Regulation of Epidermal Tight Junctions by Calcium ATPases and p38

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Laura Raiko, MD, from the Department of Dermatology and Venereology, and Department of Cell Biology and Anatomy, University of Turku defended her PhD thesis: "Regulation of epidermal tight junctions by calcium ATPases and p38" on September 6th, 2013. The Opponent was Professor Raija Tammi from the University of Eastern Finland and the Custos was Professor Veli-Matti Kähäri. The thesis work was supervised by Docent Sirkku Peltonen. The thesis is available from http://www.doria.fi/handle/10024/91723.

The epidermis is the upper layer of the skin and keratinocytes are its most abundant cells. Tight junctions are cell junctions located in the granular layer of the epidermis. They maintain the polarity of the cells and regulate the movement of water-soluble molecules.

Epidermal tight junctions may lose their integrity when there are defects in the intercellular calcium regulation in blistering diseases such as Hailey-Hailey and Darier's disease.

Hailey-Hailey disease is caused by mutations in the *ATP2C1* gene encoding a calcium/manganese ATPase SPCA1 of the Golgi apparatus while Darier's disease is caused by mutations in the *ATP2A2* gene encoding a calcium ATPase SERCA2 of the endoplasmic reticulum. p38 regulates the differentiation of keratinocytes. The overall regulation of epidermal tight junctions is not well understood. The present study examined the regulation of tight junctions in the human epidermis with a focus on calcium ATPases and p38. Skin from patients with Hailey-Hailey and Darier's disease was studied by using immunofluorescence labeling which targeted intercellular junction proteins.

Transepidermal water loss was also measured. *ATP2C1* gene expression was silenced in cultured keratinocytes, by siRNA, which modeled Hailey-Hailey disease. Expression of intercellular junction proteins was studied at the mRNA and protein levels. Squamous cell carcinoma and normal human keratinocytes were used as a model for impaired and normal keratinocyte differentiation, and the role of p38 isoforms alpha and delta in the regulation of intercellular junction proteins was studied. Both p38 isoforms were silenced by adenovirus cell transduction, chemical inhibitors or siRNA and keratinocyte differentiation was assessed.

The results of this thesis revealed that: *i*) intercellular junction proteins are expressed normally in acantholytic skin areas of patients with Hailey-Hailey or Darier's disease but the localization of ZO-1 expanded to the stratum spinosum; *ii*) tight junction proteins, claudin-1 and -4, are regulated by *ATP2C1* in non-differentiating keratinocytes; and *iii*) p38 delta regulates the expression of tight junction protein ZO-1 in proliferating keratinocytes and in squamous cell carcinoma derived cells. ZO-1 silencing, however, did not affect the expression of other tight junction proteins, suggesting that they are differently regulated.

Fig. 1. Laura Raiko (second from right) defended her PhD thesis on September 6th, 2013. The Opponent was Professor Raija Tammi (second from left) and the Custos was Professor Veli-Matti Kähäri (right). The thesis work was supervised by Docent Sirkku Peltonen (left).

This thesis introduces new mechanisms involved in the regulation of tight junctions revealing new interactions. It provides novel evidence linking intracellular calcium regulation and tight junctions.