

**Table 1** Integrin Binding Proteins

| Binding target                      | Binding protein  | Characteristics                            | Function                                                                                   | Reference |
|-------------------------------------|------------------|--------------------------------------------|--------------------------------------------------------------------------------------------|-----------|
| <b><math>\beta</math> subunits</b>  |                  |                                            |                                                                                            |           |
| $\beta 2$                           | Cytohesin-1      | PH- and SEC7 domains                       | Enhances $\alpha L\beta 2$ binding to ICAM                                                 | 1         |
| $\beta 3$                           | Endonexin        | Small cytoplasmic protein                  | Affinity modulation                                                                        | 2         |
| $\beta 4$                           | p27BBP           | Intermediate filament association          | ?                                                                                          | 3         |
| $\beta$                             | ILK-1            | Serine/threonine kinase                    | Negatively modulates integrin-cytoskeleton interactions? growth control                    | 4         |
| $\beta$                             | ICAP1            | Phosphoprotein                             | Affinity modulation? integrin-cytoskeleton modulation?                                     | 5         |
| $\beta$                             | CD98             | Transmembrane protein                      | Affinity modulation                                                                        | 6         |
| $\beta 1$                           | Melusin          | Cytoplasmic protein                        | Regulated by calcium; role in muscle                                                       | 7         |
| $\beta 7$                           | Wait 1           | WD repeat                                  | ?                                                                                          | 8         |
| $\beta$ subunits                    | Rack-1           | WD repeat                                  | Binds active PKC                                                                           | 9         |
| $\beta$ subunits                    | Talin            | Focal contact protein                      | Links to actin filaments                                                                   | 10        |
| $\beta$ subunits                    | $\alpha$ actinin | Focal contact protein                      | Links to actin filaments                                                                   | 10        |
| <b><math>\alpha</math> subunits</b> |                  |                                            |                                                                                            |           |
| Multiple $\alpha$ 's                | Calreticulin     | Calcium regulatory protein                 | Modulates integrin-triggered $Ca^{2+}$ influx and $Ca^{2+}$ -dependent cytoskeletal events | 11        |
| $\alpha IIb$                        | CIB              | Similarities to calmodulin and calcineurin | Affinity modulation?                                                                       | 12        |
| $\alpha 5$                          | Nischarin        | Large cytoplasmic protein                  | Inhibits cell motility                                                                     | 13        |
| $\alpha 4$                          | Paxillin         | Focal contact protein                      | Regulates cell motility                                                                    | 14        |
| certain $\alpha$ subunits           | Caveolin         | Lipid raft protein                         | Signaling to Erk                                                                           | 15        |
| <b>Transmembrane domains</b>        |                  |                                            |                                                                                            |           |
|                                     | TM4 proteins     | Four membrane-spanning helices             | Signal transduction?                                                                       | 16        |

**Table 2** Recent examples of synergisms between integrins and RTK signaling

| RTK         | Integrin                      | Observed effects                                                                       | Reference |
|-------------|-------------------------------|----------------------------------------------------------------------------------------|-----------|
| EGFR, PDGFR | $\beta 1$                     | Lack of $\beta 1$ integrin results in reduced growth factor driven cell motility       | 17        |
| Various     | $\beta 1$                     | $\beta 1$ dominant negative effects keratinocyte differentiation                       | 18        |
| EGFR        | $\beta 1$                     | RTK /integrin interactions influence differentiation of breast epithelial 3-D cultures | 19        |
| RON         | Various                       | RON tyrosine phosphorylation                                                           | 20        |
| ErbB-2      | $\alpha 6 \beta 4$            | PI-3-kinase dependent invasiveness                                                     | 21        |
| Met         | Fibronectin binding integrins | Cell survival (anoikis)                                                                | 22        |
| IGF-1 R     | $\alpha v \beta 3$            | Phosphorylation of IRS-1                                                               | 23        |
| Insulin R   | $\beta 1$                     | Stimulation of PI-3-K and Akt                                                          | 24        |
| Several     | $\alpha 5, \alpha 6, \beta 1$ | Myoblast growth and differentiation                                                    | 25        |
| Insulin-R   | $\alpha 6 \beta 1$            | Mammary epithelial cell differentiation                                                | 26        |
| EGFR, PDGFR | $\alpha 5 \beta 1$            | Reduced apoptosis in response to growth factor deprivation                             | 27        |

**Table 3** Associations between signaling components and the cytoskeleton

| <b>Cytoskeletal component</b>                  | <b>Signaling component</b> | <b>Effect</b>              | <b>Reference</b> |
|------------------------------------------------|----------------------------|----------------------------|------------------|
| Microtubule polymerization                     | Rac-1                      | Activation                 | 28               |
| Microtubule or actin filament depolymerization | JNK, p38                   | Activation                 | 29               |
| Microtubule disruption                         | MEKK1                      | Activation                 | 30               |
| Actin treadmilling; decreases in G actin       | SRF                        | Activation                 | 31               |
| Tensin overexpression                          | JNK, p38                   | Activation                 | 32               |
| Actin filament depolymerization                | Insulin signaling to Erk   | Inhibition                 | 33               |
| Actin filaments                                | Ras, Raf, MEK, Erk         | Association with filaments | 34               |
| Ezrin                                          | PI-3-kinase                | Activation                 | 35               |

