The role of integrin clustering in signal transduction by collagen receptors

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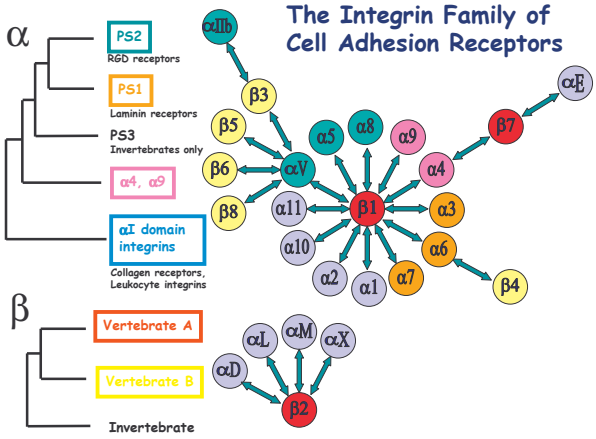
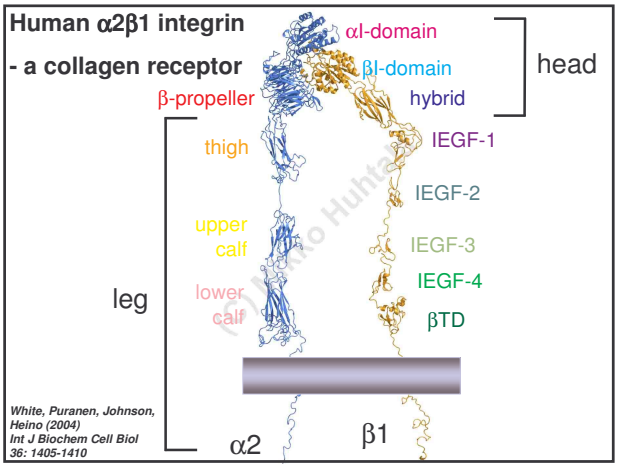
Bergen 09/2005

The Integrin Family of Cell Adhesion Receptors



Human α2β1 integrin - a collagen receptor



White, Puranen, Johnson, Heino (2004) Int J Biochem Cell Biol 36: 1405-1410

The Collagen Receptor Integrins

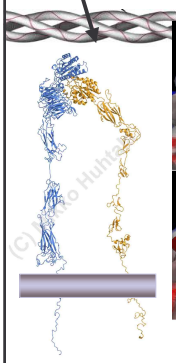
Integrin α1β1
Smooth muscle cells, fibroblasts, endothelial cells, chondrocytes, osteoblasts, leukocytes

Integrin α2β1
Epithelial cells, fibroblasts, endothelial cells, platelets, chondrocytes, osteoblasts, leukocytes

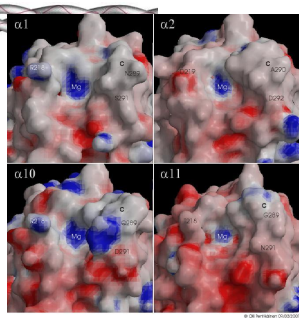
Integrin α10β1
Cartilage

Integrin α11β1
Mesodermal tissues (perichordium, periosteum, ectomesenchyme in the head, non-muscle)

αI domain



α1 structure: Salminen, Nymalm, Kankare, Käpylä, Heino, Johnson (1999) *Acta Crystallograph D* 55: 1365
Nymalm, Puranen, Nyholm, Käpylä, Kidron, Pentikäinen, Airenne, Heino, Slotte, Johnson, and Salminen (2004) *J Biol Chem* 279:7962



α2 structure: Emsley, Knight, Farndale, Barnes, Liddington (2000) *Cell* 100: 47

α10 and α11 models: Tulla, Pentikäinen, Viitasalo, Käpylä, Impola, Nykvist, Nissinen, Johnson, Heino (2001) *J Biol Chem* 276: 48206

