BAP31, a resident integral protein of the endoplasmic reticulum membrane, regulates the export of other integral membrane proteins to the downstream secretory pathway. Here we show that cell surface expression of the tetraspanins CD9 and CD81 is compromised in mouse cells from which the Bap31 gene has been deleted. CD9 and CD81 facilitate the function of multiprotein complexes at the plasma membrane, including integrins. Of note, BAP31 does not appear to influence the egress of α5β1 or αvβ3 integrins to the cell surface, but in Bap31-null mouse cells, these integrins are not able to maintain cellular adhesion to the extracellular matrix in the presence of reduced serum. Consequently, Bap31-null cells are sensitive to serum starvation-induced apoptosis. Reconstitution of wild-type BAP31 into these Bap31-null cells restores integrin-mediated cell attachment and cell survival after serum stress, whereas interference with the functions of CD9, α5β1, or αvβ3 by antagonizing antibodies makes BAP31 cells act similar to Bap31-null cells in these respects. Finally, in human KB epithelial cells protected from apoptosis by BCL-2, the caspase-8 cleavage product, p20 BAP31, inhibits egress of tetraspanin and integrin-mediated cell attachment. Thus, p20 BAP31 can operate upstream of BCL-2 in living cells to influence cell surface properties due to its effects on protein egress from the endoplasmic reticulum.

BAP31 is an evolutionarily conserved polytopic integral protein of the endoplasmic reticulum (ER) membrane implicated in regulating the export of selected membrane proteins from the ER to downstream compartments of the secretory pathway. It forms part of a large BAP hetero-oligomeric complex (1–5). Examples of newly synthesized integral membrane proteins in the ER with which the BAP proteins associate and regulate their egress from the organelle include mIgD (5), cellubrevin (6), major histocompatibility complex class I (7, 8), and cystic fibrosis transmembrane conductance regulator (9). Additionally, BAP31 has been shown to regulate the turnover of the resident ER integral membrane protein tyrosine phosphatase-like B and, therefore, may also have a quality control function (10). BAP31 is emerging, therefore, as a putative chaperone/quality control factor that regulates the fate of integral membrane proteins in the ER membrane. Because BAP31 has also been shown to be an important target of caspases in certain apoptosis pathways (2, 11–15), inactivation of this protein might be expected to influence a variety of cellular functions.

Regulation of the transport of newly synthesized integral membrane proteins of the ER has important implications for maintaining the integrity of many cell surface functions, and defects in this process are well known to contribute to numerous diseases (16, 17). In this study, we have investigated the role of BAP31 in maintaining the cell surface expression of small integral membrane proteins called tetraspanins, which are implicated in the regulation of diverse plasma membrane activities. Tetraspanins comprise a large 4-spanning transmembrane super family (TM4SF) of proteins, which have been conserved throughout evolution, are ubiquitously expressed, and include the differentiation antigens CD9, CD81, CD82, and CD151 (18). Tetraspanins have been functionally implicated in different cellular processes, including cell adhesion, migration, cell signaling, metastasis, and growth (18–21). They act as molecular adaptors or facilitators and associate with large cell surface-signaling complexes to form the “tetraspanin web” (18, 22, 23). Among the functions dependent on tetraspanins are those associated with several integrins (α5β1, α4β1, αβ3, α6β1) (20, 22, 24–26), major histocompatibility complex class I and II molecules (27), co-receptors (e.g. CD4 and CD8 antigens on T cells) (28), and other tetraspanins (22). In addition, some TM4SF proteins associate with intracellular signaling molecules on the cytoplasmic side of the plasma membrane, including tyrosine phosphatases (29), phosphatidylinositol 4-kinase (30), and small GTP-binding proteins (31).