### Literature Cited

1. Kolanus W, Nagel W, Schiller B, Zeitlmann L, Godar S, et al. 1996.  $\alpha$  L  $\beta$  2 integrin/LFA1 binding to ICAM1 induced by cytohesin-1, a cytoplasmic regulatory molecule. *Cell* 86:233--42
2. Kashiwagi H, Schwartz MA, Eigenthaler M, Davis KA, Ginsberg MH, Shattil SJ. 1997. Affinity modulation of platelet integrin  $\alpha$ IIb $\beta$ 3 by  $\beta$ 3 endonexin, a selective binding partner of the  $\beta$ 3 integrin cytoplasmic tail. *J. Cell Biol.* 137:1433--43
3. Biffo S, Sanvito F, Costa S, Preve L, Pignatelli R, et al. 1997. Isolation of a novel beta4 integrin-binding protein (p27(BBP)) highly expressed in epithelial cells. *J. Biol. Chem.* 272:30314--21
4. Hannigan GE, Leung-Hagesteijn C, Fitz-Gibbon L, Coppolino MG, Radeva G,. 1996. Regulation of cell adhesion and anchorage-dependent growth by a new beta1-integrin-linked protein kinase. *Nature* 379:91--96
5. Chang DD, Wong C, Smith H, Liu J. 1997. ICAP-1, a novel beta 1 integrin cytoplasmic domain-associated protein, binds to a conserved and functionally important NPXY sequence motif of beta 1 integrin. *J. Cell Biol.* 138:1149--57
6. Fenczik CA, Sethi T, Ramos JW, Hughes PE, Ginsberg MH. 1997. Complementation of dominant suppression implicates CD98 in integrin activation. *Nature* 390:81--85
7. Brancaccio M, Guazzone S, Menini N, Sibona E, Hirsch E, et al. 1999. Melusin is a new muscle-specific interactor for beta(1) integrin cytoplasmic domain. *J. Biol. Chem.* 274:29282--88
8. Rietzler M, Bittner M, Kolanus W, Schuster A, Holzmann B. 1998. The human WD repeat protein WAIT-1 specifically interacts with the cytoplasmic tails of beta7-integrins. *J. Biol. Chem.* 273:27459--66
9. Liliental J, Chang DD. 1998. Rack1, a receptor for activated protein kinase C, interacts with integrin beta subunit. *J. Biol. Chem.* 273:2379--83
10. Calderwood DA, Shattil SJ, Ginsberg MH. 2000. Integrins and actin filaments: reciprocal regulation of cell adhesion and signaling. *J. Biol. Chem.* 275:22607--10
11. Coppolino MG, Woodside MJ, Demaurex N, Grinsten S, St-Arnaud R, Dedhar S. 1997. Calreticulin is essential for integrin-mediated calcium signalling and cell adhesion. *Nature* 386:843--47
12. Naik UP, Patel PM, Parise LV. 1997. Identification of a novel calcium-binding protein that interacts with the integrin  $\alpha$ II $\beta$  cytoplasmic domain. *J. Biol. Chem.* 272:4651--54
13. Alahari SK, Lee JW, Juliano RL. 2000. Nischarin, a novel protein that interacts with the integrin  $\alpha$ 5 subunit and inhibits cell migration. *J. Cell Biol.* 151:1141--54
14. Liu S, Thomas SM, Woodside DG, Rose DM, Kiosses WB, et al. 1999. Binding of paxillin to  $\alpha$ 4 integrins modifies integrin-dependent biological responses. *Nature* 402:676--81
15. Wary KK, Mariotti A, Zurzolo C, Giancotti FG. 1998. A requirement for caveolin-1 and associated kinase Fyn in integrin signaling and anchorage-dependent cell growth. *Cell* 94:625--34
16. Berdichevski F, Talias KF, Wong K, Carpenter CL, Hemler ME. 1997. A novel link between integrins, transmembrane superfamily proteins (CD63 and CD81), and phosphatidylinositol 4-kinase. *J. Biol. Chem.* 272:2595--98

