Saposins A, B, C, and D are small lysosomal glycoproteins released by proteolysis from a single precursor polypeptide, prosaposin. We have presently investigated the conformational states of saposins and their interaction with membranes at acidic pH values similar to those present in lysosomes. With the use of phase partitioning in Triton X-114, experimental evidence was provided that, upon acidification, saposins (Phase) A, C, and D acquire hydrophobic properties, while the hydrophilicity of Sap B is apparently unchanged.

The pH-dependent exposure of hydrophobic domains of Sap C and D paralleled their pH-dependent binding to large unilamellar vesicles composed of phosphatidylcholine, phosphatidylycerine, and cholesterol. In contrast, the binding of Sap A to the vesicles was very restricted, in spite of its increased hydrophobicity at low pH. A low affinity for the vesicles was also shown by Sap B, a finding consistent with its apparent hydrophilicity both at neutral and acidic pH.

At the acidic pH values needed for binding, Sap C and D powerfully destabilized the phospholipid membranes, while Sap A and B minimally affected the bilayer integrity. In the absence of the acidic phospholipid phosphatidylserine, the induced destabilization markedly decreased.

Of the four saposins, only Sap C was able to promote the binding of glucosylceramidase to phosphatidylserine-containing membranes. This result is consistent with the notion that Sap C is specifically required by glucosylceramidase to exert its activity. Our finding that an acidic environment induces an increased hydrophobicity in Sap A, C, and D, making the last two saposins able to interact and perturb phospholipid membranes, suggests that this mechanism might be relevant to the mode of action of saposins in lysosomes.

Saposins (Sap)° A, B, C, and D are glycoproteins released by proteolytic processing of a single precursor called prosaposin (1–6). The mature forms of Sap B and C have been localized in lysosomes by various biochemical and immunochemical techniques (7–9). There is histochemical evidence that Sap C is partly bound to the lysosomal membrane (9). The amino acid sequences of saposins are highly similar. Each saposin consists of ~80 amino acids, including six identically placed cysteine residues (1-4). Recently, we have established that human Sap B and C have the same disulfide structure, with a central big loop surrounded by two smaller ones (10). Most likely, this disulfide arrangement is present also in Sap A and D, where the six cysteine residues are at strictly conserved positions. Consistently with their structural similarity, saposins show common physicochemical characteristics; they are heat-stable, acidic proteins resistant to most proteinases (1–4).

One assessed function of saposins is the promotion of the enzymatic degradation of specific sphingolipids in lysosomes (1–4). Sap C appears to be required in vivo by glucosylceramidase for the hydrolysis of glucosylceramide since a genetic defect of Sap C causes a juvenile variant of Gaucher’s disease with glucosylceramide accumulation in tissues (11). A defect of Sap B results in a variant form of metachromatic leukodystrophy with sulfatide accumulation in tissues (12, 13). The fact that the absence of one or another saposin causes different pathologies indicates that each saposin has distinct biological functions. When all four saposins are absent due to a genetic defect that prevents the synthesis of prosaposin (14), accumulation of several sphingolipids has been observed in lysosomes with symptoms similar to those of Gaucher’s and Faber’s diseases (15).

Several attempts have been made to elucidate the role of saposins in sphingolipid enzymatic degradation. Sap C was originally purified on the basis of its ability to activate the lysosomal enzyme glucosylceramidase in the presence of phosphatidylserine (PS) (16). The enzyme activation was thought to be caused by a direct interaction of the saposin with the enzyme (16, 17). In previous studies, we reinvestigated the role of Sap C, and the use of model lipid membranes provided us information on the mechanism whereby glucosylceramidase is stimulated by Sap C and PS. We found that, in order to express its activity, glucosylceramidase must be bound to acidic phospholipid-containing membranes (18, 19) and that Sap C promoted the enzyme binding by interacting with the bilayer (20). We next examined the effects of Sap C on the physical properties of PS bilayers and showed that the saposin induced destabilization at acidic pH values (21). The finding that the glucosylceramidase-stimulating ability of Sap C primarily depended on its interaction with acidic phospholipids prompted us to further investigate the mechanism of the saposin membrane action. In the present study, we examined 1) whether the pH-dependent binding of Sap C to PS-containing bilayers depended on a pH-dependent change of conformational state; 2) whether the other three saposins (A, B, and D), which possess similar structure, shared the Sap C ability to act on phospholipid mem-
branes; and 3) whether a relation could be found between conformation of saposins, membrane binding, and bilayer perturbation. Finally, the specificity of Sap C in promoting the binding of glucosylceramidase to PS-containing membranes was evaluated.