Two TM4SF proteins, CD9 and CD81, have been implicated in the maintenance of functional integrins at the cell surface (20, 24, 26), transmembrane receptors that function in cell adhesion, migration, proliferation, differentiation, and survival (32, 33). The integrin family comprises non-covalent heterodimers of different type I transmembrane protein subunits called α and β, which facilitate cell adhesion to extracellular matrix (ECM) substrates, including fibronectin (α5β1 and α4β1), laminin (αβ3β1), and collagens (αβ2β1) (33, 34). The ability of integrins to decrease or increase binding of cells to ECM ligands depends on the transition between inactive and active conformations of these receptors (35). Cellular factors known to induce the activation of integrins include inside-out signaling pathways, integrin clustering, the concentration of Mg2+ and Mn2+ in the extracellular medium, and temperature (35–38). Additionally, specific “activating” and “antagonizing” monoclonal antibodies have been generated that induce a high af-

* This work was supported by the Canadian Institutes of Health Research and the National Cancer Institute of Canada through funds provided by the Canadian Cancer Society. The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† To whom correspondence should be addressed: Dept. of Biochemistry, McIntyre, Medical Sciences Bldg., McGill University, 3655 Promenade Sir William Osler, Montreal, Quebec H3G 1Y6, Canada. Tel.: 514-398-7282; Fax: 514-398-7384; E-mail: gordon.shore@mcgill.ca.

‡ Recipient of the Canadian Institutes of Health Research Doctoral Research award.

§ Recipient of the Canadian Institutes of Health Research Doctoral Research award.

¶ Recipient of the Canadian Institutes of Health Research Doctoral Research award.

1 The abbreviations used are: ER, endoplasmic reticulum; ECM, extracellular matrix; FBS, fetal bovine serum; FACS, fluorescence-activated cell sorter; PBS, phosphate-buffered saline.
Regulation of Cell Surface Activities by BAP31

EXPERIMENTAL PROCEDURES

Cell Culture, Antibodies, Reagents, and Viral Infection—A C57BL/6 mouse embryonic stem cell line was generated following deletion of the Bap31 gene by homologous recombination and differentiated into epithelial-like cells (13). The cells were reconstituted with plasmid stably expressing either neomycin (Bap31-null) or Bap31-FLAG (10) and the cell lines maintained at 37 °C and 5% CO2 in KNOCKOUT Dulbecco’s modified Eagle’s medium (Invitrogen) supplemented with 15% FBS, 1 mm minimal essential medium, nonessential amino acids, 2 mm l-glutamine, 100 units/ml streptomyein sulfate and penicillin, and 1 mm β-mercaptoethanol. KB epithelial cells stably expressing BCL-2 (Bcl-2 cells) have been described previously (51). The following antibodies were used in this study: chicken or rabbit anti-human BAP31 (10); rat anti-mouse CD9 (clone KM8) (Research Diagnostics, Inc.); hamster anti-mouse CD81/TAPA1 (clone EAT2) (eBioscience); mouse anti-β3 actin (clone C4) (ICN Pharmaceuticals); rabbit anti-mouse CD29 (integrin αv, clone H-104) (Santa Cruz Biotechnology); goat anti-mouse CD49e (clone α5, clone H9.2B8) (BD Biosciences); goat anti-mouse CD49b (clone α2, clone Ha1/29) (BD Biosciences); goat anti-mouse CD49a (clone α1, clone K1) (BD Biosciences); goat anti-mouse CD49f (clone α6, clone 5H10-27) (BD Biosciences); rat anti-mouse CD49e (clone H9.2B8) (BD Biosciences); rat anti-mouse CD90 (clone 3D1) (BD Biosciences); mouse anti-β1 integrin (clone 3F1) (ICN Pharmaceuticals); hamster anti-mouse CD81 (clone 3F1) (ICN Pharmaceuticals); mouse anti-β2 integrin (clone 12G5) (BD Biosciences); mouse anti-β3 integrin (clone 1D4) (BD Biosciences); goat anti-mouse CD29 (clone 2C9.G2) (BD Biosciences); mouse anti-BCL-2 (clone 12C10) (BD Biosciences); goat anti-BAX (clone 1E12) (Santa Cruz Biotechnology). The cells were visualized by conventional fluorescence microscopy using an inverted microscope (TE-FM Epi-fl, Nikon).

