ECM signalling: orchestrating cell behaviour and misbehaviour

Matvey E. Lukashev and Zena Werb

The extracellular matrix (ECM) provides signalling cues that regulate cell behaviour and orchestrate functions of cells in tissue formation and homeostasis. The composition of the ECM, its three-dimensional organization and proteolytic remodelling are major determinants of the microenvironmental signalling context that controls cell shape, motility, growth, survival and differentiation. In recent years, the importance of ECM signalling has been underscored by the evidence that misregulation of cell–ECM interactions can contribute to many diseases, including developmental, immune, haemostasis, degenerative and malignant disorders. This review discusses recent insights into the regulatory functions of the ECM and their role in disease, focusing on cancer as a paradigm.

The normal formation and function of multicellular tissues require correct expression and function of genes that control interactions of cells with the extracellular matrix (ECM). Mutations in genes encoding ECM proteins and receptors cause diseases of the bone, cartilage, skin, muscle, brain, eye and cardiovascular system. Interestingly, a number of such defects occur as a result of mutations that alter the structural properties of ECM proteins and the function of ECM-degrading proteases, particularly those of the matrix metalloprotease (MMP) family[1], suggesting that the organization of the ECM is important for its regulatory functions (Table 1). In transgenic animal models, ablation or misexpression of ECM proteins, components of ECM–cytoplasmic linkages and MMPs produce a variety of developmental, structural and disease-like phenotypes, including cancer (reviewed in Refs 1 and 2). The multifaceted cellular and tissue responses to genetic modification of ECM organization, interaction with cells and remodelling illustrate that the ECM serves a number of distinct signalling functions. The regulatory effects of the ECM involve the modulation of signalling pathways that control cell growth, differentiation, survival and morphogenesis. This article focuses on two aspects of ECM signalling: the regulation of cell behaviour through changes in cytoarchitecture, and new evidence of cooperation between the ECM and tumour suppressors.

ECM signalling and cytoarchitecture

Many aspects of ECM signalling depend on changes in cytoarchitecture. The degree of cell spreading defined by properties of the ECM substrate controls anchorage-dependent cell growth (reviewed in Ref. 3). Similarly, cell spreading is required for ECM-dependent suppression of apoptosis[4,5] and modulates differentiation and gene expression[6]. How are changes in cell shape translated into signals that regulate cellular processes, such as proliferation and apoptosis? The precise mechanisms are just beginning to be elucidated, but several insights (summarized in Fig. 1) have been provided by recent studies on anchorage-dependent cell-cycle progression. Cell adhesion to the ECM modulates the expression and functional state of several cell-cycle regulators, including cyclin-dependent kinases (cdk2 and cdc2), cyclins (A, B, D and E), cyclin-dependent kinase inhibitors (p21 and p27) and Rb (reviewed in Refs 3 and 7). Anchorage to the ECM is crucial for the progression through the G1–S cell-cycle checkpoint and controls two of its central events: induction and translation of the cyclin D1 mRNA and Rb hyperphosphorylation[3]. Cyclin D1 translation is stimulated through activation of the p70S6 kinase (p70S6K) pathway[8]. The activity of p70S6K is in turn regulated by cell–ECM contact, and its activation can be modulated by ECM organization and, apparently, also by the degree of cell spreading and microfilament organization[9,10], suggesting that the p70S6K–cyclin-D1 pathway might form one link between cell shape and growth control. Although the upstream mechanisms that control p70S6K activity are not fully understood, this kinase can be stimulated by the Rho-like small GTPases Rac1 and Cdc42, and by the Cdc42 GDP–GTP exchange factor Dbl[11], which are key regulators of the actin cytoskeleton. Interestingly, Rho1p, which regulates actin organization in yeast, is activated by defects in the cell wall via the nucleotide exchange factor Rom2p[12]. Since mammalian RhoA is activated by adhesion to the ECM and by mechanical stress, it has been proposed that a mechanism similar to the yeast Rom2p–Rho1p pathway operates in mammalian cells and mediates cellular responses to mechanical forces[12]. Although the molecular nature of the sensor that could detect the mechanical stress and activate the Rho-like GTPases is unknown, such a mechanism could involve microtubules. This is suggested by the evidence that disruption of microtubules, like activation of the RhoA pathway, can induce assembly of cell–ECM adhesion complexes, microfilament organization and entry into the cell cycle[13].

