Nature Reviews Molecular Cell Biology | AOP, published online 10 February 2010; doi:10.1038/nrm2856

SIGNAL TRANSDUCTION

Integrin's new partner

Integrins are heterodimeric membrane receptors that mediate cell adhesion and typically perform bidirectional signalling. Signals from inside the cell activate the binding of integrin to extracellular ligands (inside–out signalling), which triggers intracellular signalling initiated by ligand-bound integrin (outside–in signalling). Outside–in signalling can initiate cell spreading, retraction, migration and proliferation, but its mechanism remains unclear. Reporting in *Science*, Gong *et al.* now show that intracellular signalling downstream of integrins is mediated by their direct binding to G proteins.

Cell spreading — an early consequence of outside–in signalling — requires activation of the protein kinase SRC, and the SRC-dependent transient inhibition of the small GTPase RHOA, which affects actin cytoskeleton dynamics. Although it is known that integrin engagement leads to SRC-dependent RHOA inhibition, the molecular mechanisms that link integrin to these signalling events have been unclear.

Heterotrimeric G proteins consist of the subunits Gα and the tightly associated Gβγ and they bind to the intracellular domain of G protein-coupled receptors (GPCRs). G proteins are activated when extracelluar ligands bind GPCRs and induce the exchange of GDP for GTP on Gα. The authors find that knockdown of $G\alpha_{13}$ in platelets inhibits their spreading on fibrinogen — an αIIbβ3 integrin ligand. Depletion of $G\alpha_{13}$ also abolishes SRC phosphorylation at Tyr416 (which is indicative of SRC activation) and accelerates RHOA activation. This suggests that $G\alpha_{13}$ functions in signalling from ligand-occupied integrins and mediates the downstream inhibition of RHOA, which promotes cell spreading.

$G\alpha_{13}$ and β3 integrin co-immunoprecipitate and purified $G\alpha_{13}$ binds to a recombinant β3 or β1 integrin cytoplasmic domain fusion protein *in vitro*, showing that $G\alpha_{13}$ binds directly to the integrin cytoplasmic domain. Using truncated versions of $G\alpha_{13}$, the authors also show that β3 integrin binds to the switch region I (SRI) of $G\alpha_{13}$. Treatment of platelets with a myristoylated SRI peptide inhibits the $G\alpha_{13}$–β3 integrin interaction *in vitro* and prevents integrin-mediated SRC activation, RHOA inhibition and platelet spreading.

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> integrins are non-canonical Gα13 protein-coupled receptors

These results show that integrins are non-canonical $G\alpha_{13}$ protein-coupled receptors and that their interaction with $G\alpha_{13}$ mediates integrin signalling to SRC and RHOA, and thus regulates cell spreading.

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ORIGINAL RESEARCH PAPER Gong, H. *et al.* G protein subunit $G\alpha_{13}$ binds to integrin $\alpha_{IIb}\beta_3$ and mediates integrin "outside-in" signaling. *Science* **327**, 340–343 (2010)

FURTHER READING Caswell, P. T., Vadrevu, S. & Norman, J. C. Integrins: masters and slaves of endocytic transport. *Nature Rev. Mol. Cell Biol.* **10**, 843–853 (2009)