Fluorescence Microscopy—Cells were seeded at 60% confluency on glass coverslips, and then 24 h later were washed in PBS and fixed in 4% paraformaldehyde, 23 mM NaH2PO4, and 77 mM Na2HPO4, pH 7.3. Cells were permeabilized in PBS/0.2% Triton X-100 and then incubated in blocking buffer (10% fetal calf serum and 0.1% Triton X-100 in PBS). Primary and secondary antibody incubations were done in blocking buffer for 1 h each at room temperature using the indicated antibody and goat anti-mouse IgG secondary antibody coupled to Alexa 488 (green) (Molecular Probes, Inc.).

Purification of ECM and Cell Adhesion Assays—The ECM secreted by the BL6 parental cell line was extracted as follows: 1 × 106 cells/cm2 were seeded in 24-well tissue culture plates and cultured for 4 days. Confluent cultures were washed twice with cold PBS, incubated for 10 min with 0.5% Triton X-100 in PBS on ice to remove cell membranes, and another 10 min with 0.25 mM ammonium acetate to remove remaining nuclei and cytoskeleton. The remaining ECM was washed twice with ice-cold PBS and incubated overnight with a solution of 1% bovine serum albumin at 4 °C to cover exposed plastic surfaces. The ECM was washed once with serum-free medium before use in the adhesion assays. To measure cell-ECM adhesion, confluent Bap31-null/Neo and Bap31-null/BAP31-FLAG cell cultures were collected by light trypsinization, incubated at 37 °C in general medium for 1 h, washed three times with serum-free medium, and suspended at a concentration of 4 × 105 cells/ml in serum-free medium. 0.25 ml/well of each cellular suspension was added to purified ECM, incubated for 1 h at 37 °C, and

finity/avidity conformational change upon binding to particular integrin epitopes (39, 40). Moreover, the activation state of integrins, including α5β1, can be monitored by monoclonal antibodies that recognize conformation-dependent integrin epitopes that become exposed only upon changes in integrin conformations associated with changes in the affinity/avidity for ligand (41, 42). Some members of the β1 integrin subfamily, including α5β1 (VLA-5), have been found associated with CD9 and CD81 in the tetraspanin web (20, 24, 43). Consistent with this, CD81 has also been implicated in the regulation of α5β1 adhesion strengthening in monocytes and primary mouse B cells (20). Tetraspanins can both increase and decrease β1 integrin-mediated cell adhesion when challenged with specific monoclonal antibodies against tetraspanins (20, 44–46). Moreover, tetraspanins contribute to adhesion-dependent signaling by stimulating recruitment of signaling molecules, such as protein kinase C and phosphoinositide 3-kinase, into integrin complexes on the cytoplasmic side of the plasma membrane (47, 48). Changes in integrin-mediated signaling in response to serum starvation, for example, interferes with integrin-transduced survival pathways, alters cytoskeletal organization, and induces a form of programmed cell death called anoikis (49). Cells with non-functional or improperly activated integrins are more susceptible to anoikis (30, 50).

