Collagen XVII and Pathomechanisms of Junctional Epidermolysis Bullosa and Gestational Pemphigoid

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Dr Laura Huilaja from the Department of Dermatology, University of Oulu, Finland, defended her PhD thesis on 18 April 2008 in Oulu. The opponent was Professor Jouni Uitto from Thomas Jefferson University, Philadelphia, USA. The thesis was supervised by Docent Kaisa Tasanen and PhD Tiina Hurskainen.

Transmembrane collagen XVII (BP180) is a structural component of hemidesmosomes that maintains the integrity of the epidermis and dermis. Collagen XVII belongs to a family of transmembrane collagens, which share a number of structural features and are involved in a broad spectrum of biological functions, ranging from cell adhesion to immunological defence. Collagen XVII is associated with both autoimmune and inherited bullous skin diseases. Mutations in collagen XVII gene cause junctional epidermolysis bullosa (JEB), and in the diseases of the pemphigoid group autoantibodies target collagen XVII.

A subtype of JEB, non-Herlitz-JEB is caused by mutation in genes encoding laminin polypeptides or collagen XVII. Since both collagen XVII and laminin 5 are crucial for hemidesmosome formation, the hemidesmosomes are rudimentary or completely lacking in the skin of these patients. Clinically, generalized blistering occurs at birth, but can improve, at least partly, from middle adulthood onwards. Blistering typically affects the extremities, but the trunk, scalp and face are also usually affected. Defects in the enamel lead to dystrophic dentition or enamel-pitting.

Gestational pemphigoid (PG) is a rare bullous disease associated with pregnancy, with an incidence of about 1 in 50,000 pregnancies. The onset of PG varies from the first trimester of pregnancy to post-partum, but most often it occurs in the second or third trimester. During subsequent pregnancies PG often recurs, appears at earlier stage and lasts longer. Clinically, urticarial papules and plaques with itching are seen and blisters develop in these erythemal areas within a few days or up to a month. Although the blistering can also affect the foetus, there is no increased risk of foetal mortality related to PG. Instead, there is an association with premature delivery and small-for-date newborns.

Transmembrane collagen XVII is well characterized, and its necessity for skin stability is distinctly established, as it is associated with both autoimmune and inherited blistering skin diseases. Despite the in-depth data about collagen XVII, studies focus mainly on the skin and less is know about collagen XVII in the extracutaneous tissues. The aim of this work was to explore and increase knowledge of the molecular role of collagen XVII in the pathogenesis of both autoimmune and inherited bullous diseases. The specific aim of the study was to detect novel mutations and understand the molecular mechanisms of COL17A1 missense mutations in JEB, and to investigate the expression of collagen XVII in extracutaneous tissues such as placenta and foetal membranes.

Two novel glycine substitution mutations were found in the largest collagenous domain of collagen XVII in patients with JEB. Analysis of recombinantly produced mutated proteins showed that these novel mutations and previously described glycine substitution mutations decrease the thermal stability of collagen XVII ectodomain and disturb the triple helical structure. In addition, these mutations were found to cause intracellular accumulation of the mutated proteins and affect the post-translational modifications of collagen XVII. Meanwhile, an in-frame deletion of 9 amino acids had no effect on the thermal stability or secretion of the collagen XVII ectodomain. However, although the consequences of the mutations in collagen XVII gene were analysed at the protein level, the evident genotype phenotype correlation of these mutations remains unclear.

Although collagen XVII is an autoantigen in gestational pemphigoid it has been mainly studied in the skin, and its expression and function during pregnancy are largely unknown. For the first time, collagen XVII was shown to be expressed by cytotrophoblasts of the first trimester human placenta and by cultured cytotrophoblasts. Transmigration assay of cytotrophoblasts indicated that collagen XVII promotes trophoblast invasion, and may thus have a role in placental formation. In addition, significant amounts of collagen XVII produced *in vivo* were found in the amniotic fluid throughout pregnancy. Collagen XVII expression was also observed in hemidesmosomes of amniotic membranes and in cells cultured from amniotic fluid. These findings suggest that collagen XVII could have a function, albeit so far unknown, during pregnancy.

The thesis publication is available at:
http://herkules.oulu.fi/isbn9789514287749/.