The glycophorin A transmembrane sequence within integrin αvβ3 creates a non-signaling integrin with low basal affinity that is strongly adhesive under force.

Integrin heterodimeric cell adhesion and signaling receptors bind ligands of the extracellular matrix and relay signals bidirectionally across cell membranes. Thereby, integrins adopt multiple conformational and functional states that control ligand binding affinity and linkage to cytosolic/cytoskeletal proteins. Here, we designed an integrin chimera encompassing the strongly dimerizing transmembrane domain (TMD) of glycophorin A (GpA) in the context of the otherwise unaltered integrin αvβ3. We hypothesized that this chimera should have a low basal affinity to soluble ligand but should be force-activatable. By cellular expression of this chimera, we found a decreased integrin affinity to a soluble peptide ligand and inhibited intracellular signaling. However, under external forces applied by an atomic force microscope or by a spinning disc device causing shear forces, the mutant caused stronger cell adhesion than the wild-type integrin. Our results demonstrate that the signaling- and migration-incapable integrin αvβ3-TMD mutant TMD-GpA shows the characteristics of a primed integrin state, which is of low basal affinity in the absence of forces, but may form strong bonds in the presence of forces. Thus, TMD-GpA may mimic a force-activatable signaling...
intermediate.