Here we show by gene deletion that BAP31 controls the egress of tetraspanins CD9 and CD81 to the cell surface and, in so doing, indirectly regulates integrin-mediated cell attachment and survival. In the Fas death pathway, BAP31 is a target of caspase-8, generating p20 BAP31, which induces a pro-apoptotic ER-mitochondrial pathway inhibited by pro-survival BCL-2 (2, 14). Of note, p20 BAP31 can also operate upstream of BCL-2 in BCL-2-protected living cells to inhibit egress of tetraspanin to the cell surface and compromise integrin-mediated cell attachment. This novel finding argues that the caspase cleavage product of BAP31 can regulate important cell surface events in cells protected from cell death.
Deletion of BAP31 Affects the Surface Expression of Tetrarpsins CD81 and CD9—To investigate the contribution of BAP31 to the cell surface expression of CD81 and CD9, we employed a differentiated C57BL/6 embryoid epithelial-like mouse cell line deleted of the BAP31 gene and stably transfected with plasmid expressing either neo (Bap31-null) or wild-type BAP31-FLAG (Bap31-null/BAP31) (10) (Fig. 1A). For the cell line expressing the wild-type BAP31-FLAG cut-back, the expression level of the BAP31-FLAG was similar to the level of Bap31 found in parental C57BL/6 cells. Bap31-null cells were found to express total cellular CD81 and CD9 at levels similar to that of Bap31-null/BAP31 cells, as judged by immunoblotting (Fig. 1B). In contrast, FACS analysis using anti-CD9 and anti-CD81 indicated a significant reduction in the cell surface levels of these proteins in cells lacking Bap31 (Fig. 1C). Consistent with the FACS analysis, immunofluorescence micros-
copy showed that CD9 was enriched and punctuated at the cell surface in Bap31-null/BAP31 cells, but in Bap31-null cells, it was enriched in a perinuclear region of the cell (Fig. 1D). The CD81 antibody was not adequate for this analysis. The results indicate, therefore, that BAP31 does not influence the total amount of CD9 and CD81 expressed by these cells but that BAP31 is required to maintain expression of CD9 and CD81 at the cell surface.

BAP31 Promotes Cell Adhesion to Fibronectin without Affecting Cell Surface Expression of α5β1 and αvβ3 Integrins—In view of the fact that CD9 and CD81 are adaptors that influence the activation status of select integrins at the cell surface, we surveyed the Bap31- and Bap31-null/BAP31 cells for their ability to manifest integrin-mediated properties, including attachment to the ECM. To that end, cell culture plates were coated with purified ECM or fibronectin (the component of the ECM that is recognized by α5β1 and αvβ3 integrins). As documented in Fig. 2A, Bap31-null/BAP31 cells displayed a significantly higher cell binding to both ECM and fibronectin compared with Bap31-null cells, whereas the two cell lines bound equally well to poly-L-lysine-coated plates. In contrast to CD9 and CD81, however, overall expression of the two main fibronectin integrin receptors at the cell surface, α5β1 and αvβ3, was not significantly different in either cell line, as demonstrated by flow cytometry; if anything, Bap31-null cells expressed slightly more α5 subunit than did Bap31-null/BAP31 cells (Fig. 2B). Thus, the absence of BAP31 decreases cell adhesion to ECM and fibronectin with no apparent effect on the cell surface expression of α5β1 and αvβ3 integrins.

Blocking Cell Surface CD9 Inhibits Attachment of Bap31-null/BAP31 Cells to Fibronectin—To examine the possibility that the reduction in cell attachment to fibronectin in the absence of BAP31 expression was because of the reduced expression of tetraspanin at the surface of these cells, we explored the use of antibodies known to interfere with the function of tetraspanin. Only one antibody was identified that binds and functionally neutralizes certain CD9 functions in mouse (52). When added to Bap31-null/BAP31 cells, this anti-CD9 antibody reduced the binding of these cells to fibronectin, whereas a control antibody (anti-α2) did not (Fig. 2C). Anti-CD9, therefore, recapitulated the reduction in the integrin-mediated cell attachment that was observed due to targeted deletion of Bap31, suggesting that BAP31 maintains integrin function by promoting tetraspanin expression at the cell surface.