EXPERIMENTAL PROCEDURES

Materials—Phosphatidylcholine (PC) from egg yolk and PS from bovine brain were from Avanti Polar Lipids, Inc. (Alabaster, AL). Cholesterol and 4-methylumbelliferyl β–D-glucopyranoside (MUGlc) were from Sigma. Calcine was from Molecular Probes, Inc. (Eugene, OR). All other chemicals were of the purest available grade.

Sap A, B, C, and D Preparation—Sap B, C, and D were purified from spleens of patients with Type 1 Gaucher’s disease following a procedure previously reported (22); it consisted of heat and acid treatment of a water homogenate, ion-exchange chromatography on DEAE-Septahex, gel filtration on Sephadex G-75, and reverse-phase high pressure liquid chromatography on a protein C4 column (Vydac). Sap A, also from Gaucher’s disease patients’ spleens, was purified according to the procedure of Morimoto et al. (23). The purity of the final saposin preparations was verified by N-terminal sequence analysis, SDS-polyacrylamide gel electrophoresis, and Western blotting.

Saposin Antibodies—Antibodies against Sap A, B, C, and D were raised in rabbits by injecting 200 μg of the individual saposins three times over a period of 2 months.

Glucosylceramidase Preparation and Assay—Glucosylceramidase was purified from human placenta following the procedure described by Murray et al. (24). To measure the glucosylceramidase activity, the standard assay mixture contained the following (in a final volume of 0.2 ml): 0.1 M citrate, 0.2% phosphate buffer, pH 5.6, 2.5 mM MUGlc, 0.1% (v/v) Triton X-100, and 0.25% (w/v) sodium taurocholate. When the aqueous phase was incubated at 37°C for 30 min and then centrifuged at low speed. Aliquots of the upper aqueous phase were analyzed by SDS-polyacrylamide gel electrophoresis, and Western blotting.

Vesicle Preparation—Large unilamellar vesicles (LUV) were prepared by filter exclusion using a high pressure extrusion apparatus. The final concentration was determined by measuring the protein content with the bicinchoninic acid method (30). The amount of liposome-bound saposin at a given pH was expressed relative to the amount of protein in the supernatant centrifuged in the absence of liposomes.

For glucosylceramidase binding studies, the enzyme (1000 units) was incubated at 37°C for 10 min with PS-containing LUV (200 μg), individual saposins (10 μg), and albumin (100 μg) in 0.4 ml of buffer A, pH 5.0, supplemented with 10 mM diethylylthritol. The mixture was then centrifuged at 130,000 × g for 1 h. The amount of glucosylceramidase in the supernatant was determined by measuring the enzyme activity according to the standard assay (see above). The amount of liposome-bound glucosylceramidase was expressed relative to the amount of enzyme in the supernatant centrifuged in the absence of saposins.

Leakage Assay—Leakage of liposome contents was monitored by the release of calcine trapped inside the vesicles (31). LUV for leakage experiments were prepared by hydrating dried films of lipids in 60 mM calcine, pH 7.4, followed by 10 cycles of freeze-thawing. The resulting multilamellar vesicles were extruded 15 times through two stacked 0.1-μm pore size polycarbonate filters. Free calcine was separated from dye-containing LUV by chromatography on a Sephadex G-75 column. Upon addition of saposins, leakage of calcine to the external medium was followed by an increase in fluorescence caused by calcine dilution and the consequent relief of self-quenching (excitation at 470 nm and emission at 520 nm). 100% leakage was established by lysing the vesicles with 0.3% (v/v) Triton X-100. Leakage of liposomes was carried out at 37°C and monitored with a Fluoromax spectrofluorometer equipped with a constant temperature cell holder and stirrer (Spex Industries, Edison, NJ).

RESULTS

Acid-induced Changes in Hydrophobicity of Saposins A, C, and D—We have recently shown that Sap C is able to bind to PS membranes at low pH (20). Since an acid-induced conformational change that triggers an increased hydrophobicity has been demonstrated for several proteins as the first step in the penetration through membranes (32–35), we have investigated whether a similar change occurred in Sap C. The property of Triton X-114 to separate into a detergent lower phase and an aqueous upper phase was exploited for obtaining information on the surface hydrophobicity of the saposin. Fig. 1 shows that, at neutral pH, Sap C was completely recovered in the aqueous phase, while at acidic pH, it moved into the detergent phase.

