Three-dimensional Structures of the Mammalian Multidrug Resistance P-glycoprotein Demonstrate Major Conformational Changes in the Transmembrane Domains upon Nucleotide Binding*§

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Published, JBC Papers in Press, December 25, 2002, DOI 10.1074/jbc.M211758200

P-glycoprotein is an ATP-binding cassette transporter that is associated with multidrug resistance and the failure of chemotherapy in human patients. We have previously shown, based on two-dimensional projection maps, that P-glycoprotein undergoes conformational changes upon binding of nucleotide to the intracellular nucleotide binding domains. Here we present the three-dimensional structures of P-glycoprotein in the presence and absence of nucleotide, at a resolution limit of \( \sim 2 \) nm, determined by electron crystallography of negatively stained crystals. The data reveal a major reorganization of the transmembrane domains throughout the entire depth of the membrane upon binding of nucleotide. In the absence of nucleotide, the two transmembrane domains form a single barrel \( 5-6 \) nm in diameter and about \( 5 \) nm deep with a central pore that is open to the extracellular surface and spans much of the membrane depth. Upon binding nucleotide, the transmembrane domains reorganize into three compact domains that are each \( 2-3 \) nm in diameter and \( 5-6 \) nm deep. This reorganization opens the central pore along its length in a manner that could allow access of hydrophobic drugs (transport substrates) directly from the lipid bilayer to the central pore of the transporter.

ATP Binding Cassette (ABC) transporters are an extended family of membrane proteins defined by a highly conserved domain, the ATP binding cassette (1); they mediate the ATP-dependent transport of a wide variety of compounds across cellular membranes (2, 3). The core ABC transporter consists of two transmembrane domains (TMDs) and two nucleotide binding domains (NBDs). The NBDs are peripherally located at the cytoplasmic face of the membrane, bind ATP, and couple ATP hydrolysis to the transport process. All NBDs whose structures have been determined have very similar tertiary folds (4–8). The TMDs bind the transported substrate and form the pathway through which it crosses the membrane. In contrast to the NBDs, the TMDs of different ABC transporters share little primary sequence similarity, except between closely related members of a subfamily; this may be because of the variety of substrates transported by different ABC proteins. Little is known about the structures of the TMDs of ABC transporters or how the binding/hydrolysis of ATP by the NBDs is coupled to transmembrane transport of solute. Hydrophobicity plots typically predict six transmembrane \( \alpha \)-helices per TMD, but there are notable exceptions with additional predicted transmembrane \( \alpha \)-helices (9, 10). The structures of two complete bacterial ABC transporters (9, 11) have confirmed that the membrane-spanning segments are indeed \( \alpha \)-helical, although the packing of these \( \alpha \)-helices within the membrane differs markedly between the two structures.

P-glycoprotein (P-gp) is a mammalian ABC transporter that pumps hydrophobic drugs across the cell membrane and can confer multidrug resistance on cells and tumors. P-gp is probably the best characterized ABC transporter, and much is known about the ATP hydrolytic cycle (12–14) and drug binding sites (15–18). There is a body of biochemical evidence suggesting that the TMDs undergo conformational changes upon nucleotide binding, including changes in epitope accessibility (19, 20), protease susceptibility (21, 22), drug binding (17), fluorescence, and spectroscopic measurements (23–26). To understand the mechanism of transport, these biochemical data need to be linked to structural information. We have previously reported low to medium resolution structures for P-gp determined by both single particle image analysis (27) and by electron crystallography of two-dimensional crystals (28). The two-dimensional projection maps for P-gp trapped at different stages of the hydrolytic cycle suggest substantial conformational changes at the extracellular face of the TMDs upon binding the non-hydrolyzable ATP analogue adenylyl-imidodiphosphate (AMP-PNP) and after vanda-date-trapping in the presence of ADP (ADP/Vi state) (28). We have now generated a three-dimensional structure for P-gp in the presence of AMP-PNP and compared this with the three-dimensional structure of P-gp in the absence of nucleotide. The data show substantial conformational changes throughout the TMDs of P-gp upon nucleotide binding, requiring significant repacking of the transmembrane \( \alpha \)-helices, and opening a central pore along its length, potentially facilitating movement of hydrophobic compounds from the lipid bilayer to the aqueous pore of the transporter.