BAP31 Promotes Cell Attachment by Maintaining Integrin Activity—The Bap31-null and Bap31-null/BAP31 cells are dif-
ferentiated epithelial-like cells, and epithelial cells are known to require α5β1 and/or αvβ3 for their attachment to fibronectin (20, 53). To further confirm that these integrins were functional in BAP31-expressing cells, treatment of cells with integrin-blocking antibodies, which bind to the activated conformers of α5β1 or αvβ3 integrins and inhibit their interactions with the ECM (53), were examined. Indeed, when Bap31-null/BAP31 cells were plated on fibronectin in the presence of inhibiting antibody to either α5 and αv integrin subunits, cell adhesion was decreased by half (Fig. 3). Thus, BAP31 maintains integrin activation to facilitate cell attachment to ECM. The fact that anti-α5 antibody also retarded the residual binding of Bap31-null cells to fibronectin suggests that inhibition of α5β1 function following deletion of Bap31 was not absolute.

**BAP31-expressing Cells Resist Apoptosis Triggered by Serum Deprivation**—Many types of cells, including epithelial cells, require appropriate cell-ECM interactions for survival, and they undergo apoptosis in response to stimuli, such as serum depletion, when these anchorage-dependent interactions are lost (54, 55). Our finding that BAP31 is required to maintain integrin activity at the cell surface suggests that BAP31 should also confer resistance to serum starvation-induced cell death. This was tested by plating Bap31-null and Bap31-null/BAP31 cells in serum-reduced medium and examining their morphology by light microscopy. Bap31-null cells displayed typical apoptotic morphological changes, such as rounding, condensation, and detachment, whereas the majority of Bap31-null/BAP31 cells remained attached and well spread even after 42 h of serum starvation (Fig. 4A). In addition to changes in cell morphology, Bap31-null cells (but not Bap31-null/BAP31 cells) displayed a strong induction of effector caspase (DEVDase) activity after 42 h of exposure to low serum (Fig. 4B), which was the time at which maximal DEVDase activity was observed (not shown). This was associated with loss of plasma membrane asymmetry, as demonstrated by annexin V staining (Fig. 4C). The results demonstrated that Bap31-null cells are susceptible to apoptosis in response to serum deprivation and that reconstitution of wild-type BAP31 in these cells maintains resistance to this apoptotic stimulus.

**Bap31-null/BAP31 Cells Die in Response to Serum Deprivation after Functional Inhibition of Integrins**—To confirm that cell surface expression of α5β1 and/or αvβ3 in Bap31-null/BAP31 cells confers resistance to serum starvation-induced cell death, we investigated this stress response in Bap31-null/BAP31 cells in either the presence or the absence of antibodies against α5 and αV, which are known to antagonize the function of the respective integrin. The cells were cultured in medium containing 0.5% FBS without (control) or with blocking antibodies, and the samples were analyzed after 0 and 48 h. Induction of apoptosis was monitored by the appearance of DEVDase activity. As shown in Fig. 5, serum withdrawal induced DEVDase activity only in Bap31-null/BAP31 cells treated with blocking antibodies to α5 or αV. Thus, interference with functional α5β1 or αvβ3 in cells expressing wild-type BAP31 recapitulated the sensitivity of Bap31-null cells to serum starvation, arguing that maintenance of functional cell surface integrins by BAP31 confers cell survival in response to serum deprivation.