The same experiments performed with the other three saposins showed that also Sap A and D separated into the lower deter-
PS-containing vesicles (Fig. 3).

In the absence of PS, the two saposins had comparable effects on the stability of liposomes. Sap C was a more powerful destabilizing agent than Sap D in PS-containing liposomes in the presence of either Sap C or D, indicating that acidity and PS contribute to membrane destabilization. At pH 4.5, LUV, while Sap A and B minimally affected the bilayer integrity, Sap C and D increased membrane permeability.

Binding of Saposins to Phospholipid Vesicles—On consideration of the hydrophobicity of Sap A and D, the interaction of saposins with liposomes was investigated under acidic conditions. Liposomes deprived of PS were used to study the interaction of saposins with phospholipids for saposin interactions. The extent of Sap C binding was higher than that of Sap A and B at pH values lower than 5.0, indicating that Sap C is a more powerful destabilizing agent than Sap D under these conditions.

Saposins are known to promote the association of glucosylceramidase with PS-containing liposomes (1–4, 23). We recently showed that the stimulation by Sap C was related to the saposin-promoted binding of the enzyme to PS-containing LUV (20). To compare the effect of the four saposins on the binding of the enzyme to membranes, glucosylceramidase was centrifuged with liposomes in the presence of each saposin. Fig. 5 shows that Sap C was the only saposin able to promote the association of glucosylceramidase with PS-containing LUV. When liposomes without PS were used for the binding experiments, no interaction between glucosylceramidase and the bilayer took place also in the presence of Sap C (data not shown).

The fact that Sap A was unable to promote enzyme binding prompted us to re-evaluate the capacity of Sap A to stimulate the enzyme activity in the presence of PS-containing LUV. Table I shows that while Sap C markedly increased the enzyme activity, Sap A, B, and D had no effect on glucosylceramidase under our experimental conditions.

DISCUSSION

Saposins presumably exert their biological activities in lysosomes (1–4), where the environment is maintained at pH values in the range 4.0–5.5 (36, 37). By studying the partitioning of the proteins between aqueous and detergent (Triton X-114) phases, we have presently found that a low pH induces changes in the hydrophobicity of Sap A, C, and D. In contrast, an acidic environment does not affect the apparent hydrophobicity of Sap B, which, at pH 4.0, segregates into the aqueous phase.

The observation that mildly acidic conditions mimicking the
and D clearly correlated with their binding to vesicles composed of cholesterol and phospholipids, the predominant lipid in biological membranes. Of the four saposins, Sap C shows the highest affinity for phospholipid membranes. Its binding to PS vesicles at low pH had been previously assessed (20). We have now found that, although the presence of an acidic phospholipid such as PS has a positive effect, Sap C can also associate with neutral phospholipid-containing vesicles. The binding properties of Sap C are consistent with the fact that Sap C is localized, at least in part, on the lysosomal membrane (9), where high levels of phospholipids are present (38).

In contrast with Sap C and D, Sap A and B show a poor binding efficiency for phospholipid vesicles. For Sap B, this finding is consistent with its apparent hydrophilicity both at neutral and acidic pH. The lack of interaction of Sap A with phospholipid membranes, in spite of its increased hydrophobicity at low pH, might be explained by the higher carbohydrate content of this saposin. In fact, two oligosaccharide side chains are present in the Sap A molecule instead of one as in the other saposins (23).

The pH-dependent binding of saposins C and D to liposomes dramatically affects the integrity of the phospholipid bilayer. The membrane destabilization is favored by the same conditions that promote the binding of the two saposins, namely the presence of PS and acidic pH. Sap A and B, which poorly interact with phospholipid vesicles, have a minimal effect on the permeability of the bilayers. Although these results suggest that saposin-induced destabilization involves saposin binding, other factors also appear to influence the rate of leakage from the liposomes. Sap C, which is completely bound to PS-containing liposomes both at pH 4.0 and 5.0, induces a very rapid calcein release at pH 4.0, but not at pH 5.0 (see Figs. 2 and 3).

