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Improved screening of integrin drugs via cell culture model of integrin-mediated adhesion

Researchers at Stanford University have discovered a new type of integrin-mediated cell adhesion, called curved adhesion, that represents the dominant structure in 3D physiological environments. Further, they have developed cell-based models and a phenotypic assay for the development of integrin therapeutics.

Integrins proteins are the primary cell membrane receptors that mediate cell adhesion in mammals, anchoring the cytoskeleton to the extracellular matrix (ECM). Integrins, composed of an alpha and beta subunit with 24 known heterodimers, are essential for cell mechanotransduction, signaling, survival and migration. Dysregulation of integrin signaling contributes to the development of various diseases, making integrins key therapeutic targets in indications including thrombosis, autoimmune disorders, fibrotic diseases, microbial infections, and many types of cancer. While several integrin inhibitors are marketed drugs, therapeutic success has only been achieved for four integrin isoforms. Inhibitors targeting other integrin isoforms, particularly those in the alpha-v subfamily, which are indicated in cancers and fibrotic diseases, including idiopathic pulmonary fibrosis (IPF), and nonalcoholic fatty liver syndrome (NASH), have faced significant challenges. In particular, inhibitors for alpha-v-containing integrins have demonstrated encouraging in vitro results, but have failed to show significant therapeutic benefits in clinical trials, despite their high safety profiles. The discrepancy between preclinical and clinical studies suggests that the preclinical models used in the drug discovery programs failed to accurately represent the in vivo physiology.

The inventors have discovered a new type of integrin function, called curved adhesion. To date, focal adhesions have been the most widely studied integrin-mediated cell adhesions likely due to their formation on ECM-coated flat surfaces,

such as in 2D cell culture. Focal adhesions, which are driven by mechanical tension and require high substrate rigidity, were believed to be the dominant adhesion structure and were the primary target for integrin therapeutic development. However, ECM in tissues is largely composed of entangled protein fibers that are often too soft to support the assembly of focal adhesions. Curved adhesions, in contrast, are driven by membrane curvature instead of mechanical tension and can thus anchor cells to soft ECM fibers. Curved adhesions can co-exist with focal adhesions but are structurally and functionally distinct. In particular, curved adhesions are exclusively mediated by the alpha-v beta-5 integrin isoform, which is upregulated in many cancers and fibrotic diseases. The present studies indicate that curved adhesions dominate in 3D physiological environments. Therefore, targeting curved adhesions rather than focal adhesions offers a promising route towards the discovery of effective integrin drugs, particularly those for alpha-v-containing isoforms.

This technology presents a new platform to induce formation of curved adhesions in cell culture for the discovery of integrin therapeutics targeting curved adhesions. Additionally, it provides a proximity-based phenotypic assay for detecting curved adhesion inhibitors in high throughput screens.

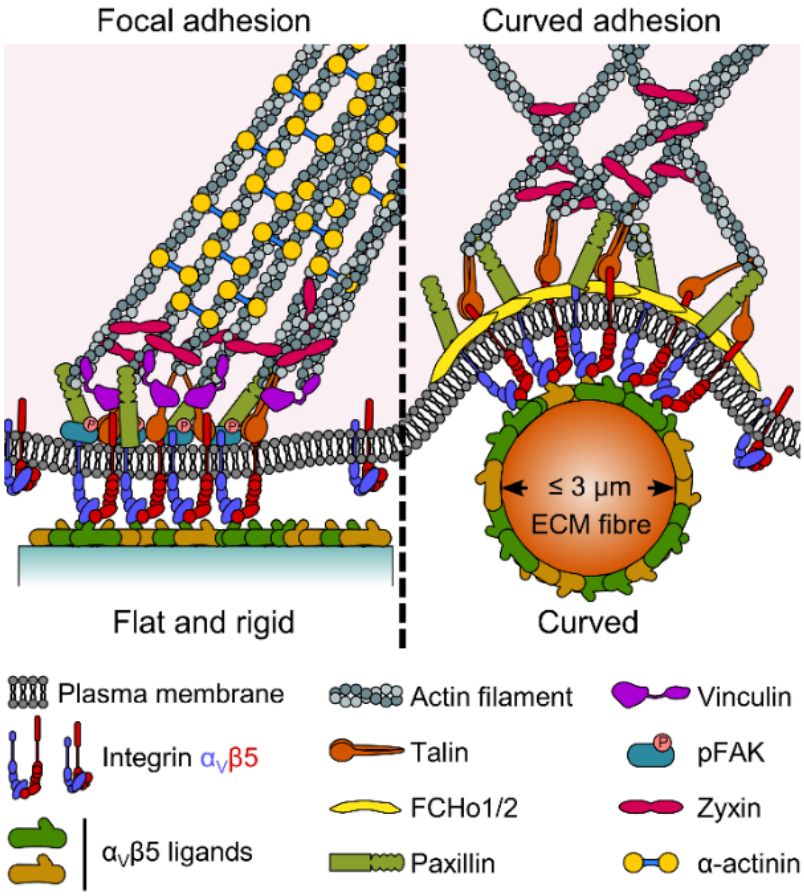

Figure 1. Schematic illustrations of focal adhesion and curved adhesion structures. (image credit to the inventors)

Stage of Development Proof of concept

Applications

- Integrin therapeutic (small molecule, biologic) development for cancers and fibrotic diseases
- Therapeutics targeting integrin alpha-v beta-5, indicated in glioblastoma, breast cancers, pancreatic cancers, cardiac fibrosis, scleroderma fibrosis, and systemic sclerosis, among other diseases.
- Phenotypic assays for high throughput screening of integrin drugs

Advantages

- Curved-adhesions represent a new target for integrin drugs

- Curved-adhesions are shown to dominate in 3D physiological environments, indicating that they represent a more physiologically relevant target compared to focal adhesions

Patents

- Published Application: WO2023230461

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