Mast cells in Atopic Dermatitis: The Role of Chymase, Tryptase, Interleukin-6 and OX40/OX40L

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An academic dissertation entitled "Mast cells in atopic dermatitis: the role of chymase, tryptase, interleukin-6 and OX40/OX40L", was presented by Tiina Ilves, MD, at the Faculty of Health Sciences, University of Eastern Finland, Kuopio, Finland, on 29 May 2016. The opponent was Docent Anita Remitz, from the University of Helsinki, Finland, and the custos was Professor Ilkka Harvima, from the University of Kuopio. The dissertation has been published in electronic form: http://urn.fi/URN:ISBN:978-952-61-2088-1

Atopic dermatitis (AD) is a multifactorial skin disease with many different aggravating factors and many cell types that contribute to its pathogenesis. Researchers have suggested the importance of mast cells (MCs) in AD pathogenesis. The purpose of this thesis was to investigate the role of some MC mediators and costimulatory molecules in AD pathogenesis. The expression and function of chymase, tryptase, IL 6, OX40 and OX40L were studied using enzyme and immunohistochemical methods and cell culture experiments. The associations between the mediators and clinical severity, filaggrin expression or reactivity to autologous sweat were also investigated.

The number of tryptase positive MCs was greater in both lesional and nonlesional AD skin compared to healthy skin, while the number of PAR2 positive MCs was increased in lesions. Tryptase was also found in sweat and was associated with reactivity to autologous sweat in intracutaneous tests. No such association was found between reactivity to sweat and the number of skin tryptase or PAR2 positive MCs. Reactivity to sweat was associated with more severe disease and higher serum total and specific IgE levels. IL6 and chymase positive MCs were increased, but MC chymase activity was decreased in AD lesions. Low recombinant human (rh) chymase concentration stimulated and higher concentration inhibited the proliferation of T cells and peripheral blood mononuclear cells (PBMCs). Rh IL6 inhibited T-cell proliferation and the proliferation induced by rh chymase. On the other hand, rh chymase prevented the effect of rh IL 6 on T cells. (Pro) filaggrin expression decreased in the lesional granulous layer in AD and correlated negatively with itch severity, but not with other severity parameters. (Pro)filaggrin expression was reversely associated with the number of tryptase positive MCs in the nonlesional granulous layer and with IL6 positive MCs in both nonlesional and lesional granulous layers in severe AD. The reduction in (pro)filaggrin expression was correlated negatively with the mean number of tryptase, chymase, and IL6 positive MCs in nonlesional skin, but not in lesional skin. The number of OX40 positive cells and the staining intensity of OX40L increased in AD lesions. OX40L was expressed on LAD2 MCs and keratinocytes, and the anti OX40L antibody inhibited the proliferation of PBMCs induced by LAD2 membranes, but stimulated that induced by keratinocytes.

The results of the thesis suggest that costimulatory pair OX40/OX40L and MC chymase and IL6 can mediate the effect of MCs on PBMC and T-cell proliferation in AD. Moreover, MC mediators can contribute to (pro)filaggrin deficiency in AD, and MC tryptase can be a wheal-inducing factor in sweat.

Fig. 1. Professor Ilkka Harvima, Tiina Ilves and Docent Anita Remitz.

List of the original publications

1. Ilves T, Harvima IT. OX40 ligand and OX40 are increased in atopic dermatitis lesions but do not correlate with clinical severity. J Eur Acad Dermatol Venereol 2013; 27: e197–205.
2. Ilves T, Harvima IT. Decrease in chymase activity is associated with increase in IL-6 expression in mast cells in atopic dermatitis. Acta Derm Venereol 2015; 95: 411–416.
3. Ilves T, Tiitu V, Suttle M-M, Saarinen J, Harvima I. The epidermal expression of filaggrin/profilaggrin is decreased in atopic dermatitis: reverse association with mast cell tryptase and IL-–6 but not with clinical severity. Dermatitis 2015; 26: 260–267.
4. Ilves T, Virolainen A, Harvima I. Immediate wheal reactivity to autologous sweat in atopic dermatitis associates with clinical severity, total and specific IgE and sweat tryptase activity. Int Arch Allergy Immunol. 2016; 170: 84–91.