Steroid-selective Initiation of Chromatin Remodeling and Transcriptional Activation of the Mouse Mammary Tumor Virus Promoter Is Controlled by the Site of Promoter Integration*

(Received for publication, July 14, 1998, and in revised form, September 18, 1998)

James R. Lambert and Steven K. Nordeen‡
From the Department of Pathology and Program in Molecular Biology, University of Colorado Health Sciences Center, Denver, Colorado 80262

The mouse mammary tumor virus (MMTV) promoter has target sequences recognized by several steroid receptors. We present evidence for a novel mechanism that confers hormone specificity to this promoter. We show that remodeling of MMTV chromatin and the concomitant activation of the MMTV promoter are induced equally by glucocorticoids and progestins in one chromosomal context but are selective for glucocorticoids in another. Furthermore, increased histone acetylation modulates MMTV promoter regulation disparately at the two chromosomal locations. Together, these data indicate that chromosomal architecture commands a crucial role in gene regulation, imposing locus-specific selectivity between regulators with similar sequence recognition.

Many of the concepts that underlie the current understanding of both steroid hormone action and the role of chromatin in the regulation of gene expression have sprung from studies employing the mouse mammary tumor virus (MMTV)1 long terminal repeat (LTR) as a model promoter. Target sequences related to a TGTTCT motif direct hormone-induced transcription by glucocorticoid receptors (GR), progesterone receptors (PR), and mineralocorticoid and androgen receptors (1–8). In stable chromatin, the MMTV LTR also directs the assembly of an ordered nucleosome array that represses loading of basal transcription factors on the promoter. Activation of GR or PR by hormones promotes the remodeling of the MMTV chromatin and the loading of basal transcription factors. In contrast, nucleosomes are dynamically arrayed on transiently transfected MMTV templates. Such templates exhibit elevated constitutive levels of transcription factor loading and promoter activity and, consequently, a reduced induction by hormones (9–11). Thus, the organization of chromatin and its remodeling by steroid hormones are critical to appropriate steroid-mediated regulation.

Although GR and PR recognize the same target elements and each induces certain genes regulated by the other receptor, the two receptors mediate very different actions in tissues such as the mammary epithelium that can express both receptors. GR and PR are expressed at comparable levels in the T47D(A1–2) mammary carcinoma cell line. This cell line also contains 10 copies of a stably transfected MMTV-luciferase (LUC) reporter gene. Surprisingly, luciferase is induced by glucocorticoids but is almost entirely refractory to progestins, whereas a transiently transfected template, MMTV-chloramphenicol acetyltransferase (CAT), is responsive to both hormones. On the MMTV-LUC template, glucocorticoids induce remodeling of chromatin, whereas progestins fail to do so (12).

Selectivity between two regulators that recognize the same target element could be a property inherent to a promoter sequence, a property that cannot be reconstituted on transient chromatin. Alternatively, the chromatin at the site of integration of a transgene may impose a selective mechanism on the integrated promoter. Examples of integration site determining whether a gene is expressed or silenced range from mating type choice in yeast and position effect variegation in Drosophila to recombinant transgenes in mice. However, there is little precedent for more subtle controls such as the imposition of selectivity between two related transcription factors that employ the same target elements. In this report, we address the mechanism that enforces a selective response of MMTV-LUC to glucocorticoids in T47D(A1–2) cells. We show that after stable integration, a second MMTV-driven reporter gene, MMTV-CAT, is responsive to both glucocorticoids and progestins in T47D(A1–2) cells. The responsiveness of MMTV to hormone treatment is reflected in the ability of the GR and PR to remodel MMTV chromatin in an integration site-specific manner. Progestin treatment leads to remodeling of the MMTV-CAT promoter but not MMTV-LUC, whereas glucocorticoids promote chromatin remodeling of both. We also investigated the effect of increased histone acetylation on chromatin remodeling and gene activation of MMTV-LUC and MMTV-CAT in this cell line. Surprisingly, the steroid-dependent induction of the MMTV promoter is potentiated at one chromosomal location but inhibited at another. These studies provide evidence for the imposition of locus-specific constraints in steroid hormone regulation of gene expression.

MATERIALS AND METHODS

Plasmids and Stable Transfection—The plasmids pHHLUC and pHHCAT contain MMTV sequences from HaeIII(–224) to HpaII(+100) upstream of the coding sequences for the firefly luciferase gene and the bacterial chloramphenicol acetyltransferase gene, respectively.

