The role of CD151 and integrin α3β1 in the pathophysiology of kidney and skin

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Preface

As multicellular organisms, animals critically depend on cell adhesion to preserve their structural integrity. The development and maintenance of ‘cell-cell’ and ‘cell-matrix adhesions’ is central to diversification of cellular function and tissue morphogenesis. Molecularly, cells bind each other or the extracellular matrix through specific cell-surface receptors. Essential for cell-matrix adhesion is the protein family of integrins which mediates adhesion of mesenchymal cells to interstitial collagenous matrices and of epithelial cells to laminin-rich basement membranes.

Integrins and their associated molecules have been the focus of the research group of Dr. Arnoud Sonnenberg since the late 1980s. His group characterized the laminin receptors on platelets and basal keratinocytes and studied their interaction with associated proteins. The groundwork for this thesis was laid by former graduate students Annemieke de Melker and Lotus Sterk who characterized the biochemical properties and tissue distribution of integrin α3β1 and the associated tetraspanin CD151. I was fortunate enough to participate in the functional characterization of both molecules in kidney and skin using mouse genetics and cell biology.

The results of this research carried out at the Division of Cell Biology of the Netherlands Cancer Institute in Amsterdam are presented in my thesis: In chapter 1, we review and highlight recent advances in the field of podocyte adhesion to the glomerular basement membrane with special emphasis to kidney disease. In chapter 2, we report that Cd151-knockout mice develop kidney failure. We suggest defective α3β1-mediated podocyte adhesion as the underlying mechanism based on the strikingly similar kidney failure of podocyte specific Itga3-knockout mice. In chapter 3, we show that loss of CD151 indeed decreases α3β1-mediated podocyte adhesion leading to blood pressure dependent kidney failure. We furthermore provide evidence that the disease can be ameliorated by medicinally lowering mechanical stress. In chapter 4, we show that epidermal α3β1 is required for efficient chemically induced skin carcinogenesis. We attribute the dramatic reduction of skin tumors in epidermis-specific Itga3-knockout mice to an increased epidermal turnover causing long-lived label retaining cells to terminally differentiate. In chapter 5, we show that loss of CD151 decreases susceptibility for TPA-dependent skin tumorigenesis and suggest the mechanism to be similar to that of epidermis-specific Itga3-knockout mice. In chapter 6, we discuss open questions and present preliminary data on which future research hopefully can build on.