Most likely, the degree of Sap C embedding into the bilayer is different at the two pH values. According to Papahadjopoulos et al. (39), the simple binding of proteins to the surface of lipid bilayers without penetration has minimal effects on membrane permeability, while the surface binding of proteins followed by their penetration into the bilayers results in a large increase in the permeability of the membranes.

It is well known that Sap C is required by glucosylceramidase to fully express its activity (16). We have recently found that the Sap C requirement is related to the saposin ability to mediate the interaction between glucosylceramidase and PS-containing liposomes (20). By comparing the effects of the four saposins, we have now found that Sap C is the only saposin able to promote the association of the enzyme with the lipid surface. Sap A, which has been also reported as a glucosylceramidase activator (23), has no effect on the enzyme binding and, under our experimental conditions (Table I), on the enzyme activity. The specificity of Sap C may depend on either a specific Sap C-induced perturbation of the bilayer or/and a specific interaction between Sap C and glucosylceramidase consequent to a saposin conformational change after insertion into the bilayer. Based on the present findings, we speculate that the exposure to the low lysosomal pH triggers a change necessary for Sap C to penetrate into acidic phospholipid-containing membranes, perturb the lipid organization, and finally promote the binding and activation of glucosylceramidase. According to this hypothesis, Sap C might play a major role in favoring the association of glucosylceramidase with the lysosomal membrane.

Recently, it was found that Sap D stimulates the lysosomal enzymatic degradation of ceramide (40). It was proposed that the stimulation of acid ceramidase activity by Sap D depends on the direct association of the saposin with the enzyme and not with the lipid substrate (41). Our present results provide the first experimental evidence that Sap D has the capacity to

---

**Table I**

| Saposin added | Glucosylceramidase activity (nmol/h) |
|--------------|-------------------------------------|
| None         | 3                                   |
| Sap A        | 3                                   |
| Sap B        | 4                                   |
| Sap C        | 28                                  |
| Sap D        | 3                                   |

The pH-dependent binding of saposins C and D to liposomes dramatically affects the integrity of the phospholipid bilayer. The membrane destabilization is favored by the same conditions that promote the binding of the two saposins, namely the presence of PS and acidic pH. Sap A and B, which poorly interact with phospholipid vesicles, have a minimal effect on the permeability of the bilayers. Although these results suggest that saposin-induced destabilization involves saposin binding, other factors also appear to influence the rate of leakage from the liposomes. Sap C, which is completely bound to PS-containing liposomes both at pH 4.0 and 5.0, induces a very rapid calcein release at pH 4.0, but not at pH 5.0 (see Figs. 2 and 3).

Most likely, the degree of Sap C embedding into the bilayer is different at the two pH values. According to Papahadjopoulos et al. (39), the simple binding of proteins to the surface of lipid bilayers without penetration has minimal effects on membrane permeability, while the surface binding of proteins followed by their penetration into the bilayers results in a large increase in the permeability of the membranes.

It is well known that Sap C is required by glucosylceramidase to fully express its activity (16). We have recently found that the Sap C requirement is related to the saposin ability to mediate the interaction between glucosylceramidase and PS-containing liposomes (20). By comparing the effects of the four saposins, we have now found that Sap C is the only saposin able to promote the association of the enzyme with the lipid surface. Sap A, which has been also reported as a glucosylceramidase activator (23), has no effect on the enzyme binding and, under our experimental conditions (Table I), on the enzyme activity. The specificity of Sap C may depend on either a specific Sap C-induced perturbation of the bilayer or/and a specific interaction between Sap C and glucosylceramidase consequent to a saposin conformational change after insertion into the bilayer. Based on the present findings, we speculate that the exposure to the low lysosomal pH triggers a change necessary for Sap C to penetrate into acidic phospholipid-containing membranes, perturb the lipid organization, and finally promote the binding and activation of glucosylceramidase. According to this hypothesis, Sap C might play a major role in favoring the association of glucosylceramidase with the lysosomal membrane.

Recently, it was found that Sap D stimulates the lysosomal enzymatic degradation of ceramide (40). It was proposed that the stimulation of acid ceramidase activity by Sap D depends on the direct association of the saposin with the enzyme and not with the lipid substrate (41). Our present results provide the first experimental evidence that Sap D has the capacity to
bind to PS-containing vesicles and perturb the bilayer. It would be of interest to investigate if the pH-dependent destabilizing activity of Sap D directly or indirectly affects the lysosomal ceramide degradation.