* This work was supported by Cancer Research UK. 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.
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The abbreviations used are: ABC, ATP binding cassette; TMD, transmembrane domain; NBD, nucleotide binding domain; P-gp, P-glycoprotein; nf-P-gp, nucleotide-free P-gp.

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**EXPERIMENTAL PROCEDURES**

P-glycoprotein was purified from CH
B30 Chinese hamster ovary cells selected for over-expression of P-gp (29). Two-dimensional crystals were grown in the presence or absence of nucleotide and negatively stained with uranyl acetate, as described previously (28), using hanging-drop methods developed by Auer et al. (30, 31). Where appropriate, 5 mM AMP-PNP, a non-hydrolyzable analogue of ATP, was added directly to the crystallization droplet. Electron microscopy was performed on a UMAX Power Look 3000 density meter at 0.41 nm/pixel at the specimen level. Lattice binding and contrast transfer function correction were as described earlier (28). Structure factors were merged with ORIGTILD and averaged with the program LLFILT to give interpolated structure factors along each lattice line (Fig. 1), as previously described (32, 33). E.g., phase residual (with the correct orientation having a significantly lower phase residual than the nearest alternative) and (b) examination of the projection of the unit cell of the crystal (e.g., identification of the strong but narrow density in the P-gp-AMP-PNP structure, as discussed under “Results”). In ~95% of the cases there was a single orientation that was better than all the others in terms of interimage phase residual. None of the crystals tested merged best with a flipped orientation, implying that the crystals preferentially adhere by only one face to the support film (see the “Results” and “Discussion” sections). The three-dimensional maps were generated using the CCP4 software (34), and modeling was carried out using XFIT within the XTALVIEW software suite (35).

**RESULTS**

**Crystallization of P-gp and Generation of Three-dimensional Structure Maps**—Two-dimensional crystals of highly purified P-glycoprotein in detergent were grown in the presence or absence of AMP-PNP, a non-hydrolyzable analogue of ATP that is known to bind to the NBDS at the same site as ATP. Three-dimensional structures were generated by electron crystallography (see “Experimental Procedures”). Two-dimensional crystals formed more readily in the presence of AMP-PNP, suggesting that this compound favored either the nucleation or stability of the two-dimensional crystals. Crystal order was also slightly better with AMP-PNP, as shown by comparison of the S.D. of the mean phases in most of the resolution ranges for untitled data (Table I). Crystals grown with and without AMP-PNP were similar in size (in excess of 1 micron across), but the unit cell area was slightly smaller in the presence of AMP-PNP (Table I). In both conditions, crystals had a p1 plane group, so that symmetry operations could not be used to judge the quality of the structural data. Instead, crystal-to-crystal variation
and resolution limits for the data were assessed by analyzing
the deviations from the (vector sum) mean phase (Table I).
These began to increase around 2 nm resolution for the P-gp-
AMP-PNP crystals, but even at this limit phase errors were
significantly lower than those expected for random data. Visual
assessment of the scatter present in the three-dimensional
data for the P-gp-AMP-PNP crystals was achieved by plotting
the structure factors of lattice lines along z* in reciprocal space
(Fig. 1), suggesting that the three-dimensional structural data
could be relied on to about 2 nm resolution. At this limit,
domains in P-gp were resolved, but secondary structures such
as transmembrane α-helices remained unresolved.

In two-dimensional crystals of nucleotide-free-P-gp (nf-P-gp),
the molecules were packed such that they are slanted across
each other (Fig. 2, panel A, angled away from the observer)
with the long axis of each molecule oriented about 25–30°
from the normal to the crystal plane. Such packing would be disal-
lowed in crystals formed by reconstitution in lipid bilayers but
can be accommodated in these crystals, which were grown in
the presence of detergent micelles. In contrast, in crystals of
P-gp-AMP-PNP the molecules were aligned with their long axis
almost exactly perpendicular to their two-dimensional crystal
plane (Fig. 2). These packing differences, at least in part, ex-
plain the smaller unit cell area of the P-gp-AMP-PNP crystals
(Table I).

