Mast Cells and Lipid Cross-Talk in Skin Inflammation

By

Piper A. Wedman

Abstract:

Atopic dermatitis (AD) is an inflammatory skin disease whose pathogenic mechanisms remain unclear. We describe a novel method of computer-assisted image analysis for in situ quantification of mast cells (MC) activation. We also define quantitative parameters to measure skin remodeling in early-stage atopic dermatitis (eczema) using a validated human AD-like mouse model. Remarkably, skin thickening was substantiated after a single application of ovalbumin (OVA), antigen used in this model, with cellular infiltration of the hypodermis. Cell recruitment correlated with augmented chemokine production, MC activation, and increased levels of a sphingolipid metabolite sphingosine-1-phosphate (S1P), produced by sphingosine kinase-1 (SphK1), we showed could be produced by and also activate MC-derived chemokine production. MC or SphK1 deficiency significantly hindered these inflammatory responses.

Skin barrier dysfunction observed in chronic AD correlates with decreased skin ceramide (CER) content. Skin lipidomics by liquid chromatography-electrospray ionization-tandem mass spectrometry revealed significant increase of local CER species C16 and C24 in OVA-treated samples, compared to controls. Increased CER may result from increased synthesis and/or decreased catabolism. Next, we analyzed skin CER synthase (CerS) and ceramidase (Asah1 and Asah2) mRNA expression. CerS4, 5 and 6 mRNA levels were statistically augmented after OVA exposure. Overall, CER exert pro-apoptotic functions. We found that OVA treatment triggered apoptosis that also correlated with
elevation of key molecules of endoplasmic reticulum (ER) stress. Surprisingly, primary mouse bone marrow-derived MC activated in vitro by S1P also exhibited elevation of C16 CER. To substantiate the importance of MC in these processes, CER profiling was similarly conducted in treated skin samples collected from MC-deficient mice. MC deficiency prevented OVA-induced CER increase and local apoptosis.

We conclude that MC and S1P could initiate the development of AD by driving inflammatory infiltration and skin remodeling through their contribution to local chemokine production. Moreover, increased CER production also constitutes an early uncovered AD feature eliciting apoptosis. Targeting the MC/S1P/CER axis offers a new prophylactic approach for this disease whose treatment remains a clinical challenge.