**The Caspase-8 Cleavage Product of BAP31 Inhibits Egress of CD9 to the Cell Surface in Human Epithelial Cells Protected by BCL-2**—BAP31 is cleaved by caspase-8 following activation of the Fas death pathway upstream of the BCL-2-regulated mitochondrial apoptosis pathway (2, 4, 11, 14) (Fig. 6A). The resulting p20 BAP31 product remains at the ER where it strongly interacts with full-length, uncleaved BAP31 and, independently of this association, initiates a BCL-2-inhibitable pathway that results in mitochondrial fragmentation and sensitization of the organelle to other pro-apoptotic stimuli (4, 14). To determine whether the caspase cleavage product of BAP31 influences egress of tetrastasps to the cell surface independently of other potential changes caused by Fas stimulation, p20 BAP31 was ectopically expressed in human KB epithelial cells employing an adenovirus vector (14) (Fig. 6B). To prevent p20-induced mitochondrial apoptosis, these cells also stably overexpressed BCL-2 (51). At 24 h post-infection with Adp20, the caspase-8/7 target p130Cas remained intact (Fig. 6B), and <5% of these p20-expressing cells were scored as apoptotic (Fig. 6D). FACS analysis of the cells revealed, however, that, compared with control adenovirus vector (Ad rTαa), p20 BAP31 had indeed interfered with expression of CD9 at the cell surface (Fig. 6C). Similar analyses of CD81 were not conducted because of the quality of the antibody recognizing the human protein. Consequently, Adp20 caused a reduction in cell attachment to fibronectin (Fig. 6E). Because these cells also expressed full-length BAP31 (Fig. 6B), the results clearly showed that the p20 cleavage product is a dominant-interfering protein that compromises the ability of BAP31 to maintain cell surface expression of tetrastasps.

In conclusion, we have provided evidence that, similar to mIgD (5), cystic fibrosis transmembrane conductance regulator (9), and major histocompatibility complex class I (7, 8), cell surface expression of the tetraspanins CD9 and CD81 is regulated by BAP31, a resident chaperone located in the ER membrane. As shown here, loss of BAP31 function, although not lethal to differentiated epithelial-like mouse embryonic stem cells, does have predictable outcomes in terms of influencing complex pathways that are expressed at the cell surface. Although loss of BAP31 did not manifest in transport defects of α5β1 or αvβ3 integrins to the cell surface, for example, the compromised transport of CD9 and CD81 tetraspanins indirectly affected the functional integrity of these integrins. As a result, loss of BAP31 correlated with increased sensitivity to the induction of apoptosis by serum starvation. An additional outcome of these findings is the fact that BAP31 exhibits selectivity for the transmembrane proteins which egress out of the ER it supports. Interrogating differences between BAP31-
dependent and -independent mechanisms will be important to better understand the export of newly synthesized integral membrane proteins.

Importantly, BAP31 itself is a target of regulation during the cellular response to death receptor stimulation (2, 4). Activation of caspase-8 is a proximal event following death receptor stimulation and results in cleavage of BAP31 upstream of the mitochondrial death pathway, destroying its ability to resist Fas-mediated cell death (2, 4, 11). Conversely, the cleavage product is pro-apoptotic and induces a rapid release of ER Ca\(^{2+}\), initiating a pathway that sensitizes mitochondria to apoptotic stimuli (11, 14). In type II epithelial cells, overexpression of BCL-2 prevents cell death induced by Fas stimulation, because the mitochondrial death pathway and ER Ca\(^{2+}\)-release

**Fig. 6.** The p20 caspase cleavage product of BAP31 lowers cell surface expression levels of CD9 and inhibits adhesion to fibronectin in the absence of apoptosis. A, schematic of BAP31 cleavage by caspase-8; the overlapping death effector-like, coiled-coil domain is designated as DECC, and the caspase cleavage sites indicated by asterisks (2, 4, 11). B, expression of Adp20 in human KB epithelial cells stably overexpressing BCL-2 (BCL-2 cells) (58) does not induce the cleavage of Bap31 or p130CAS. Untreated or cells infected with either Adp20 or AdrtTa (control) were collected, and equivalent samples of cell lysates were analyzed by immunoblotting at 24 h post-infection with anti-BAP31, anti-p130CAS, and anti-actin antibodies.

C, cell surface expression of CD9 detected by flow cytometry of BCL-2 cells, infected either with Adp20 or AdrtTa for 24 h, stained with anti-mouse CD9 (KMC8). The graph represents the average of three independent experiments (Counts = relative fluorescence intensity). D, BCL-2 cells were infected either with Adp20 or AdrtTa, and at 24 h post infection, the percent of apoptotic cells was assessed by trypan blue uptake and staining. E, the indicated cells were cultured on plates coated with fibronectin under serum starvation conditions for 1 h, and the number of adherent cells was determined as described under “Experimental Procedures.” The graphs present the mean results of three independent determinations ± S.D.
are blocked (14, 56). What we have demonstrated here, however, is that upstream generation of p20 BAP31 by activated caspase-8 in living cells overexpressing BCL-2 could influence the integrity of cell surface functions, including integrin-mediated attachment to extracellular matrices.

