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Publications

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DIVISION OF CELL BIOLOGY I

RECEPTORS FOR MATRIX ADHESION

The main objective of our group is to study the mechanisms involved in cell adhesion. We are specifically interested in understanding the significance of and characterizing the interactions that take place between cells and the extracellular matrix component laminin in both the epidermis and the glomerulus of the kidney. A second line of research involves the outer nuclear membrane protein nesprin-3, which binds to the cytoskeletal linker protein plectin, thereby establishing a link between the intermediate filament system and the nucleus. The physiological roles of these proteins and their interaction are studied in model organisms, including mice and zebrafish.

Integrins and tumor progression The integral components of cellular mediated adhesion are the integrin heterodimers, which specify ligation to particular extracellular matrix (ECM) proteins and focus signaling responses while connecting cytoskeletal structures intracellularly. Outside-in activation of downstream signaling events mediated by integrin ligation leads to activation of pathways similar to the activated signals initiated by growth factor receptors. During the progression of cancer, tumor cells must overcome many implemented points of regulation to sustain uninhibited growth, invasion, and survival in new microenvironments in tissues. This work aims to investigate if signaling initiated by integrin expression leads to enhanced survival of tumor cells during metastasis.

We have identified several breast cancer cell lines that express minimal amounts of $\alpha 1$ integrin. Using these cells we have overexpressed $\alpha 3$, $\alpha 5$ and $\alpha 6$, known to be expressed during carcinoma progression. Expression of $\alpha 5$ leads to a morphologic change reminiscent of EMT and altered survival signaling pathways via Akt. Using a zebrafish embryo metastasis model we were able to demonstrate that $\alpha 5$ promotes survival of breast tumor cells in the circulation. This is a novel model for understanding the rate limiting step of metastasis and should reveal new mechanisms of integrin biology involved in metastatic dissemination of tumor cells.

Kindlins, talin, and integrins Loss-of-function mutations in kindlin-1 cause the blistering disorder Kindler syndrome (KS). KS keratinocytes express $\alpha 1$ -integrins at lower levels than normal keratinocytes, resulting in poor cell adhesion and spreading, low numbers of focal adhesions (FAs), and disturbed cytoskeletal organization, all of which are restored by kindlin-1 re-expression. Treatment with a $\alpha 1$ -activating antibody partially rescues the defects, indicating that the integrins are functional. Integrin activation depends on binding of an NPXY motif in the $\alpha 1$ -tail by talin, connecting the integrin to the cytoskeleton, whereas the kindlins bind a different NPXY motif. To address the regulation of $\alpha 1$ functions by talin and the kindlins, we generated $\alpha 1$ -mutants defective in talin-binding ($\alpha 1^{Y783A}$), kindlin-binding ($\alpha 1^{Y795A}$), or both ($\alpha 1^{Y783/795A}$), and stably expressed these in $\alpha 1$ -null cells. Wild-type $\alpha 1$ induces an EMT-like morphological change characterized by a loss of cell-cell contacts, cell scattering, increased motility, high RhoA activity, fibronectin fibrillogenesis, and a contractile morphology with multiple protrusions and large peripheral FAs. This phenotype is recapitulated by $\alpha 1^{Y795A}$ but not by $\alpha 1^{Y783A}$ or $\alpha 1^{Y783/795A}$, indicating that binding to talin but not to kindlin is critical for $\alpha 1$ functions. However, $\alpha 1^{Y795A}$ accumulates in intracellular vesicles and is expressed at low levels on the cell surface, which results in reduced numbers of FAs, much like in the KS cells. In conclusion, whereas talin is a critical regulator of $\alpha 1$ activity, kindlin regulates its cell surface expression.

Regulation of hemidesmosome disassembly by growth factors receptors

Hemidesmosomes (HDs) are specialized junctional complexes that mediate firm adhesion of keratinocytes to the underlying basement membrane. Migration of keratinocytes requires a regulated and dynamic turnover of HDs. We have previously identified three serine residues on the $\alpha 4$ cytoplasmic domain that play a critical