**Comparison of the Three-dimensional Structures of P-gp in
the Presence or Absence of AMP-PNP**—The three-dimensional
maps of nf-P-gp and P-gp-AMP-PNP (Fig. 2) each comprise
high and low density regions (the high density region is closest
to the observer in panels A and B and at the top in panel C). The
high and low density regions were more pronounced for nf-Pgp
(Fig. 2, panel A). Because the high density region is the side of
the molecule in contact with the support film, the differences in
the two regions are likely to be because of the well documented
‘differential staining’ effect (36, 37) in which better contrast,
and hence higher apparent protein density, is observed in the
region closest to the support film. We have previously shown by
lectin-gold labeling (27, 28) that the surface of the P-gp mole-
cule in contact with the support film corresponds to that ex-
posed at the extracellular face of the membrane. Thus, the
high-density region corresponds to the TMDs, whereas the low
density region corresponds to the NBDs.

The three-dimensional structure of nf-P-gp is shown in panel
A of Fig. 2. The high density region, corresponding to the
TMDs, resembles a barrel 5 to 6 nm in diameter and about 5
nm long. The barrel surrounds a central pore, which appears to

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**Fig. 2.** Comparison of nf-P-gp and
P-gp-AMP-PNP three-dimensional
structures. A, stereo pair of the nf-P-gp
three-dimensional structure, displayed
using netting at 1.0 σ (red) and 1.5 σ
(yellow) above the mean density level and
viewed perpendicular to the crystal plane
from the more heavily stained side (corre-
sponding to the extracellular surface). B,
equivalent views of the P-gp-AMP-PNP
structure. The arrow indicates the gap
along one side of the central pore. The
locations of the three discrete densities A,
B, and C are indicated. C, stereo pair of a
side view of P-gp-AMP-PNP with the
same color scheme as above. The direc-
tions of the principle crystallographic
axes a and b are shown. Scale bar = 2.2
nm.
be open at the top (equivalent to the extracellular face of the membrane) and closed at the bottom (intracellular). The overall structure of the TMDs is very similar to that determined previously by the entirely different method of single particle image analysis (27). The three-dimensional netting display used here gives a clear impression of the full three-dimensional volume, allowing the identification of features in the map not seen previously, in particular a density that protrudes toward the central axis of the pore folding in from the bottom wall of the barrel and a smaller density protruding into the pore from the top of the barrel. After suitable rotation of the structure (see legend to Fig. 3), a view directly down the barrel was obtained (Fig. 3a, bottom panel). Note that the walls of the barrel are roughly 1–1.5 nm thick, which roughly equates to the diameter of a transmembrane α-helix (see below).

In contrast to the nf-P-gp structure, the high density (TMD) region of P-gp-AMP-PNP consists of three clearly segregated domains (designated A, B, and C in Fig. 2B). Two of these domains are roughly equivalent in size and shape, with a footprint of about 3 × 1.5 nm and a length perpendicular to the crystal plane of about 4.5 nm. The third domain (C) has a smaller footprint (about 2 nm diameter) but is somewhat longer perpendicular to the plane of the membrane (about 6 nm). Domain C was a useful reference point in the data merging procedure, because its smaller footprint but higher density allowed it to be distinguished from the other two domains in projection maps of individual crystals (see Fig. 2, panel B). The three domains of P-gp-AMP-PNP also enclose a central ‘pore.’ However, unlike nf-P-gp the pore is less obviously closed at the bottom (intracellular face of the membrane) and, additionally, is open to the lipid phase along one side with a gap appearing between two domains (Fig 2, panel B, arrow). The opening up of this gap may explain why the P-gp-AMP-PNP crystals are less affected by differential staining with apparently better penetration of stain through the molecule (compare Fig. 3, a and d, top panels).

![Comparison of ABC transporters](image)

**Fig. 3.** Comparison of ABC transporters. The three-dimensional structures of nf-P-gp (a) and P-gp-AMP-PNP (d) are compared with the published structures of MsbA (b) and BtuCD (c), all to the same scale. For each protein a side view (top panels) and a top view (looking down onto the equivalent of the extracellular surface) (bottom panels) are shown. Yellow mesh shows protein at ~1.0σ above mean density level in (a) and (d). a, nf-P-gp is viewed along the main barrel of protein density after rotation of the molecule to correct for the slight tilting in the crystal (see "Results"). To achieve this, the structure shown in Fig. 2 was rotated by 26° with respect to the horizontal axis and by 8° about the vertical axis. b, MsbA structure with six transmembrane α-helices per TMD. White and yellow Ca traces show separate MsbA monomers, connecting at the top via the TMDs and with widely separated NBDs at the bottom. c, BtuCD (blue Ca traces) with two TMDs each containing 10 α-helices. The NBDs and TMDs are closely associated. d, the P-gp-AMP-PNP structure. The P-gp structures are distinct from both MsbA and BtuCD in the putative transmembrane regions. Note that the MsbA and BtuCD structures were in the nucleotide-free form.