For stable transfection, 1 × 10⁶ T47D(A1–2) cells/10-cm dish were plated and allowed to grow for 24 h before transfection in minimal essential medium plus 200 μg/ml G418. One hour before transfection, the culture medium was changed to allow proper pH equilibrium. A calcium phosphate/DNA precipitate was prepared essentially according to Wigler et al. (13). One milliliter of this mixture containing a total of 21 μg/ml DNA (20 μg/ml pHHCAT plus 1 μg/ml pSV2hygro) was added...
Steroid-selective Chromatin Remodeling

RESULTS

Steroid-selective Induction of the MMTV Promoter Is Determined by the Locus of Integration of MMTV—To distinguish whether selective induction of the MMTV-LUC genes in T47D(A1–2) cells is an inherent property of stable versus transient chromatin or is imposed on MMTV by the properties of integration site(s), we stably introduced another MMTV-driven transcription unit (MMTV-CAT) into T47D(A1–2) cells and examined its regulation in response to glucocorticoids or progestins. A clone derived from this transfection, T47D(C&L), expressed comparable levels of GR and PR like the parent T47D(A1–2) line and contained one to two copies of MMTV-LUC. BMP-induced LUC (Fig. 1A). BMP-2

**Fig. 1.** The MMTV promoter is regulated differently when integrated into different chromosomal sites. A, hormonal induction of luciferase activity directed by pHLHUC. B, hormonal induction of CAT activity directed by pHHCAT. C, hormonal induction of ALP activity directed by the liver/bone/kidney alkaline phosphatase gene. T47D(C&L) cells were seeded at a density of 0.6 × 10^6 cells/60-mm dish and 18 h later were treated with dexamethasone (100 nM), R5020 (10 nM), or vehicle for 24 h. Luciferase, CAT, and ALP activities were determined on aliquots of the same extract, and the data were normalized to protein content of the extract. Results represent the average of three experiments, where each condition was done in duplicate.
ticos induced CAT activity to a similar level in T47D(C&L) cells (Fig. 1B). We also examined expression of an endogenous hormone-regulated gene, the liver/bone/kidney form of alkaline phosphatase (ALP). R5020 induces ALP to levels as high or higher than seen with dexamethasone (Fig. 1C). Virtually identical LUC, CAT, and ALP induction results were observed in a second, independent MMTV-CAT-transfected clone (data not shown). It is unlikely that the difference in inducibility of MMTV-CAT and MMTV-LUC is attributable to the reporter gene itself. Stably integrated MMTV-LUC is inducible by both progestins and glucocorticoids in another cell line we have constructed. Also, a recent report describes a cell line with integrated MMTV-CAT genes that are differentially induced by glucocorticoids and mineralocorticoids (15). Together, these data indicate that differential induction is not determined by the structural gene or simply the packaging into stable chromatin but, as we suggest, by the chromosomal context of the transcription unit. Thus, the chromatin environment at the site of MMTV integration can have a profound influence on the nature of its regulation by steroid hormones.

Steroid-selective Chromatin Remodeling of the MMTV Promoter Correlates with MMTV Promoter Activity—In stable chromatin, an ordered array of nucleosomes is assembled on the MMTV LTR (9). The steroid receptor target elements are present in DNA assembled into nucleosome B (10). These sequences are relatively inaccessible until hormone stimulation induces a remodeling event at nucleosome B. Previous studies using an in vivo nuclease accessibility assay showed that the differential inducibility of the MMTV promoter in T47D(A1–2) cells was associated with the failure of progestins to promote the remodeling of MMTV chromatin (12). We used a similar assay to assess the action of GR and PR at the MMTV promoter in T47D(C&L) cells (Fig. 2A). Glucocorticoids induced chromatin remodeling (increased SacI sensitivity) of nucleosome B of MMTV from both LUC and CAT loci. Progestins likewise induced chromatin remodeling of MMTV-CAT yet at the same time failed to induce remodeling of the MMTV-LUC transgenes in the same cells (Fig. 2, B and C).

Further evidence that differential hormone induction of MMTV-LUC is functionally linked to rearrangement of nucleosome B in the MMTV-LUC promoter was provided when we used the histone deacetylase inhibitor butyric acid. Hormone-induced chromatin remodeling of the MMTV-LUC promoter was unchanged or enhanced following butyrate (Fig. 2B) at the same time butyrate consistently suppressed remodeling at the MMTV-CAT promoter (Fig. 2C). These results correlate with the enhancement of GR-mediated transcription of MMTV-LUC and the suppression of GR- and PR-mediated transcription of MMTV-CAT (see below).