The signalling properties of the ECM depend on its organization. In mammary epithelial cells, the ECM suppresses apoptosis by coordinating the expression and function of c-Myc, cyclin D1, Rb and p21/WAF-1 in a way that results in withdrawal of the cells from the cell cycle. This regulatory effect requires a three-dimensional organization of the

The authors are in the Dept of Anatomy and Program in Cell Biology, University of California San Francisco, Box 0452, San Francisco, CA 94143, USA. E-mail: zena@itsa.ucsf.edu

 0962-8924/98/$ – see front matter
PII: S0962-8924(98)01362-2

TABLE 1 – TISSUE DEFECTS CAUSED BY MUTATIONS IN GENES CONTROLLING CELL–ECM INTERACTIONS

Affected tissue/organ	Condition	Mutant gene	Gene function	Source
Brain, kidney, gonads	Kallmann's syndrome	KAL-1	Putative ECM protein	–[a]
Brain (mouse)	Mouse *reeler* phenotype	Reelin	ECM protein	–[b]
Eye	Familial retinal degeneration (Sorsby's fundus dystrophy)	TIMP-3	Inhibitor of matrix metalloproteases	–[c]
Bone	Osteogenesis imperfecta	Collagen I	ECM protein	–[d]
Cartilage	Chondrogenesis imperfecta	Collagen II	ECM protein	–[d]
Muscle	Muscular dystrophy	Merosin	ECM protein	–[e]
Muscle	Muscular dystrophy	Dystroglycan	ECM receptor	–[f]
Skeleton, eye, cardiovascular system	Marfan's syndrome	Fibrillin-1	ECM protein	–[g]
Skeleton, muscle, heart	Contractural arachnodactyly	Fibrillin-2	ECM protein	–[g]
Kidney	Alport syndrome	Collagen IV(α5)	ECM protein	–[h]
Smooth muscle	Leiomyomatosis	Collagen IV(α5) Collagen IV(α6)	ECM protein	–[i]
Skin	Epidermolysis bullosa dystrophica	Collagen VII	ECM protein	–[j]
Skin	Herlitz's junctional epidermolysis bullosa	Laminin V(γ2)	ECM protein	–[k]
Skin	Junctional epidermolysis bullosa	Integrin α6	ECM receptor	–[l]

Abbreviation: ECM, extracellular matrix.

References: [a]Ballabio, A. and Camerino, G. (1992) *Curr. Opin. Genet. Dev.* 2, 417–421; [b]D'Arcangelo, G. *et al.* (1995) *Nature* 374, 719–723; [c]Weber, B. H. *et al.* (1994) *Nat. Genet.* 8, 352–356; [d]Byers, P. H. (1990) *Trends Genet.* 6, 293–300; [e]Guicheney, P. *et al.* (1997) *Neuromuscular Disord.* 7, 180–186; [f]Henry, M. D. and Campbell, K. P. (1996) *Curr. Opin. Cell Biol.* 8, 625–631; [g]Dietz, H. C. and Pyeritz, R. E. (1995) *Hum. Mol. Genet.* 1799–1809; [h]Kashtan, C. E. and Michael, A. F. (1996) *Kidney Int.* 50, 1445–1463; [i]Zhou, J. *et al.* (1993) *Science* 261, 1167–1179; [j]Korge, B. P. and Krieg, T. (1996) *J. Mol. Med.* 74, 59–70; [k]Aberdam, D. *et al.* (1994) *Nat. Genet.* 6, 299–304; [l]Pulkkinen, L. *et al.* (1997) *Hum. Mol. Genet.* 6, 669–674.

