Hyaluronan and CD44 in Epidermis with Special Reference to Growth Factors and Malignant Transformation

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Susanna Hartmann-Petersen, MD, defended her PhD thesis in Kuopio, Finland, on March 27, 2009. The opponent was Dr Vincent C. Hascall from Lerner Research Institute, Cleveland Clinic Foundation, Ohio, USA. The thesis was supervised by Docent Raija Tammi, and Professor Markku Tammi from the Institute of Biomedicine, Department of Anatomy, and Professor Veli-Matti Kosma, Department of Pathology and Forensic Medicine University of Kuopio. The thesis can be found in the internet at: http://www.uku.fi/vaitokset/2009/isbn978-951-27-1165-9.pdf. Dr. Hartmann-Petersen is now specializing in dermatology in the department of Dermato-Allergology at Gentofte Hospital in Hellerup, Denmark.

Hyaluronan is a glycosaminoglycan which forms the main part of the extracellular matrix in the epidermis of skin. Its metabolism in the epidermis is a complex process that can be influenced by several growth factors. Hyaluronan, first thought to be passive space filler, is now known to contri–bute to several important physiological events such as cell proliferation, migration and differentiation, often mediated through its cell surface receptor CD44. Besides normal tissue homeostasis, hyaluronan and its receptor are involved in the carcinogenesis of several cell types.

The aim of the first part of this thesis was to study the effects of epidermal growth factor, keratinocyte growth factor, and transforming growth factor beta (TGF-β) on hyaluronan metabolism in epidermal keratinocytes and in an *in vitro* organotypic culture model of epidermis. The changes in hyaluronan metabolism were correlated with keratinocyte proliferation, migration, differentiation as well as epidermal permeability barrier formation. The second part studied changes in hyaluronan, CD44 and versican during keratinocyte carcinogenesis on histological sections of basal cell carcinoma (BCC), *in situ* squamous cell carcinoma (SCC), and different grades of SCC. Tumor samples were also analyzed for correlations between the expression of hyaluronan/CD44, and MMP-7 and MMP-9, the latter linked to malignant progression due to their ability to degrade matrix components and thus aid in cancer cell invasion.

It was found that mitogenic growth factors (epidermal and keratinocyte growth factors) increased the synthesis of hyaluronan by epidermal keratinocytes via activation of hyaluronan synthase 2. This increase in epidermal hyaluronan content correlated to increased cell proliferation, migration and epidermal thickness, while keratinocyte differentiation was inhibited. On the other hand, TGF-β decreased the proliferation of keratinocytes causing epidermal atrophy. This was accompanied by decreased Has2 expression and epidermal hyaluronan content, and unchanged keratinocyte differentiation. The study showed a close link between epidermal hyaluronan content, epidermal thickness and keratinocyte differentiation.

In epidermal keratinocyte tumors, hyaluronan and CD44 expressions varied according to the type of the tumor. In BCC, both hyaluronan and CD44 expressions were very low. *In situ* SCC, the levels were high with an irregular staining distribution. In SCC, well-differentiated tumors showed abundant hyaluronan and CD44, while reduced hyaluronan and CD44 signals were found in poorly differentiated, aggressive tumors. The levels of the HA-binding protein versican were increased in the stroma of BCC but not in SCC. Furthermore, expression of MMP-7 was higher in SCC than BCC, and correlated with the loss of CD44 in poorly differentiated SCC. The levels of MMP-9 did not differ between the different tumor types or stages of differentiation.

In conclusion, this study suggested that hyaluronan and CD44 are important mediators of the epidermal homeostasis, regulated by local growth factors. They also correlate with the origin and invasive properties of the epidermal cancers, and the expression of MMP-7.