The inability of PR to remodel MMTV chromatin and induce LUC expression is unlikely to be due to a failure to bind to the PR target elements. We infer that receptor target sites in MMTV-LUC are available to PR because coadministration of R5020 with dexamethasone inhibits the glucocorticoid induction of MMTV-LUC (12). These data suggest that ligand-bound PR competes for binding to target sites on the MMTV promoter with hormone-activated GR. It is unlikely that this inhibition is attributable to competition for coactivators rather than competition for binding target elements, because transcriptionally inactive PR bound to a ligand antagonist also suppresses the glucocorticoid induction of luciferase (16).

The mechanistic implication of the data is that MMTV chromatin at the LUC loci is structured in a novel fashion under the influence of the surrounding chromatin so as to abrogate the remodeling and concomitant gene induction that would normally occur following PR binding to its target elements. This abrogation may result from the inability of PR to interact with chromatin remodeling proteins that are necessary for steroid receptor-mediated gene induction (17–21). In contrast, the ability of GR to initiate remodeling of MMTV-LUC chromatin and transcriptional induction is not impaired.

Chromosomal Architecture Surrounding MMTV Luciferase Integration Sites—To explore the nature of the integration site(s) of MMTV-LUC transgenes in T47D(A1–2) cells, FISH analysis was performed with a probe specific for luciferase. Approximately 50 metaphases were analyzed per hybridization site. Four fluorescent bands were detected in the long arm of a
single, C size, submetacentric, marker chromosome in all cells analyzed (Fig. 3A). Cot-1 repetitive DNA was used to paint metaphase chromosomes. Cot-1 DNA sequences are extremely repetitive and highly represented in constitutive heterochromatin. The LUC loci were relatively devoid of Cot-1 signal, whereas the flanking regions were intensely highlighted (Fig. 3B). Similar evidence that the MMTV-LUC loci differ distinctly from the flanking chromosomal domains is revealed by GTG banding and DAPI staining. The MMTV-LUC loci corresponded to light G bands flanked by distinctive, dark G bands (Fig. 3E). DAPI staining exhibited a similar pattern whereby the LUC loci were flanked by bright DAPI bands (Fig. 3C). The exclusion of luciferase from the Cot-1 and DAPI staining chromosomal domains is evidenced in Fig. 3D, in which the luciferase, Cot-1, and DAPI signals are overlaid. DAPI has affinity for AT-rich regions of DNA, and dark G-bands are also rich in AT sequences, poor in coding sequences, and rich in L1 type interspersed repeats (23). Summarized schematically in Fig. 3F, the presence of distinctive, defined chromosomal domains flanking each of the MMTV-LUC loci suggest that chromatin structure contributes to the novel, locus-specific, selective regulation of the MMTV promoter.

**Differential Effects of Histone Acetylation at the MMTV Promoter Determined by MMTV Integration Sites**—Additional evidence that the integration sites of MMTV-LUC and MMTV-CAT endow the promoter with functionally distinct properties comes from experiments in which we used inhibitors of histone deacetylation. Histone acetylation modifies chromatin architecture, and histone acetyltransferases have been demonstrated to interact with nuclear receptors and to serve as transcriptional coactivators (24–27). Treatment of T47D(C&L) cells with the deacetylase inhibitor butyrate led to a dose-dependent increase in histone acetylation (Fig. 4A). At all doses, butyrate dramatically potentiated the glucocorticoid induction of luciferase (Fig. 4B). While butyrate did not lead to restoration of progesterone induction of luciferase to levels comparable with that seen with glucocorticoid activation, the small induction seen with progestins was also potentiated by butyrate (note scale difference, Fig. 4B). In contrast, the hormonal induction of MMTV-CAT in the same cells was inhibited at all doses of butyrate (Fig. 4C). Hormone-induced chromatin remodeling of the MMTV-LUC promoter was unchanged or enhanced follow-
ing butyrate (Fig. 2B) at the same time butyrate consistently suppressed remodeling at the MMTV-CAT promoter (Fig. 2C). A differential action upon the hormone induction of the MMTV-LUC and MMTV-CAT genes was also seen with the more specific deacetylase inhibitor trichostatin A. Trichostatin A potentiated hormone induction of MMTV-LUC activity much like butyrate but had little effect on induction of MMTV-CAT (data not shown). Thus, while a differential effect is still observed with trichostatin A, the data suggest that the butyrate inhibition of CAT induction may be through mechanisms other than deacetylase inhibition or involve deacetylases not inhibited by trichostatin A. These data confirm that the activity of the MMTV promoter can be regulated in a very distinct manner at different chromosomal locations. Moreover, these data provide a likely basis to account for the conflicting findings regarding the effect of butyrate on hormone responsiveness of MMTV (28, 29).

