Composition and function of integrin adhesions

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PREFACE

The human body is made up of trillions of cells that have to interact with each other and with the extracellular matrix (ECM) to regulate tissue and organ development and homeostasis. Cell adhesion to the ECM is primarily mediated by the integrin family of heterodimeric transmembrane receptors. Integrin-containing adhesions have two main functions: link the ECM to the intracellular cytoskeleton to form cell-ECM adhesions and transduce bidirectional signals from the ECM to the intracellular compartments. In this way, cells can sense topographical and mechanical features of the ECM. Integrins possess no enzymatic activity of their own and cannot bind the cytoskeleton directly. To exert their function, they rely on the intracellular recruitment of many different adaptor proteins that connect to the cytoskeleton and mediate signal transduction. Thus, to completely understand integrin functioning we must map the different proteins that reside in adhesion complexes.

Advancements in proteomic technologies have enabled in-depth analysis of integrin adhesion complexes. When I joined the research group of Arnoud Sonnenberg in 2015, the group had started to use proximity biotinylation identification assays (BioID) combined with mass spectrometry. In the next years, we have used this method extensively to characterize the proximitomes of integrin adhesion complexes in epithelial tissues. The results of these studies are presented in my thesis.

Chapter 1 describes the different adhesion complexes found in epithelial tissues in more detail and discusses how they integrate information about the physical composition of the surrounding matrix. In **chapter 2 and 3**, we present the proximitome of integrin αVβ5 and uncover the mechanisms that control its clustering in flat clathrin lattices versus focal adhesions. Intriguingly, we found that integrin αVβ5 localized predominantly in clathrin lattices in keratinocytes that formed hemidesmosomes. Because actomyosin-generated contractility regulates the localization of integrin αVβ5, we explored the role of hemidesmosomes in modulating force transduction (**chapter 4**). In **chapter 5**, we report the identification of the scaffold protein PEAK1 as a novel component of FAs. The identification of PEAK1 was also of interest to our colleagues Beatriz Carvalho and Gerrit Meijer (NKI, Translational Gastrointestinal Oncology group), who found that PEAK1 was differentially phosphorylated in benign polyps versus malignant colorectal cancer samples. We continued to study the role of PEAK1 in colorectal cancer progression and present the first results of this study in **chapter 6**. **Chapter 7** provides a general discussion and outlook for future research.