Functional Analysis of Collagen XVII in Epithelial Cancers and a Mouse Model

Jyri Moilanen, MD
Faculty of Medicine, University of Oulu, Finland

An academic dissertation entitled "Functional analysis of collagen XVII in epithelial cancers and a mouse model", was presented by Jyri Moilanen, MD, at the Faculty of Medicine, University of Oulu, Finland, on 4 May 2016. The opponent was Professor Jyrki Heino, from the University of Turku, Finland, and the custos was Professor Kaisa Tasanen-Määttä, from the University of Oulu. The dissertation has been published in electronic form: http://jultika.oulu.fi/files/isbn9789526211695.pdf

Basement membranes (BM) underlie epithelia and endothelia and surround many tissues. In cutaneous BM epithelial cells are attached to the stroma via multiprotein complexes called hemidesmosomes (HD). Collagen XVII and integrin α6β4 are components of HD and they bind to laminin 332, a component of anchoring filaments, extracellularly. The main interest of this study is the function of collagen XVII and its interactions with these proteins.

What is known about the function of collagen XVII is mostly derived from its role as an adhesive component in cutaneous HD. Here we demonstrate for the first time that collagen XVII is expressed by podocytes in the human and murine glomerulus and that mutant mice lacking collagen XVII in addition to small size, blisters and diffuse hair loss, also have deficient glomerular development and a high mortality rate.

We also show for the first time at the protein level that collagen XVII is expressed, and probably has a functional interaction with laminin 332, in normal colon epithelia. We demonstrate that collagen XVII is expressed by the invasive cells of human colorectal carcinoma (CRC) samples and its immunostaining is increased in metastasis in CRC. The higher proportion of collagen XVII positive tumour cells correlates with decreased disease-free survival and cancer-specific survival times and we also suggest a functional interaction between collagen XVII and laminin 332 in CRC.

Previous studies have suggested that collagen XVII participates in keratinocyte migration by affecting the correlation of HD disassembly and assembly, its expression is increased in squamous cell carcinoma (SCC) and it may have a role in cell adhesion and migration in SCC carcinogenesis. Here we demonstrate upregulated collagen XVII, integrin β4 and laminin γ2 expression in actinic keratosis, Bowen's disease and SCC. The expression of collagen XVII was increased with a high degree of variation, especially in samples taken from areas where SCC is particularly invasive. We also demonstrate

Fig. 1. Professor Jyrki Heino, Jyri Moilanen and Professor Kaisa Tasanen-Määttä.

in the SCC-25 cell line that lack of collagen XVII or integrin β4 severely disrupts the adhesion, migration and invasivity of these cells.

Taken together, in this study we show that collagen XVII is needed for normal glomerular development, is expressed in normal colon epithelia, and participates in CRC and SCC carcinogenesis together with laminin 332 and integrin β4.

List of original publications

1. Hurskainen T, Moilanen J, Sormunen R, Franzke CW, Soininen R, Löffek S, et al. Transmembrane collagen XVII is a novel component of the glomerular filtration barrier. Cell Tissue Res 2012; 348: 579–588.
2. Moilanen J, Kokkonen N, Löffek S, Väyrynen JP, Syväniemi E, Hurskainen T, et al. Collagen XVII correlates with the invasion and metastasis of colorectal cancer. Hum Pathol 2015; 46: 434–442.
3. Moilanen J, Löffek S, Kokkonen N, Salo S, Väyrynen JP, Hurskainen T, et al. Collagen XVII and integrin β4 show similar expression in squamous cell carcinoma and their knockdown suppresses migration and invasion only of the less aggressive squamous cell carcinoma cells. Manuscript.