![Modeling of nf-P-gp with 2 x 6 transmembrane α-helices](image)

**Fig. 4.** Modeling of nf-P-gp with 2 × 6 transmembrane α-helices. The nf-Pgp structure (yellow netting) accommodates 2 × 6 transmembrane α-helices (red Ca traces) in a pseudo-symmetrical arrangement with a good fit. Two monomers of MsbA were used to provide the 2 × 6 transmembrane α-helices after removal of the NBDs. The nf-P-gp structure is displayed as in Fig. 3, while the truncated MsbA monomers have been separately rotated and translated for the fitting.
The low density regions of each P-gp map correspond to the NBDS (28). Because the NBDSs are farther from the grid support film, they are less contrasted by heavy atom stain and less well protected against the damaging effects of the high vacuum and electron beam in the microscope (36, 37). Thus, densities in this region are weak, especially for nf-P-gp (Fig. 3a), and are therefore more difficult to interpret than the densities for the TMDs (4, 8). The characterization of the NBDSs must await a three-dimensional structure for unstained two-dimensional crystals of P-gp obtained by cryo-electron microscopy.

Comparison of P-gp with Bacterial ABC Transporters—The crystal structures of two bacterial ABC transporters, MsbA and BtuCD, have recently been determined (9, 11). These structures differ substantially from each other. We attempted to fit high-resolution coordinates for the protein backbone of the TMDs from both bacterial transporters to the high-density (TMD) region of nf-P-gp (the bacterial ABC structures were determined in the absence of nucleotide ligand). The global structure of BtuCD is similar to that of nf-P-gp (Fig. 3), but the 20 transmembrane α-helices of BtuCD could not be readily modeled onto the nf-P-gp map. This is presumably, in part, because the BtuCD TMDs contain a total of 20 transmembrane α-helices, in contrast to the 12 of P-gp. However, it should be noted that the lack of sequence similarity is such that it is not possible to determine which α-helices, if any, of P-gp correspond to which of BtuCD. Similarly, the TMDs of the intact MsbA homodimer (MsbA is equivalent to a half-molecule of P-gp, and a homodimer of two monomers is believed to form the functional molecule) could not be fitted to the P-gp densities (Fig. 3). However, making the assumption that the dimer interface in the MsbA crystals is not the natural interface (38, 39; see also under “Discussion”), the transmembrane regions of two separated MsbA monomers could readily be modeled into the high density (TMD) region of nf-P-gp (Fig. 4). The ‘arcuate’ arrangement of the α-helices in each of the two MsbA monomers almost exactly forms the barrel shape of the TMDs of nf-P-gp. The nf-P-gp map is slightly larger than the volume occupied by two MsbA monomers, probably because of different resolution thresholds for the electron versus x-ray crystallography data.

DISCUSSION

We have determined and compared the three-dimensional structures of nf-P-gp and P-gp-AMP-PNP. Because of the way the crystals were grown and stained, the NBDSs were not clearly seen. Their role in the transport process is unknown.

The new structural data show substantial reorganization of the TMDs of P-gp upon binding nucleotide. We have previously reported such structural changes (28), but because these were observed from projections of the molecule the maps were restricted to two-dimensions. The three-dimensional structures presented here show that these conformational changes occur throughout the depth of the membrane and must therefore involve repacking of the transmembrane α-helices within the membrane. They show the transformation of a cylindrical, barrel-like structure into three discrete domains, one of which is slightly smaller than the other two but longer perpendicular to the membrane. This conformational change opens one side of the pore throughout much of its length, equivalent to most of the depth of the lipid bilayer. In a membrane environment, this would create access from the lipid bilayer to the central pore. Because hydrophobic drugs interact with P-gp from the lipid phase (40–42), this suggests a model in which the TMDs part to enable hydrophobic drugs in the bilayer to enter the central pore prior to extrusion, rather than a model in which the drug moves across the membrane along a lipid-protein interface at the outer surface of the P-gp molecule. The conformational changes observed are consistent with a ‘helix rotation’ model for transport (39) but would be difficult to square with a ‘tilting helix’ model (11). Finally, it is significant that major conformational change occurs upon ATP binding rather than ATP hydrolysis. Although it has often been assumed that ATP hydrolysis drives the transport process, recent biochemical data show that reductions in drug binding affinity to P-gp are also due to ATP binding rather than hydrolysis (17, 18, 28).

