

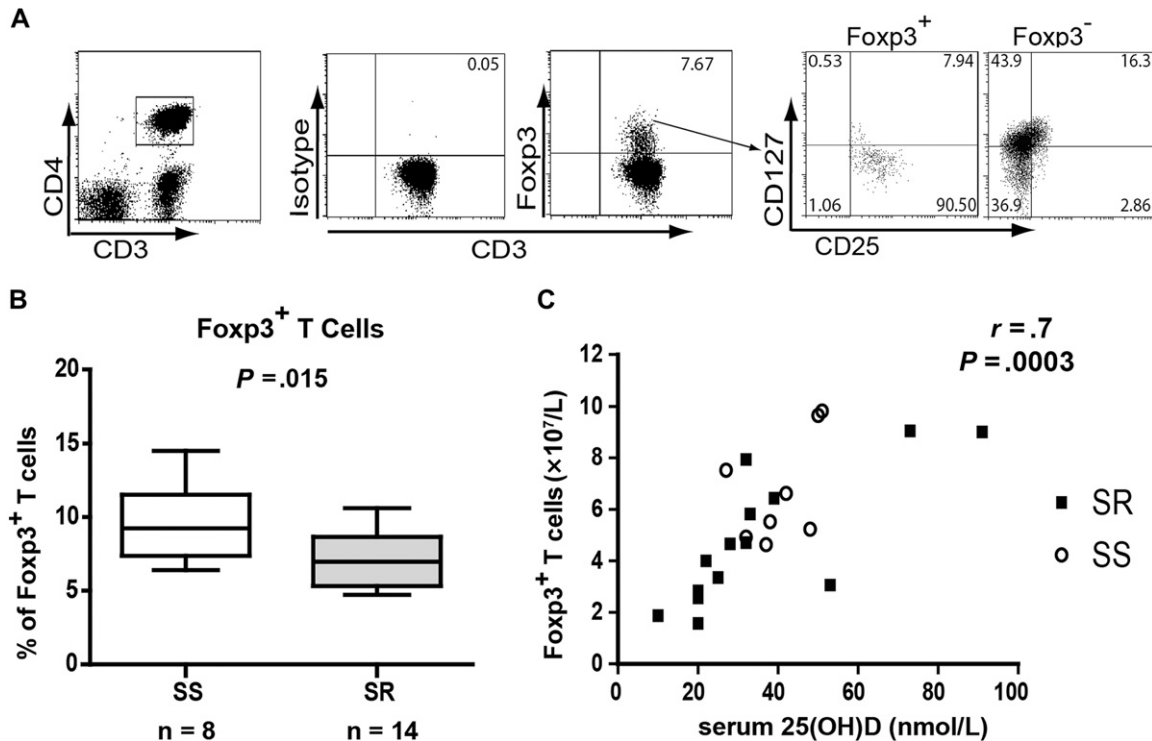


FIG 1. SR asthmatic patients have a lower frequency of Foxp3⁺ Treg cells than do SS asthmatic patients, and serum 25(OH)D concentration correlates positively with Foxp3⁺ Treg cells in the peripheral blood. **A**, Representative dot plots demonstrating the gating strategy to define Treg cells. Values represent % of gated live CD4⁺CD3⁺ lymphocyte population. **B**, Frequency of Foxp3⁺ Treg cells in SS and SR asthmatic patients. Data shown as mean, 5%-95% CI, assessed by *t* test. **C**, Correlation of Foxp3⁺ Treg cells with serum 25(OH)D in all the patients with moderate to severe asthma. Assessed by Pearson correlation test.