ECM and cells and cannot be observed on a planar ECM substrate[14], suggesting that one key feature of ECM signalling might reside in defining the spatial organization of cells within tissues, such that cell shape, intercellular spacing and three-dimensional positioning of the cells become additional factors determining cellular responses to regulatory signals. A recently identified ECM signalling pathway that depends on both the structure and proteolytic degradation of the ECM is represented by tyrosine kinases of the discoidin domain receptor (DDR) family. Intact collagen ligands, but not denatured collagen, specifically activate the DDR kinase activity and phosphorylation, followed by the induction of collagenase-1. Interestingly, collagenase-1-mediated cleavage of collagen (but not its nonspecific proteolysis) abrogates the receptor activation, thus creating a unique, specific negative-feedback regulatory loop that might provide a novel mechanism of ECM remodelling[15,16].

Malignant phenotype: an ECM signalling disorder?

The ECM signalling mechanisms elucidated in *in vitro* models play a significant role in disease processes in which cell–ECM interactions are altered. One example of such significance is the evidence that alterations in the spectrum of molecules involved in cell–ECM interactions constitute an integral part of the mechanism that regulates malignant transformation of cells. Transformed cells are generally characterized by decreased expression of ECM proteins, ECM receptors and cytoplasmic components of adhesion plaques. The downregulation of these molecules is important for transformation in a variety of cell types because restoration of their levels reverts features of the tumorigenic phenotype such as abnormal cell morphology, anchorage-independent growth and the ability to form tumours in transplantation models[17]. For example, exogenous fibronectin restores normal cell morphology and cytoskeletal organization in Src-transformed fibroblasts in culture[18,19], and, *in vivo*, enhanced fibronectin matrix assembly inhibits tumorigenesis and metastasis[20]. In a similar fashion, transformation with Ras causes selective downregulation of the collagen α2(I) chain, and its re-expression inhibits anchorage-independent growth, invasion and transformation-specific transcription of the VL30 transposon[21]. The malignant cellular phenotype can also be suppressed by cellular components of ECM-cytoplasmic linkages. Overexpression of the α5β1 and α3β1 integrins inhibits the tumorigenic phenotype and metastatic capacity of several tumour cell lines[22–24], and overexpression of the adhesion-plaque proteins vinculin and α-actinin decreases the tumorigenic potential of oncogene-transformed fibroblasts (reviewed in Ref. 17).

Just as certain cell–ECM interactions provide a mechanism that inhibits the tumorigenic cellular

phenotype, a different set of such interactions can enhance its manifestation in a specific cellular context, as illustrated by experimental modulation of integrin ECM receptors. Overexpression of the α2β1 integrin in a rhabdomyosarcoma cell line increases its tumorigenic and metastatic potential[23], and β1 integrins promote the tumorigenic phenotype of mammary carcinoma cells[25]. Although the molecular mechanisms involved in this regulation are largely unknown, they might involve protein kinases regulated by integrins. Persistent deregulated activation of the focal-adhesion kinase (pp125FAK) induces tumorigenic transformation of epithelial cells[26]. Overexpression of another integrin-associated protein kinase, ILK, produces a similar effect, activating anchorage-independent growth[27]. Thus, the regulatory contribution of ECM signalling in the expression of the malignant cellular phenotype can vary depending on the cell type, the state of other signalling mechanisms and the cellular context of the ECM signals.

Altered cell–ECM interactions not only regulate malignant transformation *in vitro* but also appear to contribute to the development of tumours *in vivo*. Mutations in the α5(IV) and α6(IV) collagen chains are associated with benign smooth muscle tumours[28], and individuals with mutations in the gene encoding collagen VII show a marked predisposition to skin carcinomas[29]. Colon tumorigenesis is regulated by the *Mom* modifier gene encoding the secreted phospholipase PLA2[30]. Interestingly, the membrane receptor for PLA2[31] promotes cell adhesion to collagens I and IV[32], and its physical interaction with PLA2 can regulate cell shape, proliferation, motility and invasion[33], suggesting that modulation of cell–ECM interactions, at least in part, mediates functions of Mom as a genetic modifier of tumour progression.