Thus, ATP binding appears to drive the major conformational changes that reduce drug binding affinity and expose the drug binding site to the extracellular milieu (central aqueous pore); ATP hydrolysis may therefore simply ‘reset’ the transporter (14).

Unlike the NBDSs, the TMDs of different ABC transporters share little sequence homology, except within very closely related sub-families. It is therefore unclear whether the TMDs of different sub-families of ABC transporters are related to each other either evolutionarily or structurally. The two high-resolution structures reported for bacterial TMDs (9, 11) are radically different from each other (Fig. 3, b and c). Furthermore, neither the TMDs of the MsbA dimer nor the TMDs of BtuCD can be modeled onto the nf-P-gp TMD structure determined here (note, the MsbA and BtuCD structures were obtained in the absence of bound nucleotide). Confidence in the P-gp structure, although at lower resolution, comes from the fact that a similar structure was obtained by the very different methods of single particle imaging and electron crystallography and that the protein used was shown to be almost fully active both in drug binding and ATP hydrolysis (27–29). The TMDs of two separated MsbA monomers could, however, readily be mapped onto the TMDs of nf-P-gp (Fig. 4) if they were rotated away from the dimer interface suggested by the original MsbA crystal structure (11). Other considerations suggest that the crystallographic dimer interface reported for MsbA may not reflect the in vivo dimer interface (38, 39). The question of whether the packing of α-helices in the monomer of MsbA actually reflects that of P-gp awaits more sophisticated modeling and a higher resolution structure for P-gp. Cross-linking data (43) already suggest that there will be important differences. Nevertheless, the present data do show that the densities of the TMDs of nf-P-gp are entirely consistent with a pseudo-symmetric structure of 2 × 6 transmembrane α-helices arranged to form a barrel (Fig. 4).

Acknowledgments—We thank Drs. K. J. Linton (Medical Research Council Clinical Sciences Centre, London) and I. Kerr (University of Nottingham) for helpful discussions, Drs. J. P. Derrick and S. Prince (Biomolecular Sciences, University of Manchester Institute of Science and Technology) for help with the XtalView software, and Dr. K. Sidhu and Dr. S. J. Hubbard and S. Oliver (Biomolecular Sciences, UMIST) for computer support.

REFERENCES

1. Higgins, C. F., Hiles, I. D., Salmond, G. P., Gill, D. R., Downie, J. A., Evan, I. J., Holland, I. B., Gray, L., Buckel, S. D., Bell, A. W., and Hermodson, M. A. (1996) Nature 383, 448–450
2. Linton, K. J., and Higgins, C. F. (1998) Mol. Microbiol. 32, 5–13
3. Higgins, C. F. (1999) Annu. Rev. Cell Biol. 8, 67–113
4. Kerr, I. D. (2002) Biochim. Biophys. Acta 1561, 47–64