BAP31 is emerging as an important regulator of the egress of a subset of newly synthesized integral membrane proteins out of the ER, which includes quality control (5, 10), export receptor (7, 8, 57), and perhaps chaperone functions. It is part of a large oligomeric structure (5), but it is not yet clear how this structure operates. Following caspase cleavage of BAP31, it loses its association with actomyosin (2, 3). This, together with potential influences of caspase cleavage on the large BAP31 complex itself, could contribute to the resulting inhibition of the role of BAP31 in supporting the transport of membrane proteins to the cell surface.

Acknowledgment—We thank Dr. Stanners for providing the antibodies to integrins α2 and β3, as well as for helpful discussions.

REFERENCES

1. Adachi, T., W.W., Schimel, K.M., Kim, T., Watanabe, B., Becker, P.J., Nielsen, and M. Reth (1996) EMBO J. 15, 1534–1541
2. Nguyen, M., Breckenridge, D.G., Ducret, A., Shore, G.C. (2000) Mol. Cell. Biol. 20, 6731–6740
3. Ducret, A., Nguyen, M., Breckenridge, D.G., Shore, G.C. (2003) Eur. J. Biochem. 270, 342–349
4. Wang, B., Nguyen, M., Breckenridge, D.G., Stojanovic, M., Clemens, P.A., Kuppig, S., Shore, G.C. (2003) J. Biol. Chem. 278, 14461–14468
5. Schamel, W.W., Kuppig, S., Becker, B., Gimborn, K., Haure, H.P., Reth, M. (2003) Proc. Natl. Acad. Sci. U. S. A. 100, 8961–8966
6. Annaert, W.G., Becker, B., Kistner, U., Reth, M., Jahn, R. (1997) J. Cell Biol. 139, 1397–1410
7. Spiliotis, E.T., Manley, H., Osorio, M., Zuniga, M.C., Edidin, M. (2000) Immunity 13, 841–851
8. Paquet, M.E., Cohen-Doyle, M., Shore, G.C., Williams, D.B. (2004) J. Immunol. 172, 7548–7555
9. Lambert, G., Becker, B., Schreiber, R., Boucherot, A., Reth, M., Kunzelmman, K. (2001) J. Biol. Chem. 276, 20340–20345
10. Wang, B., Pelletier, J., Massaad, M.J., Herscovics, A., Shore, G.C. (2004) Mol. Cell. Biol. 24, 2767–2778
11. Ng, F.W., Nguyen, M., Kwan, T., Branton, P.E., Nicholson, D.W., Cromlish, J.A., Shore, G.C. (1997) J. Cell Biol. 138, 327–338
12. Grauville, D.J., Carthy, C.M., Jiang, H., Shore, G.C., McManus, B.M., Hunt, D.W. (1998) FEBS Lett. 437, 5–10
13. Breckenridge, D.G., Nguyen, M., Kuppig, S., Reth, M., Shore, G.C. (2002) Proc. Natl. Acad. Sci. U. S. A. 99, 4331–4336
14. Breckenridge, D.G., Stojanovic, M., Marcellus, R.C., Shore, G.C. (2003) J. Cell Biol. 160, 1115–1127
15. Chandra, D., Cho, G., Deng, X., Bhatia, B., Daniel, P., Tang, D.G. (2004) Mol. Cell. Biol. 24, 6602–6607
16. Amara, J.F., Cheng, S.H., Smith, A.E. (1992) Trends Cell Biol. 2, 145–149