Collagen receptors and selective binding to distinct collagen subtypes

	α1I	α2I	α10I	α11I
Fibril-forming collagens				
I	+/++	+++	+/++	++
II	+/++	+++	+/++	++
III	+/++	+++	+/++	?
V	+/++	+/++	+	?
Network-forming collagens				
IV	+++	+/++	++	+
Beaded filament -forming collagens				
VI	+++	+	++	+/-
Transmembrane collagens				
XIII	++	+/-	++	?
XVII (COL15)	-	-	-	?
FACITs				
IX	+++	+++	+++	+++

Red = Best ligands for each αI domain

Ivaska, Käpylä, Pentikäinen, Hoffren, Hermonen, Huttunen,Johnson, Heino (1999) *J Biol Chem* 274:3513
Käpylä, Ivaska, Riikonen, Nykvist, Pentikäinen, Johnson, Heino (2000) *J Biol Chem* 275:3348
Nykvist, Tu, Ivaska, Käpylä, Pihlajaniemi, Heino (2000) *J Biol Chem* 275:8255
Nykvist, Tasanen, Viitasalo, Käpylä, Jokinen, Bruckner-Tuderman, Heino (2001) *J Biol Chem* 276:38673
Tulla, Pentikäinen, Viitasalo, Käpylä, Impola, Nykvist, Nissinen, Johnson, Heino (2001) *J Biol Chem* 276:48206
Zhang, Käpylä, Puranen, Tiger, Knight, Pentikäinen, Johnson, Farndale, Heino, Gullberg (2003) *J Biol Chem* 278:7270
Käpylä, Jäälinoja, Tulla, Ylöstalo, Nissinen, Viitasalo, Säämänen, Vehviläinen, Marjomäki, Farndale, Birk, Ala-Kokko, Heino (2004) *J Biol Chem* 279: 51677
Jokinen, Dadu, Nykvist, Käpylä, White, Ivaska, Vehviläinen, Reunanen, Larjava, Häkkinen, Heino (2004) *J Biol Chem* 279: 31956

Integrin α1β1 signaling

ERK

PROLIFERATION

COLLAGEN

Integrin α2β1 signaling

CONTRACTION

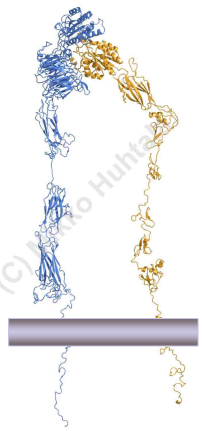
p38

MMPs

COLLAGEN

MATRIX REMODELING

Structural basis of α2β1 integrin signaling



α2β1 integrin: Inactive conformation

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α2β1 integrin: Active / αI domain closed conformation

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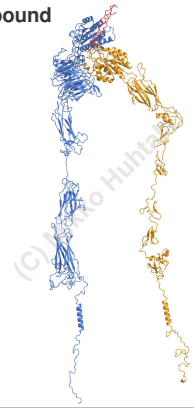
α2β1 integrin: αI domain open / ligand bound conformation



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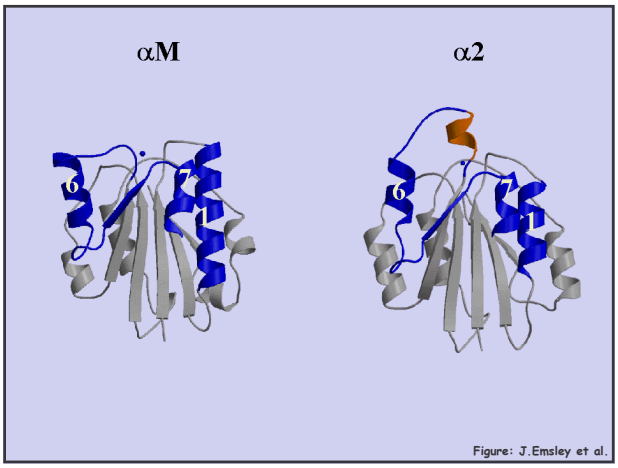
QuickTime™ and a GIF decompressor are needed to see this picture.