The proteolytic turnover of the ECM mediated by ECM-degrading MMPs is another important factor in the regulation of tumorigenesis. Overexpression of collagenase in the skin of transgenic mice enhances chemically induced carcinogenesis[34], and stromelysin-1 can trigger mammary epithelial cell transformation and tumorigenesis[35,36]. Conversely, ablation of the gene encoding matrilysin decreases intestinal tumour formation in mice heterozygous for the *Apc* tumour suppressor gene[37], and loss of stromelysin-3 inhibits chemical carcinogenesis and stroma-dependent tumour implantation[38]. In accordance with these observations, the MMP inhibitor TIMP-1 inhibits tumour progression and dissemination in experimental models of carcinoma and lymphoma[39–41]. Taken together, these observations indicate that ECM degradation and the altered cell–ECM interactions that result from it can promote tumour progression.

ECM cooperation with tumour suppressors

Tumour progression is driven by the accumulation of somatic mutations that are selected in the tumour cell population to allow progressive expansion of transformed cells. The importance of the ECM in the regulation of tumour development is emphasized by the evidence that interactions of cells with the ECM can modulate two crucial elements of the genetic basis of tumorigenesis: the cellular response to genotoxic stress and the function of the key tumour suppressors p53 and Rb.

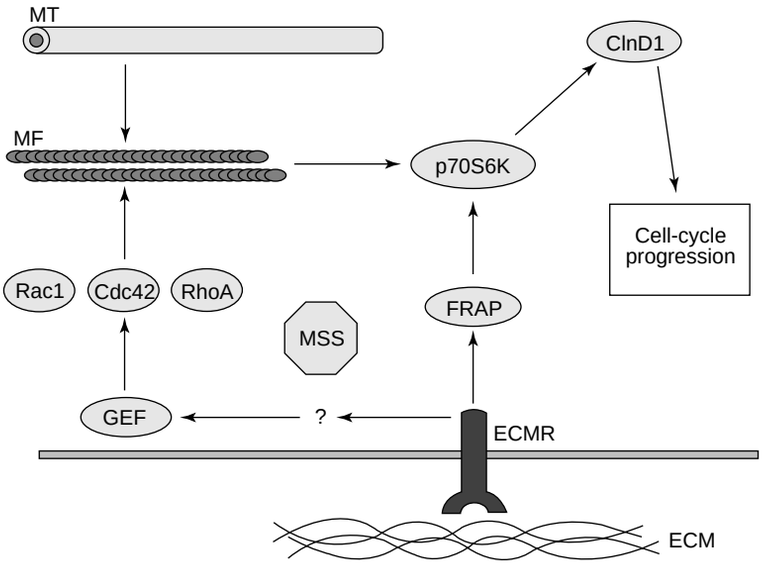

FIGURE 1

Cell shape-dependent regulation of cell-cycle progression by the extracellular matrix (ECM). This figure proposes the working model of a potential signal-transduction mechanism through which the ECM can regulate the activity of p70 ribosomal S6 protein kinase (p70S6K) and cyclin D1 (ClnD1) expression. Cell adhesion to the ECM, mediated by the ECM receptors (ECMRs), leads to p70S6 activation through two pathways: activation of the FK506-binding protein/rapamycin-associated protein (FRAP; reviewed in Ref. 66) and modulation of microfilament (MF) organization through the activation of Rho-family small GTPases (RhoA, Cdc42 and Rac1). According to the proposed model, the regulation of MFs might be mediated by an as-yet-uncharacterized mechanical stress sensor (MSS) that regulates the activity of GDP–GTP exchange factors controlling the activation state of the small Rho-like GTPases. The function of the regulatory mechanism outlined in this scheme is likely to be modulated by the microtubules (MTs) through the regulation of the assembly and organization of MFs and MF-associated focal adhesions.

