Tight junction defects in patients with atopic dermatitis.

Atopic dermatitis (AD) is characterized by dry skin and a hyperactive immune response to allergens, 2 cardinal features that are caused in part by epidermal barrier defects. Tight junctions (TJs) reside immediately below the stratum corneum and regulate the selective permeability of the paracellular pathway. We evaluated the expression/function of the TJ protein claudin-1 in epithelium from AD and nonatopic subjects and screened 2 American populations for single nucleotide polymorphisms in the claudin-1 gene (CLDN1). Expression profiles of nonlesional epithelium from patients with extrinsic AD, nonatopic subjects, and patients with psoriasis were generated using Illumina's BeadChips. Dysregulated intercellular proteins were validated by means of tissue staining and quantitative PCR. Bioelectric properties of epithelium were measured in Ussing chambers. Functional relevance of claudin-1 was assessed by using a knockdown approach in primary human keratinocytes. Twenty-seven haplotype-tagging SNPs in CLDN1 were screened in 2 independent populations with AD. We observed strikingly reduced expression of the TJ proteins claudin-1 and claudin-23 only in patients with AD, which were validated at the mRNA and protein levels.
levels. Claudin-1 expression inversely correlated with T(H)2 biomarkers. We observed a remarkable impairment of the bioelectric barrier function in AD epidermis. In vitro we confirmed that silencing claudin-1 expression in human keratinocytes diminishes TJ function while enhancing keratinocyte proliferation. Finally, CLDN1 haplotype-tagging SNPs revealed associations with AD in 2 North American populations. Collectively, these data suggest that an impairment in tight junctions contributes to the barrier dysfunction and immune dysregulation observed in AD subjects and that this may be mediated in part by reductions in claudin-1.