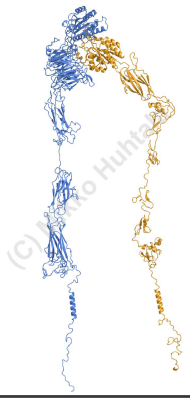
Figure: J.Emsley et al.



Structural basis of α2β1 integrin signaling

- Ligand binding to α2I-domain
- Conformational change in α2I-domain (α7 helix)
- E336 interacts with β1I-domain
- Conformational change in β1 subunit
- α2 / β1 tail separation

α2β1 integrin:
Active / αI domain open conformation



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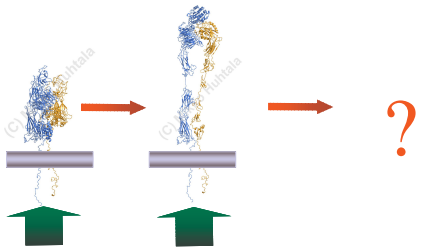
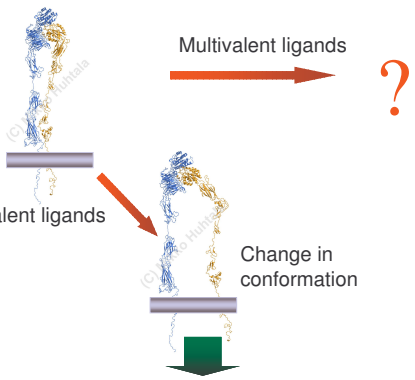
Inside-out signaling

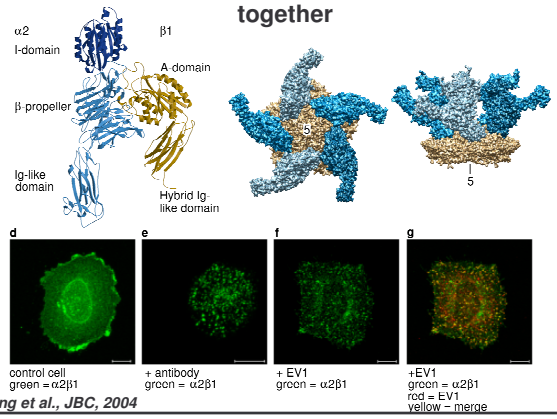
Inactive Active "Superactive"



Outside-in signaling

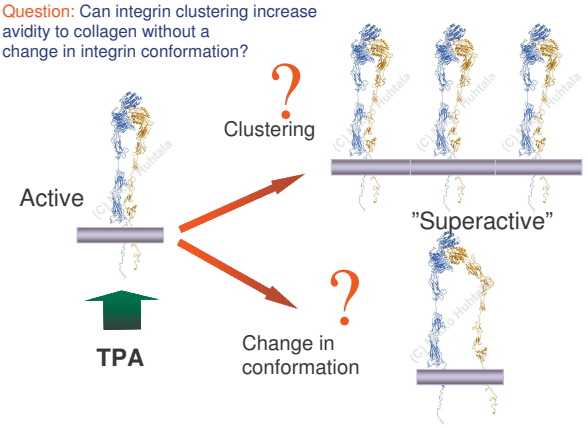


EV1 particle may cluster up to five α2β1 integrins together

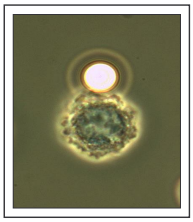


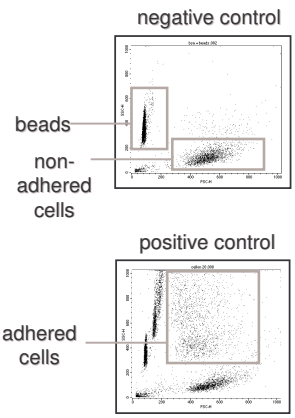
Xing et al., JBC, 2004

Question: Can integrin clustering increase avidity to collagen without a change in integrin conformation?