The response to DNA damage is a crucial determinant of the plasticity of the cellular genome and depends on signalling mechanisms that regulate the cell cycle and apoptosis. Cell adhesion to the ECM modulates several of these mechanisms, including the SAPK/JNK, c-Abl and p53 pathways[42–44]. Like DNA damage-induced apoptosis, the apoptosis induced by loss of cell–ECM contact is accompanied by JNK activation and is mediated by p53 and Rb[42–46]. Cell–ECM interactions modulate a crucial step in the control of Rb function, its phosphorylation through the upregulation of cyclin D1[47], and regulate the transcriptional activity, nuclear translocation and protein levels of p53[48–50]. The significance of this regulation for the genotoxic stress response is illustrated by evidence that interactions with the ECM can define the mode of cellular response to DNA-damaging agents. In keratinocytes, integrin-mediated adhesion to the ECM activates a p53-dependent apoptotic pathway in response to UV irradiation, whereas inhibition of integrins blocks this pathway and triggers p53-independent apoptosis[43]. The mechanisms of the p53-dependent regulation of cell survival by the ECM might differ in different cell types. In endothelial cells, in which

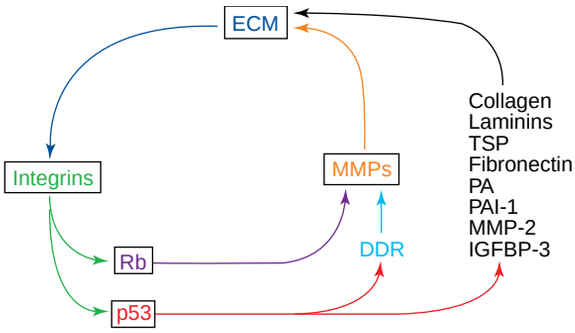

FIGURE 2

The extracellular matrix (ECM) and the tumour suppressors p53 and Rb form regulatory feedback loops. The ECM and integrins regulate the phosphorylation of Rb and the transcriptional activity, translocation and degradation of p53. Rb regulates the expression of ECM-degrading matrix metalloproteases (MMPs), whereas p53 regulates cell–ECM interactions and the state of the ECM through transcriptional control of ECM proteins and mediators of cell–ECM contact and ECM remodelling. Abbreviations: DDR, discoidin domain receptor; IGFBP-3, insulin-like growth factor binding protein 3; PA, plasminogen activator; PAI-1, plasminogen activator inhibitor 1; Rb, retinoblastoma protein; TSP, thrombospondin.

integrin-mediated adhesion has been shown to inhibit p53 activation[49], cell adhesion to ECM and integrin activation suppress cell death induced by cytotoxic and genotoxic agents[51]. In fibroblasts, anchorage to the ECM promotes 'irreversible' growth arrest in response to X irradiation, and transient disruption of substrate adhesion allows the arrested cells to re-enter the cell cycle[52]. Interestingly, the sensitivity of cells to ionizing radiation can also be modulated by the spatial structure of the ECM environment and by the state of cytoskeletal structures[53].

The regulatory cooperation of the ECM with the tumour suppressors p53 and Rb might be as physiologically significant as the more extensively characterized cross-talk between the ECM and oncogenes. This cooperation is reciprocal in that both tumour suppressors are not only regulated by ECM but also regulate cell–ECM interactions (Fig. 2). Active Rb suppresses, and its loss stimulates, invasion of the ECM by tumour cells, while having little apparent effect on the migration rate of the cells[54]. Experimental inactivation of Rb by the SV40 large T protein also stimulates invasive activity and alters expression of MMPs[55], suggesting that regulation of MMP expression is one mechanism through which Rb controls cell invasion. Like Rb, p53 also regulates invasion and expression of ECM-degrading proteases. Overexpression of p53 suppresses, and its inactivation by the HPV 18 E6 gene product stimulates, cell invasiveness[56]. The transcriptional targets of p53 include plasminogen activators and their inhibitor PAI-1[57,58], MMP-2[59] and the MMP-1-inducing collagen receptor DDR1[60]. One interesting aspect of this regulation is that, in keeping with its tumour-suppressor function, p53 represses expression of the plasminogen activators that are key promoters of ECM degradation and cell invasion and upregulates their inhibitor PAI-1[57,58]. In a similar fashion, p53 activates the expression of thrombospondin, which inhibits tumour growth by blocking angiogenesis and suppresses the expression of its tumour-growth-promoting counterpart fibronectin[61,62]. Although the functional significance of these findings awaits experimental verification, consensus p53-binding sites have been found in several other genes encoding ECM proteins, including tenascin X, tropoelastin, collagens α2(VI), α2(IX), α1(VI), α1(II) and type IV[63], suggesting that regulation of ECM components might be a generally important regulatory function of p53. Therefore, p53 is an important player in ECM signalling that both regulates interactions of cells with the ECM and participates in the interpretation of ECM-derived signalling cues.

