Calcium Signalling in Epithelium: Special Focus on Hailey-Hailey and Darier Diseases, Neurofibromatosis 1 and Transitional Cell Carcinoma

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Dr Pekka Leinonen, MD, from the Department of Anatomy and Cell Biology, and Department of Dermatology and Venereology, University of Oulu, Finland, defended his PhD thesis on 9 January 2009 in Oulu, Finland. The opponent was Professor Ulpu Saarialho-Kere from the Department of Dermatology and Venereology, University of Helsinki, and the custos was Professor Juha Peltonen. The thesis was supervised by Professors Juha Peltonen and Aarne Oikarinen, and Dr Timo Korkiamäki. The thesis book is available at: http://herkules.oulu.fi/isbn9789514290008/

This study utilized normal and defective epithelial cell cultures and epidermal skin samples to examine intra- and intercellular calcium signalling. The main focus was on Hailey-Hailey disease, Darier's disease, neurofibromatosis 1 (NF1), and transitional cell carcinoma.

Hailey-Hailey and Darier's diseases are rare autosomal dominant skin disorders characterized by dissociation of epidermal keratinocytes (acantholysis) at the suprabasal layer of the epidermis. Hailey-Hailey disease and Darier's disease are caused by mutations in the genes encoding the calcium pumps in the Golgi apparatus (hSPCA1) and endoplasmic reticulum (SERCA2b), respectively. Due to these mutations calcium uptake into the Golgi apparatus or endoplasmic reticulum is diminished, and this is thought to cause abnormal cell junction protein processing and dissociation of keratinocytes. This study utilized electron probe microanalysis (EPMA) and demonstrated for the first time that lesional areas of Hailey-Hailey disease and Darier's disease and non-lesional areas of Darier's disease epidermis display abnormally low calcium content in the basal cell layer. Furthermore, ATP-mediated calcium signalling was impaired in cultured Hailey-Hailey disease and Darier's disease keratinocytes and epidermal ATP receptor localization was disrupted. In conclusion, these results suggest that the low calcium content in the basal cell layer is the reason for suprabasal ruptures in Hailey-Hailey disease, but not necessarily in Darier's disease lesions, and that abnormal ATP receptor localization contributes to the defects in calcium signalling.

Keratinocytes with mutation in the neurofibromatosis 1 (NF1) gene display abnormally low resting cytosolic calcium levels, and it has been suggested that the calcium concentration in the lumen of the endoplasmic reticulum is decreased. This study demonstrated that NF1 keratinocytes rely mostly on ATP-mediated calcium signalling, while normal keratinocytes rely mostly on gap junctional intercellular communication.

Fig. 1. Pekka Leinonen (*middle*) defended his PhD thesis on Calcium signalling in epithelium in the University of Oulu, Finland. The opponent was Professor Ulpu Saarialho-Kere (*left*) from the Department of Dermatology and Venereology, University of Helsinki, and the custos was Professor Juha Peltonen (*right*) from the University of Turku.

Studies with transitional cell carcinoma cells have demonstrated that gap junctions participate in intercellular calcium wave propagation. This thesis demonstrated that the ATP-mediated pathway was also operational in calcium wave propagation in normal uroepithelial and transitional cell carcinoma (TCC) cell cultures. Furthermore, impaired calcium wave propagation in the TCC cell culture could be improved through PKC α/βI–isoenzyme inhibition with Gö6976. Gö6976 treatment increased connexin 26 clustering at plasma membrane but did not alter the expression level of the protein.

This thesis contains a wide repertoire of calcium detection techniques, including a new cutting edge technology for elemental calcium detection of epidermal samples. These techniques can be used for molecular-specific analysis of calcium signalling in epithelial cells.