17. Sakai T, de la Pena JM, Mosher DF. 1999. Synergism among lysophosphatidic acid, beta1A integrins, and epidermal growth factor or platelet-derived growth factor in mediation of cell migration. *J. Biol. Chem.* 274:15480--86
18. Zhu AJ, Haase I, Watt FM. 1999. Signaling via  $\beta$ 1 integrins and mitogen-activated protein kinase determines human epidermal stem cell fate in vitro. *Proc. Natl. Acad. Sci. USA* 96:6728--33
19. Wang F, Weaver VM, Petersen OW, Larabell CA, Dedhar S, et al. 1998. Reciprocal interactions between beta1-integrin and epidermal growth factor receptor in three-dimensional basement membrane breast cultures: a different perspective in epithelial biology. *Proc. Natl. Acad. Sci. USA* 95:14821--26
20. Danilkovitch-Miagkova A, Angeloni D, Skeel A, Donley S, Lerman M, Leonard EJ. 2000. Integrin-mediated RON growth factor receptor phosphorylation requires tyrosine kinase activity of both the receptor and c-Src. *J. Biol. Chem.* 275:14783--86
21. Gambaletta D, Marchetti A, Benedetti L, Mercurio AM, Sacchi A, Falcioni R. 2000. Cooperative signaling between alpha(6)beta(4) integrin and ErbB-2 receptor is required to promote phosphatidylinositol 3-kinase-dependent invasion. *J. Biol. Chem.* 275:10604--10
22. Qiao H, Saulnier R, Patryzkat A, Rahimi N, Raptis L, Rossiter J, Tremblay E, Elliott B. 2000. Cooperative effect of hepatocyte growth factor and fibronectin in anchorage-independent survival of mammary carcinoma cells: requirement for phosphatidylinositol 3-kinase activity. *Cell Growth Differ.* 11:123--33
23. Zheng B, Clemmons DR. 1998. Blocking ligand occupancy of the alphaVbeta3 integrin inhibits insulin-like growth factor I signaling in vascular smooth muscle cells. *Proc. Natl. Acad. Sci. USA* 95:11217--22
24. Guilherme A, Czech MP. 1998. Stimulation of IRS-1-associated phosphatidylinositol 3-kinase and Akt/protein kinase B but not glucose transport by beta1-integrin signaling in rat adipocytes. *J. Biol. Chem.* 273:33119--22
25. Sastry SK, Lakonishok M, Wu S, Truong TQ, Huttenlocher A, et al. 1999. Quantitative changes in integrin and focal adhesion signaling regulate myoblast cell cycle withdrawal. *J. Cell Biol.* 144:1295--1309
26. Farrelly N, Lee YJ, Oliver J, Dive C, Streuli CH. 1999. Extracellular matrix regulates apoptosis in mammary epithelium through a control on insulin signaling. *J. Cell Biol.* 144:1337--48
27. Lee JW, Juliano JL. 2000.  $\alpha$ 5 $\beta$ 1 Integrin protects intestinal epithelial cells from apoptosis through a phosphatidylinositol 3-kinase and protein kinase B dependent pathway. *Mol. Biol. Cell* 11:1973--87
28. Waterman-Storer CM, Worthylake RA, Liu BP, Burridge K, Salmon ED. 1999. Microtubule growth activates Rac1 to promote lamellipodial protrusion in fibroblasts. *Nat. Cell Biol.* 1:45--50
29. Oren A, Herschkovitz A, Ben-Dror I, Holdengreber V, Ben-Shaul Y, et al. 1999. The cytoskeletal network controls c-Jun expression and glucocorticoid receptor transcriptional activity in an antagonistic and cell-type-specific manner. *Mol. Cell. Biol.* 19:1742--50
30. Yujiri T, Fanger GR, Garrington TP, Schlesinger TK, Gibson S, Johnson GL. 1999. MEK kinase 1 (MEKK1) transduces c-Jun NH2-terminal kinase activation in response to changes in the microtubule cytoskeleton. *J. Biol. Chem.* 274:12605--10

31. Sotiropoulos A, Gineitis D, Copeland J, Treisman R. 1999. Signal-regulated activation of serum response factor is mediated by changes in actin dynamics. *Cell* 98:159--69
32. Katz BZ, Zohar M, Teramoto H, Matsumoto K, Gutkind JS, et al. 2000. Tensin can induce Jnk and p38 activation. *Biochem. Biophys. Res. Commun.* 272:717--20
33. Tsakiridis T, Bergman A, Somwar R, Taha C, Aktories K, et al. 1998. Actin filaments facilitate insulin activation of the src and collagen homologous/mitogen-activated protein kinase pathway leading to DNA synthesis and c-fos expression. *J. Biol. Chem.* 273:28322--31
34. Carraway CA, Carvajal ME, Carraway KL. 1999. Association of the Ras to mitogen-activated protein kinase signal transduction pathway with microfilaments. *J. Biol. Chem.* 274:25659--67
35. Gautreau A, Poulet P, Louvard D, Arpin M. 1999. Ezrin, a plasma membrane-microfilament linker, signals cell survival through the phosphatidylinositol 3-kinase/Akt pathway. *Proc. Natl. Acad. Sci. USA* 96:7300--5