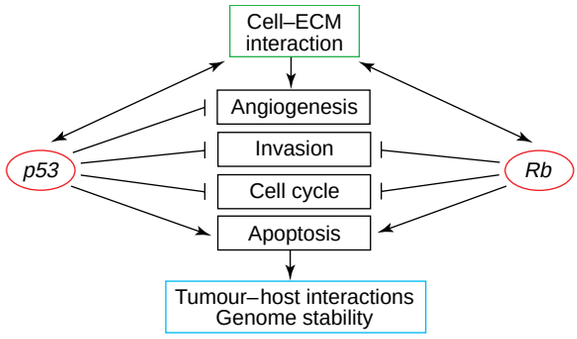

FIGURE 3

The extracellular matrix (ECM) and the tumour suppressors p53 and Rb cooperate in the regulation of tumorigenesis. Both p53 and Rb mediate the regulation of ECM-dependent processes such as cell-cycle progression, programmed cell death, invasion and angiogenesis. By regulating the cell cycle and apoptosis, the ECM can modulate the maintenance of genome stability, whereas ECM-dependent regulation of invasion and angiogenesis form the basis of tumour–host interactions and metastasis.

Although the above data show that the ECM can regulate a number of important processes that are thought to control tumour initiation and progression, the significance of extensive ECM remodelling during tumorigenesis is not clear. One tantalizing finding comes from the observation that mutations in p53 can occur at high frequency in nonmalignant connective tissue disease. Rheumatoid arthritis (RA) is a disease that is largely driven by extensive degradation of the ECM in the synovium and is characterized by aberrant growth regulation of synovial fibroblasts, which, like transformed cells, become invasive and capable of anchorage-independent growth. Synovial fibroblasts from RA patients express abnormally high levels of p53 and display a high frequency of potentially inactivating mutations in this gene – features typical of malignant tumour cells. The spectrum of p53 mutations found in RA synovial fibroblasts is remarkably similar to that of malignant tumours, and their pattern is consistent with the metabolic DNA damage by reactive oxygen species (ROS) that has been implicated as a major source of mutations associated with tumorigenesis[64]. Because the production of ROS can be stimulated by integrins through the induction of ECM-degrading proteases and release of ECM fragments or as a proximal event following integrin

engagement (see Ref. 65 and references therein), it is tempting to speculate that cell–ECM interactions and ECM remodelling could provide a mechanism for ROS-mediated mutational inactivation of p53.

The convergence of signal-transduction pathways regulated by the ECM, p53 and Rb shows that the ECM can play a dual role as a regulator and mediator of tumour-suppressor functions. The above data suggest a model, in which the ECM cooperates with tumour suppressors in the regulation of the cell cycle, apoptosis, DNA-damage response, invasion and angiogenesis, which are central to the control of genome plasticity and tumour–host interactions (Fig. 3). According to this scheme, aberrant cell–ECM interactions might cause misregulation of the cell cycle and apoptosis and possibly even lead to the mutational inactivation of p53, thus compromising a key mechanism maintaining genome stability. At the same time, appropriate regulation of genes involved in cell–ECM interaction by the tumour suppressors should provide a set of safeguards of the normal cellular microenvironment and phenotype.

