**ADDRESSING POTENTIAL CROSS-TALK BETWEEN ADHESION RECEPTORS AND GPCRS USING LABEL-FREE APPROACHES.**

**Project Code:** 09-REG  
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**Aim:**  
Addressing GPCR-mediated adhesion receptor signaling by time-resolved holistic approaches being capable of monitoring the dynamic cell response and the functional state of cell-matrix adhesion

**Background / Methodology:**  
Knowledge about GPCR-mediated signal transduction has emerged over the years from the initial concepts that assumed a “one receptor – one signaling pathway” relationship. In the meantime, a considerable signaling plasticity was discovered. The current picture of GPCR-mediated signaling is no longer confined to the stimulation of a given G-protein subtype by a given receptor but involves the interaction of the receptor with other proteins (e.g. β-arrestin), a biased signaling of a given receptor dependent on the chemical structure of the agonist and also a location bias which refers to signaling that is dependent on whether the receptor is localized in exo- or endomembranes (endosome, Golgi). There is no reason to assume that this is the final level of complexity in particular when cross-talk with other signal transduction cascades is considered as well. It has been shown that adhesion receptors – most notably integrins – and their outside-in signaling may interfere with GPCR-mediated signal transduction and vice versa. But to the best of our knowledge no systematic analysis has been performed thus far.

This project aims to address this issue experimentally by time-resolved holistic approaches that are capable of monitoring (i) the dynamic cell response to GPCR activation and also (ii) the functional state of cell-matrix adhesion. It is the rationale of the approach to grow a model cell line with endogeneous receptor expression on different extracellular matrices and to monitor their holistic time-resolved response profile to receptor activation using the endogeneous agonist in increasing concentrations. The extracellular matrices will be composed of single recombinant ECM proteins (vitronectin, collagen I, collagen IV, laminin I, fibronectin) or well-defined mixtures thereof dependent on the physiological origin of the model cell line. Moreover, we aim to grow the model cells on endogeneous extracellular matrices that have been produced by very different cell types (endothelial, epithelial, fibroblastic) leading to correspondingly different matrix compositions. The experimental protocols for this type of assay are well established in the Wegener lab. This initial part of the project is rather explorative in nature screening for possible signaling crosstalk. It will identify extracellular matrix proteins that change the time-dependent response profile to receptor activation so that the cell-matrix interaction can be characterized in more detail only for these instances. Besides molecular approaches to characterize the expression of adhesion receptor subtypes, we will study their interaction with the given ECM proteins by means of cell spreading kinetics in presence and absence of peptides representing the recognition site on the ECM protein to pinpoint more specifically the relevant molecular interactions. On the GPCR side we will apply the well-known pathway deconvolution tools to identify the change in signaling due to an altered cell-ECM interaction. The project may shed light on a potential matrix-bias in GPCR signaling.

**International Collaborators:**  
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**Key Publications:**