Presumably, saposins play several critical roles in lysosomes. A well-documented function is that of stimulating the lysosomal degradation of sphingolipids (1–4). In addition, it has been reported by Hiraiwa et al. (42) that all four saposins and also their precursor, prosaposin, form high affinity complexes with gangliosides and transport them from one membrane to the other. This finding prompted the authors to propose that prosaposin and saposins might serve in vivo as transport proteins for gangliosides. Our present results showing that saposins C and D possess a potentiality to modify the phospholipid assembly at low pH values suggest that, independently of the presence of sphingolipids, these two saposins might have a further role in the organization of lysosomal and intralysosomal membranes. When all saposins are absent for a genetic defect in the start codon of the prosaposin gene (14), the accumulation of intralysosomal vesicles has been observed (43). This finding suggested that saposins are essential for the degradation of intralysosomal vesicles (4); it is conceivable that the pH-dependent membrane-destructing activities of Sap C and D are relevant in this lysosomal process.

Acknowledgments—We thank E. Raia for technical assistance and G. Spinelli for reading the manuscript.

REFERENCES

1. O’Brien, J., and Kishimoto, Y. (1991) FASEB J. 5, 301–308
2. Kishimoto, Y., Hiraiwa, M., and O’Brien, J. S. (1992) J. Lipid Res. 33, 1255–1267
3. Fürst, W., and Sandhoff, K. (1992) Biochim. Biophys. Acta 1126, 1–16
4. Sandhoff, K., Harzer, K., and Fürst, W. (1995) in The Metabolic and Molecular Bases of Inherited Disease (Scriver, C. R., Beaudet, A. L., Sly, W. S., and Valle, D., eds) pp. 2427–2441, McGraw-Hill Book Co., New York
5. Fujibayashi, S., and Wenger, D. A. (1986) J. Biol. Chem. 261, 15,339–15,343
6. Fujibayashi, S., and Wenger, D. A. (1986) Biochim. Biophys. Acta 875, 554–562
7. Chiao, Y. B., Chambers, J. P., Glew, R. H., Lee, R. E., and Wenger, D. A. (1978) Arch. Biochem. Biophys. 186, 42–51
8. Tamaru, T., Fujibayashi, S., Brown, W. R., and Wenger, D. A. (1985) Histochemistry 86, 195–200
9. Paton, B. C., Hughes, J. L., Harzer, K., and Polous, A. (1989) Eur. J. Cell Biol. 51, 157–164
10. Vaccaro, A. M., Salvioi, R., Barca, A., Tatti, M., Ciaffoni, F., Maras, B., Siciliano, R., Zappacosta, F., Amoresano, A., and Pucci, P. (1995) J. Biol. Chem. 270, 9953–9960
11. Christomanou, H., Chabas, A., Pampolis, T., and Guardiola, A. (1989) Klin. Wochenschr. 67, 999-1003
12. Wenger, D. A., De Gala, G., Williams, C., Taylor, H. A., Stevenson, R. E., Prütt, J. R., Miller, J., Garen, P. D., and Balentine, J. D. (1989) Am. J. Med. Genet. 33, 255–265
13. Schlote, W., Harzer, K., Christomanou, H., Paton, B. C., Kustermann-Kuhn, B., Schmidt, B., Seeger, J., Beudt, U., Schuster, I., and Langenbeck, U. (1991) Eur. J. Pediatr. 150, 584–591
14. Schnabel, D., Schwider, M., Fürst, W., Klein, A., Hurwitz, R., Zenk, T., Weber, J., Harzer, K., Paton, B. C., Polous, A., Suzuki, K., and Sandhoff, K. (1992) J. Biol. Chem. 267, 3312–3315
15. Bradova, V., Smid, F., Ulrich-Bott, B., Roggendorw, W., Paton, B. C., and Harzer, K. (1993) Hum. Genet. 92, 143–152
16. Glew, R. H., Basu, A., La Maro, K., and Prance, E. (1988) Lab. Invest. 58, 5–25