Concluding remarks

Regulatory cues provided by the ECM are essential for the formation and normal function of tissues, and mechanisms that mediate ECM signalling contribute to a broad range of diseases, ranging from developmental abnormalities to cancer. Recent studies have shown that ECM signals feed into central signalling cascades that operate in cytoskeletal organization, cell-cycle checkpoint control, apoptosis, gene expression and genome plasticity. However, it is still unclear what cytoskeletal and other molecules form the machinery allowing cells to sense three-dimensional and mechanical properties of the ECM. Similarly, the precise mechanisms through which the ECM mediates the functions of tumour suppressors, as well as the molecular pathways involved in the development of genomic instability as a result of altered cell adhesion, are yet to be characterized in detail. Clarification of these mechanisms of ECM signalling is of major importance for our understanding of tissue biology in health and disease and will be an exciting area for research efforts in the years to come.

References

1 Werb, Z. (1997) *Cell* 91, 439–442
2 Hynes, R. O. (1996) *Dev. Biol.* 180, 402–412
3 Assoian, R. K. and Zhu, X. (1997) *Curr. Opin. Cell Biol.* 9, 93–98
4 Re, F. *et al.* (1994) *J. Cell Biol.* 127, 537–546
5 Chen, C. S. *et al.* (1997) *Science* 276, 1425–1428
6 Mooney, D. *et al.* (1992) *J. Cell Physiol.* 151, 497–505
7 Howe, A. *et al.* (1998) *Curr. Opin. Cell Biol.* 10, 220–231
8 Thomas, G. and Hall, M. N. (1997) *Curr. Opin. Cell Biol.* 9, 782–787
9 Koyama, H. *et al.* (1996) *Cell* 87, 1069–1078
10 Malik, R. K. and Parsons, J. T. (1996) *J. Biol. Chem.* 271, 29785–29791
11 Chou, M. M. and Blenis, J. (1996) *Cell* 85, 573–583
12 Bickle, M. *et al.* (1998) *EMBO J.* 17, 2235–2245
13 Bershadsky, A. *et al.* (1996) *Curr. Biol.* 6, 1279–1289
14 Boudreau, N., Werb, Z. and Bissell, M. J. (1996) *Proc. Natl. Acad. Sci. U. S. A.* 93, 3509–3513
15 Vogel, W. *et al.* (1997) *Mol. Cell* 1, 13–23
16 Shrivastava, A. *et al.* (1997) *Mol. Cell* 1, 25–34
17 Ben-Ze'ev, A. (1997) *Curr. Opin. Cell Biol.* 9, 99–108
18 Hynes, R. O. *et al.* (1979) *J. Supramol. Struct.* 11, 95–104
19 Yamada, K. M. and Olden, K. (1978) *Nature* 275, 179–184
20 Ruoslahti, E. (1996) *Tumour Biol.* 17, 117–124
21 Travers, H., French, N. S. and Norton, J. D. (1996) *Cell Growth Differ.* 7, 1353–1360
22 Giancotti, F. G. and Ruoslahti, E. (1990) *Cell* 60, 849–859
23 Chan, B. M. *et al.* (1991) *Science* 251, 1600–1602
24 Weitzman, J. B., Hemler, M. E. and Brodt, P. (1996) *Cell Adhes. Commun.* 4, 41–52
25 Weaver, V. M. *et al.* (1997) *J. Cell Biol.* 137, 231–245
26 Frisch, S. M. *et al.* (1996) *J. Cell Biol.* 134, 793–799
27 Radeva, G. *et al.* (1997) *J. Biol. Chem.* 272, 13937–13944