Bead-Based Cell Adhesion Assay



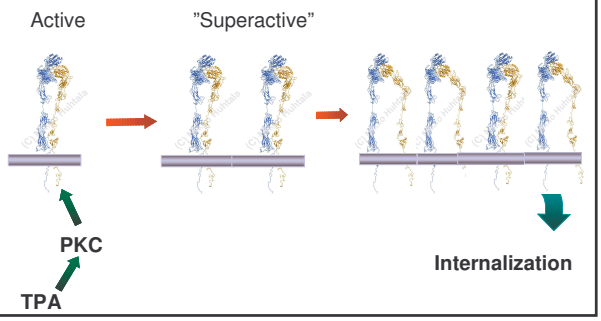


Connors and Heino, Analytical Biochemistry, 2005

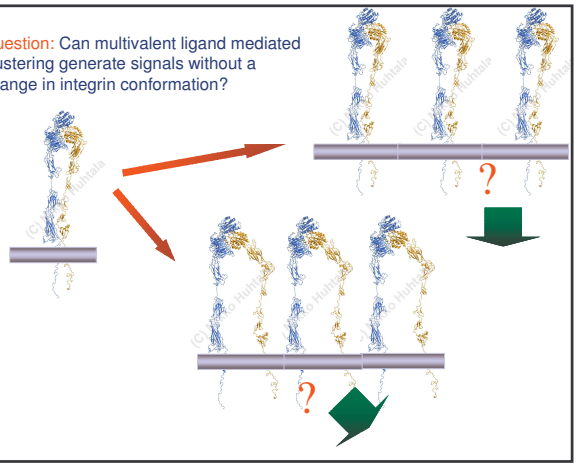
Custering and Inside-out Signaling - Conclusions:

1° Superactivation after inside-out signaling occurs at the same time as α2β1 clustering and conformational change in α2I domain

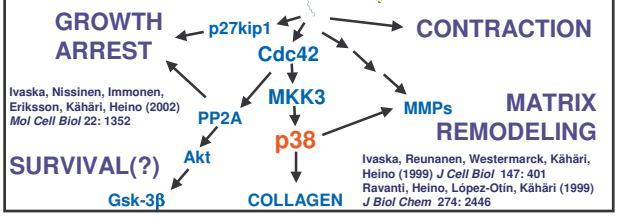
2° Superactivation is possible without the conformational change in α2I domain



Question: Can multivalent ligand mediated clustering generate signals without a change in integrin conformation?



Integrin α2 specific signaling pathways

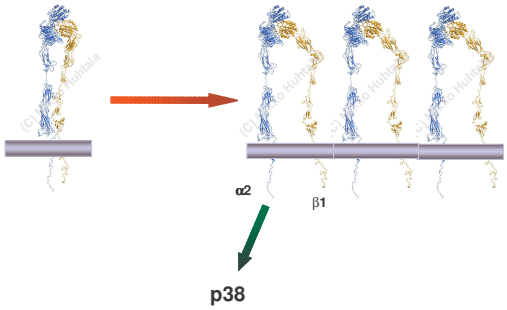


Ivaska, Nissinen, Immonen, Eriksson, Kähäri, Heino (2002) *Mol Cell Biol* 22: 1352

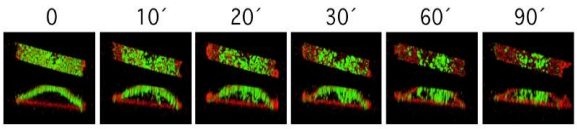
Ivaska, Reunanen, Westermarck, Kähäri, Heino (1999) *J Cell Biol* 147: 401
Ravanti, Heino, López-Otín, Kähäri (1999) *J Biol Chem* 274: 2446

Multivalent Ligand Mediated Clustering - Conclusions:

Change in integrin conformation required for signaling mediated by α2 cytoplasmic domain



Clustering of α2β1 integrin is alone sufficient to induce internalization



Upla et al., MBC 2004