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REFERENCES

- Lloyd CM, Hawrylowicz CM. Regulatory T cells in asthma. *Immunity* 2009;31:438-49.
- Hawrylowicz C, Richards D, Loke T-K, Corrigan C, Lee T. A defect in corticosteroid-induced IL-10 production in T lymphocytes from corticosteroid-resistant asthmatic patients. *J Allergy Clin Immunol* 2002;109:369-70.
- Xystrakis E, Kusumakar S, Boswell S, Peek E, Urry Z, Richards DF, et al. Reversing the defective induction of IL-10-secreting regulatory T cells in glucocorticoid-resistant asthma patients. *J Clin Invest* 2006;116:146-55.
- Litonjua AA, Weiss ST. Is vitamin D deficiency to blame for the asthma epidemic? *J Allergy Clin Immunol* 2007;120:1031-5.
- Brehm JM, Celedon JC, Soto-Quiros ME, Avila L, Hunninghake GM, Forno E, et al. Serum vitamin D levels and markers of severity of childhood asthma in Costa Rica. *Am J Respir Crit Care Med* 2009;179:765-71.
- Bennett CL, Christie J, Ramsdell F, Brunkow ME, Ferguson PJ, Whitesell L, et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. *Nat Genet* 2001;27:20-1.
- Jeffery LE, Burke F, Mura M, Zheng Y, Qureshi OS, Hewison M, et al. 1,25-Dihydroxyvitamin D₃ and IL-2 combine to inhibit T cell production of inflammatory cytokines and promote development of regulatory T cells expressing CTLA-4 and FoxP3. *J Immunol* 2009;183:5458-67.
- Liu W, Putnam AL, Xu-Yu Z, Szot GL, Lee MR, Zhu S, et al. CD127 expression inversely correlates with FoxP3 and suppressive function of human CD4⁺ T reg cells. *J Exp Med* 2006;203:1701-11.
- Maunsell Z, Wright DJ, Rainbow SJ. Routine isotope-dilution liquid chromatography-tandem mass spectrometry assay for simultaneous measurement of the 25-hydroxy metabolites of vitamins D₂ and D₃. *Clin Chem* 2005;51:1683-90.

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The broad spectrum of interepithelial junctions in skin and lung

To the Editor:

Asthma and atopic dermatitis represent the biggest group of chronic noncontagious diseases in children and adults with the largest burden on health care costs. The better understanding of the molecular mechanisms has opened a way for the development of many novel treatment modalities.^{1,2} Two recent articles published in the *Journal of Allergy and Clinical Immunology* demonstrated the disruption of epithelial barrier function of keratinocytes in the skin of patients with atopic dermatitis and bronchial epithelial cells in the lungs of asthmatic patients.^{3,4} These studies suggest that tissue integrity is disturbed in patients, and allergens, bacterial toxins, and other particles are able to penetrate the epidermis and the lung epithelium, where they may activate the immune system leading to severe chronic inflammation in both diseases. Therefore, paracellular sealing of keratinocytes and bronchial epithelial cells appears to be very important to prevent the infiltration of the dermis and submucosa by factors that induce allergic inflammation.

There are several types of cell-cell adhesion and sealing complexes in between epithelial cells: tight junctions (TJs), adherens junctions, gap junctions, and desmosomes (Fig 1, A). Main contributors to the barrier function of epithelia are TJs. These form the most apical cell-cell adhesion complexes regulating the paracellular flux of water and ions as well as of larger compounds.⁵ They are able to regulate the apical-basolateral