28 Zhou, J. *et al.* (1993) *Science* 261, 1167–1169
29 Slater, S. D. *et al.* (1992) *Histopathology* 20, 237–241
30 MacPhee, M. *et al.* (1995) *Cell* 81, 957–966
31 Lambeau, G. *et al.* (1994) *J. Biol. Chem.* 269, 1575–1578
32 Ancian, P., Lambeau, G. and Lazdunski, M. (1995) *Biochemistry* 34, 13146–13151
33 Kundu, G. C. and Mukherjee, A. B. (1997) *J. Biol. Chem.* 272, 2346–2353
34 D'Armiento, J. *et al.* (1995) *Mol. Cell. Biol.* 15, 5732–5739
35 Sympson, C. J., Bissell, M. J. and Werb, Z. (1995) *Semin. Cancer Biol.* 6, 159–163
36 Lochter, A. *et al.* (1997) *J. Cell Biol.* 139, 1861–1872
37 Wilson, C. L. *et al.* (1997) *Proc. Natl. Acad. Sci. U. S. A.* 94, 1402–1407
38 Masson, R. *et al.* (1998) *J. Cell Biol.* 140, 1535–1541
39 Kruger, A., Fata, J. E. and Khokha, R. (1997) *Blood* 90, 1993–2000
40 Martin, D. C. *et al.* (1996) *Oncogene* 13, 569–576
41 Soloway, P. D. *et al.* (1996) *Oncogene* 13, 2307–2314
42 Cardone, M. H. *et al.* (1997) *Cell* 90, 315–323
43 Gniadecki, R., Hansen, M. and Wulf, H. C. (1997) *J. Invest. Dermatol.* 109, 163–169
44 Nikiforov, M. A. *et al.* (1996) *Oncogene* 13, 1709–1719
45 McGill, G. *et al.* (1997) *J. Cell Biol.* 138, 901–911
46 Day, M. L. *et al.* (1997) *J. Biol. Chem.* 272, 8125–8128
47 Assoian, R. K. (1997) *J. Cell Biol.* 136, 1–4
48 Nigro, J. M. *et al.* (1997) *Cancer Res.* 57, 3635–3639
49 Stromblad, S. *et al.* (1996) *J. Clin. Invest.* 98, 426–433
50 Bates, R. C. *et al.* (1994) *J. Cell Biol.* 125, 403–415
51 Hoyt, D. G. *et al.* (1996) *Cancer Res.* 56, 4146–4149
52 Gadbois, D. M., Bradbury, E. M. and Lehnert, B. E. (1997) *Cancer Res.* 57, 1151–1156
53 Stevenson, A. F. and Lange, C. S. (1997) *Acta Oncol.* 36, 599–606
54 Li, J. *et al.* (1996) *Oncogene* 13, 2379–2386
55 Hansell, E. J. *et al.* (1995) *Biochem. Cell Biol.* 73, 373–389
56 Aipperle, K. *et al.* (1998) *Am. J. Pathol.* 152, 1091–1098
57 Kunz, C. *et al.* (1995) *Nucleic Acids Res.* 23, 3710–3717
58 Andreasen, P. A. *et al.* (1997) *Int. J. Cancer* 72, 1–22
59 Bian, J. and Sun, Y. (1997) *Mol. Cell. Biol.* 17, 6330–6338
60 Sakuma, S. *et al.* (1996) *FEBS Lett.* 398, 165–169
61 Dameron, K. M. *et al.* (1994) *Cold Spring Harbor Symp. Quant. Biol.* 59, 483–489
62 Iotsova, V. and Stehelin, D. (1996) *Cell Growth Differ.* 7, 629–634
63 Bourdon, J. C. *et al.* (1997) *Oncogene* 14, 85–94
64 Ambs, S., Hussain, S. P. and Harris, C. C. (1997) *FASEB J.* 11, 443–448
65 Kheradmand, F. *et al.* (1998) *Science* 280, 898–902
66 Bottazzi, M. E. and Assoian, R. K. (1997) *Trends Cell Biol.* 7, 348–352

Acknowledgements

Supported by grants from the National Cancer Institute (CA57621), The Bay Area Breast Cancer SPORE (CA58207), the Breast Cancer Research Foundation and a National Research Service Award (ES07106).