2 D. R. Stenham, J. D. Campbell, M. S. P. Sansom, C. F. Higgins, I. D. Kerr, and K. J. Linton, manuscript in preparation.
14. Sauna, Z. E., and Ambudkar, S. V. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 8009–8014
15. Martin, C., Berridge, G., Mistry, P., Higgins, C. F., Charlton, P., and Callaghan, R. (2000) J. Biol. Chem. 275, 19383–19390
16. Al-Shawi, M. K., and Senior, A. E. (1993) Biochemistry 32, 7502–7507
17. Martin, C., Berridge, G., Mistry, P., Higgins, C. F., Charlton, P., and Callaghan, R. (2001) Biochemistry 40, 15733–15742
18. Loo, T. W., and Clarke, D. M. (1996) J. Biol. Chem. 271, 16685–16694
19. Liu, R., and Shai, N. (1996) Science 273, 1019–1022
20. Rosenberg, M. F., Velarde, G. S., Ford, R. C., Martin, C., Berridge, G., Kerr, I. D., Callaghan, R., Schmidlin, A., Wolting, C., Linton, K. J., and Higgins, C. F. (2000) EMBO J. 20, 5615–5625
21. Liu, R., and Shai, N. (1996) Biochemistry 35, 4332–4339
22. Liu, R. H., Siemiarczuk, A., and Sharom, F. J. (2000) Biochemistry 39, 14927–14938
23. Rosenberg, M. F., Velarde, G. S., Ford, R. C., Martin, C., Berridge, G., Kerr, I. D., Callaghan, R., Schmidlin, A., Wolting, C., Linton, K. J., and Higgins, C. F. (2000) EMBO J. 20, 5615–5625
24. Rosenberg, M. F., Velarde, G. S., Ford, R. C., Martin, C., Berridge, G., Kerr, I. D., Callaghan, R., Schmidlin, A., Wolting, C., Linton, K. J., and Higgins, C. F. (2000) EMBO J. 20, 5615–5625
25. Liu, R., and Shai, N. (1996) Biochemistry 35, 11865–11873
26. Sonveaux, N., Shapiro, A. B., Goormaghtigh, E., Ling, V., and Ruysschaert, J. M. (1996) J. Biol. Chem. 271, 24617–24624
27. Rosenberg, M. F., Callaghan, R., Ford, R. C., and Higgins, C. F. (1997) J. Biol. Chem. 272, 10685–10694
28. Rosenberg, M. F., Velarde, G. S., Ford, R. C., Martin, C., Berridge, G., Kerr, I. D., Callaghan, R., Schmidlin, A., Wolting, C., Linton, K. J., and Higgins, C. F. (2000) EMBO J. 20, 5615–5625
29. Callaghan, R., Berridge, G., Ferry, D. R., and Higgins, C. F. (1997) Biochim. Biophys. Acta 1328, 109–124
30. Auer, M., Scarborough, G. A., and Kuhlbrandt, W. (1998) Nature 392, 840–843
31. Auer, M., Scarborough, G. A., and Kuhlbrandt, W. (1999) J. Mol. Biol. 297, 961–968
32. Crowther, R. A., Henderson, R., and Smith, J. M. (1996) J. Struct. Biol. 116, 9–16
33. Ames, L. A., Henderson, R., and Unwin, P. N. T. (1982) Proc. Natl. Acad. Sci. U. S. A. 97, 2515–2520
34. Bailey, S. (1994) Acta Crystallogr. Sect. D Biol. Crystallogr. 50, 44–47
35. Brillinger, D. R., Downing, K. H., and Glaeser, R. M. (1990) J. Stat. Plan. Inf. 27, 39–5615
36. Harris, J. R., and Holzenburg, A. (1995) J. Mol. Graphics 13, 348–354
37. Ruffle, S. V., Mustafa, A., Kitmitto, A., Holzenburg, A., and Ford, R. C. (2002) J. Biol. Chem. 277, 25492–25509
38. Lee, J-Y., Urbatsch, I. L., Senior, A. E., and Wilkens, S. (2002) J. Biol. Chem. 277, 40125–40131
39. Higgins, C. F., and Linton, K. J. (2001) Science 293, 782–784
40. Higginson, C. F., and Gottesman, M. M. (1992) Trends. Biochem. Sci. 17, 18–21
41. Raviv, Y., Pollard, H. B., Bruggeman, E. P., Pasteur, I., and Gottesman, M. M. (1990) J. Biol. Chem. 265, 3975–3980
42. Hollo, Z., Homolya, L., Davis, C. W., and Sarkadi, B. (1994) Biochim. Biophys. Acta 1191, 384–388
43. Loo, T. W., and Clarke, D. M. (1996) J. Biol. Chem. 271, 27482–27487
44. Brillinger, D. R., Downing, K. H., and Glasser, R. M. (1990) J. Stat. Plan. Inf. 25, 253–259
45. Glasser, R. M., and Downing, K. H. (1992) Ultramicroscopy 47, 256–265
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J. Biol. Chem. 2003, 278:8294-8299.
doi: 10.1074/jbc.M211758200 originally published online December 25, 2002

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