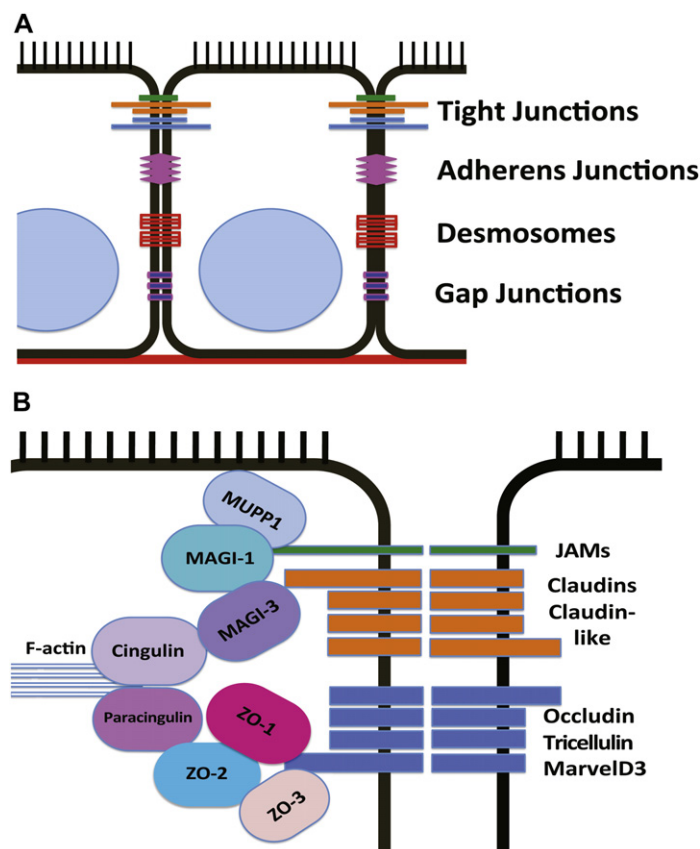


FIG 1. Junctional complexes of epithelial cells and protein composition of TJs. **A**, Scheme of the junctional complexes in epithelial cells: TJs, adherens junction, desmosomes, and gap junctions. **B**, Protein composition of TJ: transmembrane proteins include junctional adhesion molecules (JAMs), claudin family, Marvel family members, and adaptor proteins. MAGI, Membrane-associated guanylate kinase inverted; MUPP1, multi-PDZ domain containing protein 1; ZO, zonula occludens.

differentiation of epithelial cells. TJs are composed of the claudin family, junctional adhesion molecules, marvel family members, and adaptor proteins (Fig 1, B). In humans, the claudin family has 24 members; however, claudin-13 is not expressed at all.⁶

In the study by Xiao et al,⁴ the circumferential band of TJs was shown to be disrupted in asthma biopsies and in bronchoepithelial cell cultures. Although the authors did not find any differences in the mRNA level, the protein expression of zonula occludens-1 was significantly reduced and occludin showed a trend of downregulation in bronchoepithelial cell cultures.⁴ Bronchial epithelial cells from asthmatic patients cultured on air-liquid interfaces showed a decreased transepithelial resistance than did cells from healthy individuals, indicating a reduced barrier function in asthma. This defective barrier function in asthma could be restored by epithelial growth factor.⁴ Cell cultures exposed to cigarette smoke extracts exert an impaired barrier function that can be restored by the addition of epithelial growth factor.⁴ In the study by De Benedetto et al,³ the expression of claudin-1 and claudin-23 was reduced in nonlesional atopic dermatitis skin. Silencing of claudin-1 led to a reduction in transepithelial resistance. This study suggests that the reduced expression of claudin-1 in atopic dermatitis epidermis is an important factor of an impaired barrier function.³

Here, we hypothesize that the whole picture of interepithelial junction molecule expression could be more complicated than suggested before.

To perform fully detailed analyses of interepithelial junction expression, we developed a low-density array microfluidic card (Applied Biosystems, Carlsbad, Calif) containing all known junctional and associated proteins that are expressed in the epidermis and epithelia. In addition to TJ proteins, desmosomes, gap junctions, and adherens junction genes were included in the analysis (see the [Methods](#) section in this article's Online Repository at www.jacionline.org). We analyzed lung and skin biopsies, primary keratinocytes, and normal human bronchial epithelial cells either grown as monolayers or in air-liquid interphase (ALI) cultures⁷ for the expression of junctional proteins (see the [Methods](#) section).

In skin and lung tissue and primary isolated keratinocyte and normal human bronchial epithelial cells, there are commonly expressed junctional proteins, such as claudin-1, claudin-4, claudin-12, and claudin-25, which is also known as claudin domain containing 1.⁸ It also appears that there are several differently expressed junctional and adaptor proteins between the skin and lung. In lung tissue, claudin-18 ($P = .02$) and JAM-C ($P = .03$) are uniquely present (Fig 2, A). In comparison, skin tissue uniquely expressed claudin-8 ($P = .05$) and claudin-10 ($P = .02$) (Fig 2, B). Skin tissue expressed connexin-26 ($P = .02$), -30 ($P = .02$), -32 ($P = .06$), desmocollin-1 ($P = .02$), desmocollin-3 ($P = .02$), desmoglein-1 ($P = .02$), desmoglein-3 ($P = .02$) (Fig 2, D), and their corresponding adaptor proteins plakophilin-1 ($P = .02$) and plakophilin-3 ($P = .02$) (Fig 2, F).

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