finally, sensitized MNECs were unable to affect the

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