17. Aridor, M., Hanner, L.A. (2000) Traffic 1, 836–851
18. Bouchieux, C., Rubinstein, E. (2001) Cell Mol. Life Sci. 58, 1189–1205
19. Lagaudriere-Gesbert, C., Le Naour, F., Lebel-Binay, S., Billaud, Lemichez, E., Boquet, P., Boucheix, C., Conjeaud, H., Rubinstein, E. (1997) Cell Immunol. 182, 105–112
20. Feigelson, S.W., Grabovsky, V., Shamri, R., Levy, S., Alon, R. (2003) J. Biol. Chem. 278, 51203–51212
21. Hemler, M. E. (2001) J. Cell Biol. 153, 1103–1107
22. Boubnov, E., Le Naour, F., Lagaudriere-Gesbert, C., Billard, M., Conjeaud, H., Boucheix, C. (1996) Eur. J. Immunol. 26, 2657–2665
23. Chang, S., Manie, S., Billard, M., Ashman, L., Gerlier, D., Boucheix, C., Rubinstein, E. (2003) Biochem. Biophys. Res. Commun. 304, 107–112
24. Billard, M., Le Naour, F., Billard, M., Mrenant, P., Boucheix, C. (1994) Eur. J. Immunol. 24, 3005–3013
25. Serru, V., Le Naour, F., Billard, M., Azzera, D.O., Lanza, F., Boucheix, C., Rubinstein, E. (1999) Biochem. J. 348, 173–179
26. Berditchevski, F., Odintsova, E. (1999) J. Cell Biol. 146, 477–492
27. Secrist, H., Levy, S., DeKruyff, R.H., Umes, T.D. (1996) Eur. J. Immunol. 26, 1435–1442
28. Imai, T., Yochie, O. (1993) J. Immunol. 151, 6470–6481
29. Carmon, A.W., Wright, M.D. (1995) Eur. J. Immunol. 25, 2090–2095
30. Sauch, R.L., Hemler, M.E. (2000) Biochem. J. 351, 629–637
31. Shigeta, M., Sanzen, N., Otsawa, M., K., Hasegawa, H., Sekiguchi, K. (2003) J. Cell Biol. 163, 165–176
32. Miranti, C.K., Brugge, J.S. (2002) Nat. Cell Biol. 4, E83–90
33. Berman, A.E., Kozlova, N.I., Morozevich, G.E. (2003) Biochemistry (Mosc.) 68, 1289–1299
34. Lussier, C., Basora, N., Bouatrouss, Y., Beaulieu, J.F. (2000) Micros. Res. Tech. 51, 169–178
35. Hughes, P.E., Pfaff, M. (1998) Trends Cell Biol. 8, 359–365
36. Tsuchida, J., Ueki, S., Takada, Y., Saito, Y., Takagi, J. (1998) J. Cell Sci. 111, 1759–1766
37. Luque, A., Gomez, M., Puzon, W., Takada, Y., Sanchez-Madrid, F., Cabanas, C. (1996) J. Biol. Chem. 271, 11067–11075
38. Aridor, M., Hannan, L.A. (2000) Trends Biochem. Sci. 25, 19800–19805
39. Aridor, M., Hannan, L.A. (2000) Trends Biochem. Sci. 25, 19800–19805
40. Mould, A.P., Travis, M.A., Askari, J.A., Mould, A.P., Craig, S.E., Newham, P., Yamada, K.M., Humphries, M.J. (2004) J. Cell Sci. 117, 103–111
41. Clark, K., Pankov, R., Travis, M.A., Askari, J.A., Mould, A.P., Craig, S.E., Newham, P., Yamada, K.M., Humphries, M.J. (2004) J. Cell Sci. (Epub ahead of print)
42. Boubnov, E., Le Naour, F., Billard, M., Lanza, D.O., Lanza, F., Boucheix, C., Rubinstein, E. (1999) Biochem. J. 348, 173–179