International Journal of
Molecular Sciences

MDPI

Article

Multifaceted Analyses of Epidermal Serine Protease Activity in Patients with Atopic Dermatitis

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Received: 18 December 2019; Accepted: 28 January 2020; Published: 30 January 2020

Abstract: The serine proteases kallikrein-related peptidase (KLK) 5 and KLK7 cleave cell adhesion molecules in the epidermis. Aberrant epidermal serine protease activity is thought to play an important role in the pathogenesis of atopic dermatitis (AD). We collected the stratum corneum (SC) from healthy individuals (n = 46) and AD patients (n = 63) by tape stripping and then measuring the trypsin- and chymotrypsin-like serine protease activity. We also analyzed the p.D386N and p.E420K of *SPINK5* variants and loss-of-function mutations of *FLG* in the AD patients. The serine protease activity in the SC was increased not only in AD lesions but also in non-lesions of AD patients. We found, generally, that there was a positive correlation between the serine protease activity in the SC and the total serum immunoglobulin E (IgE) levels, serum thymus and activation-regulated chemokine (TARC) levels, and peripheral blood eosinophil counts. Moreover, the p.D386N or p.E420K in *SPINK5* and *FLG* mutations were not significantly associated with the SC's serine protease activity. Epidermal serine protease activity was increased even in non-lesions of AD patients. Such activity was found to correlate with a number of biomarkers of AD. Further investigations of serine proteases might provide new treatments and prophylaxis for AD.

Keywords: atopic dermatitis; serine proteases; kallikrein-related peptidases; epidermal barrier dysfunction; lympho-epithelial Kazal-type-related inhibitor (LEKTI); *SPINK5*; filaggrin

1. Introduction

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disease that affects up to 25% of children and 2–3% of adults [1]. AD has a complex pathogenesis involving genetic, immunologic, and environmental factors which lead to a dysfunctional skin barrier and dysregulation of the immune system [1]. Aberrant epidermal serine protease activity is related to the pathogenesis of inflammatory skin diseases such as Netherton syndrome, AD, psoriasis, and rosacea [2–8]. Kallikrein-related peptidases (KLKs) are a family of 15 trypsin- or chymotrypsin-like serine proteases encoded by a cluster of protease-encoded genes (*KLK1-15*) in the human genome [9]. KLK5, a trypsin-like serine protease, and KLK7, a chymotrypsin-like serine protease, are major epidermal KLKs. These