17. Morimoto, S., Kishimoto, Y., Tomich, J., Weiler, S., Ohashi, T., Barranger, J. A., Kretz, K. A., and O’Brien, J. S. (1990) J. Biol. Chem. 265, 1933–1937
18. Vaccaro, A. M., Tatti, M., Salvioi, R., Ciaffoni, F., and Galli, E. (1990) Biochim. Biophys. Acta 1033, 73–79
19. Vaccaro, A. M., Tatti, M., Ciaffoni, F., Salvioi, R., and Roncagli, P. (1991) Biochim. Biophys. Acta 1129, 239–246
20. Vaccaro, A. M., Tatti, M., Ciaffoni, F., Salvioi, R., Maras, B., and Barca, A. (1993) FEBS Lett. 1, 159–162
21. Vaccaro, A. M., Tatti, M., Ciaffoni, F., Salvioi, R., Serafini, A., and Barca, A. (1994) FEBS Lett. 349, 181–186
22. Sano, A., Radin, N. S., Johnson, L. L., and Tarr, G. E. (1988) J. Biol. Chem. 263, 15997–15961
23. Morimoto, S., Martin, B. M., Yanamoto, Y., Kretz, K. A., O’Brien, J. S., and Kishimoto, Y. (1989) Proc. Natl. Acad. Sci. U.S.A. 86, 3389–3393
24. Murray, G. J., Youle, R. J., Gandy, S. E., Zirzow, G. C., and Barranger, J. A. (1985) Anal. Biochem. 147, 301–310
25. Mayer, L. D., Hope, M. J., and Cullis, P. R. (1986) Biochim. Biophys. Acta 858, 161–168
26. Vaccaro, A. M., Tatti, M., Ciaffoni, F., Salvioi, R., Barca, A., and Roncagli, P. (1993) Biochim. Biophys. Acta 1149, 55–62
27. Bartlett, G. R. (1959) J. Biol. Chem. 234, 466–468
28. Bordier, C. (1981) J. Biol. Chem. 256, 1604–1607
29. Schagger, H., and Von Jagow, G. (1987) Anal. Biochem. 166, 368–379
30. Redinbaugh, M. G., and Turley, R. B. (1986) Anal. Biochem. 153, 267–271
31. Straubinger, R. M., Hong, K., Friend, D. S., and Papahadjopoulos, D. (1983) Cell 32, 1069–1079
32. Fricker, L. D., Das, B., and Hogue Angeletti, R. (1990) J. Biol. Chem. 265, 2476–2482
33. Doms, R. W., Helenius, A., and White, J. (1985) J. Biol. Chem. 260, 2973–2981
34. Escuyer, V., Baquè, P., Perrin, D., Montecucco, C., and Muck, M. (1986) J. Biol. Chem. 261, 10891–10898
35. Yoshimura, T., Maezawa, S., and Hong, K. (1987) J. Biochem. (Tokyo) 101, 1265–1272
36. Meliman, I., Fuchs, R., and Helenius, H. (1986) Annu. Rev. Biochem. 55, 663–700
37. Bohley, P., and Seglen, P. O. (1992) Experientia 48, 151–157
38. Hottman, E. (1989) Lysosomes, Plenum Press, New York
39. Papahadjopoulos, D., Moscarello, M., Eylar, E. H., and Isac, T. (1975) Biochim. Biophys. Acta 370, 317–335
40. Klein, A., Hersel, A., Klein, C., Suzuki, K., Harzer, K., and Sandhoff, K. (1994) Biochim. Biophys. Res. Commun. 200, 1440–1448
41. Azuma, N., O’Brien, J. S., Moser, H. W., and Kishimoto, Y. (1994) Arch. Biochem. Biophys. 311, 354–357
42. Hiraiwa, M., Soeda, S., Kishimoto, Y., and O’Brien, J. S. (1992) Proc. Natl. Acad. Sci. U.S.A. 89, 11254–11258
43. Harzer, K., Paton, B. C., Polous, A., Kustermann-Kuhn, B., Roggendorw, W., Grisar, T., and Popp, M. (1989) Eur. J. Pediatr. 149, 31–39
pH-dependent Conformational Properties of Saposins and Their Interactions with Phospholipid Membranes
Anna Maria Vaccaro, Fiorella Ciaffoni, Massimo Tatti, Rosa Salvioli, Alessandra Barca, Deborah Tognozzi and Chiara Scerch

J. Biol. Chem. 1995, 270:30576-30580.
doi: 10.1074/jbc.270.51.30576

Access the most updated version of this article at http://www.jbc.org/content/270/51/30576

Alerts:
• When this article is cited
• When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 41 references, 13 of which can be accessed free at http://www.jbc.org/content/270/51/30576.full.html#ref-list-1