**DISCUSSION**

Specificity is a central question in the regulation of gene expression. Within a family, transcription factors expressed in the same cell can have identical DNA sequence recognition properties yet distinct activities. For example, GR and PR are both expressed in mammary epithelial cells, but the two hormones have very different effects. The mechanisms by which such specificity is generated are not well understood. In this report, we have presented evidence for a novel mechanism that confers specificity so that a promiscuously hormone responsive promoter is enabled to respond selectively to one of the two receptors.
The MMTV promoter has been widely used as a model system for studying the role of chromatin structure in the regulation of gene expression by steroid hormone receptors. In stable chromatin, the MMTV LTR directs the assembly of an ordered nucleosome array (9, 10). The target sites for steroid receptor binding lie within the region occupied by nucleosome B, and this nucleosome is remodeled upon activation of the MMTV promoter by hormones. This is evidenced by an increased accessibility of the chromatinized DNA to cleavage by restriction enzyme digestion and increased loading of basal factors (9–11). Beginning with the demonstration that the activity of GR expressed in yeast requires the SWI-SNF chromatin remodeling complex (17), subsequent work has supported a role for chromatin remodeling in steroid hormone action (18–21). Recently, preparation in vivo

Glucocorticoids and progestins can induce many of the same promoters including MMTV. This is not surprising, since the DNA binding domains of GR and PR have very high sequence identity (32) and target sequence utilization (33, 34). Thus, the question of how these two transcriptional activators can generate specific responses in tissues where both may be expressed is an important issue. We previously made the surprising observation that in T47D(A1–2) cells engineered to express comparable levels of GR and PR, a stably integrated MMTV-luciferase template can be induced by glucocorticoids but is almost completely refractory to progestins. Unlike glucocorticoids, progestins fail to initiate remodeling of the MMTV promoter (12). Here we explored the unique possibility that the MMTV integration site determines the ability of the PR to remodel MMTV chromatin and activate transcription. Our approach involved the stable introduction of an additional MMTV-driven reporter gene (MMTV-CAT) into T47D(A1–2) cells. We then examined the induction of this reporter in response to treatment with glucocorticoids and progestins. In contrast to the differential induction of MMTV-LUC, a robust induction of MMTV-CAT was observed after treatment with either the synthetic glucocorticoid dexamethasone or the synthetic progestin R5020. Because the MMTV LTR sequences used in the construction of MMTV-LUC and MMTV-CAT are the same, the observed differential capacity of PR to induce transcription from MMTV-LUC and MMTV-CAT cannot be attributed to differences in MMTV promoter sequences. Additionally, the full complement of factors required for PR activation appears to be present in T47D(C&L) cells as evidenced by PR-mediated induction of MMTV-CAT or the endogenous ALP gene. The specific characteristics of these chromosomal domains, which either allow or prevent PR from activating MMTV, remains unknown. Efforts are currently under way to explore the nature of these MMTV integration sites and their role in the differential activation of MMTV by steroid hormone receptors.

Previously, it has been reported that histone acetylation can have either inhibitory or stimulatory effects on MMTV promoter activity, depending on the experimental system. Hager and colleagues (29) reported that the histone deacetylase inhibitor butyrate inhibits GR activation of MMTV by blocking remodeling of nucleosome B. Beato and colleagues (28) have shown that the response of the MMTV promoter can be modulated by the degree of histone acetylation; moderate histone acetylation led to activation of MMTV, while higher levels of histone acetylation led to a reduction of MMTV activity. In this paper, we show that increased histone acetylation is interpreted very differently at different chromosomal sites. At one, the hormonal induction of MMTV promoter activity is potentiated, whereas at another it is inhibited or unaffected. These results suggest a mechanism, perhaps a specific chromatin architecture at the integration site, that can impose selectivity on a promiscuously responsive promoter. The ramifications of this suggestion are of enormous importance, implying that such chromosomal regulatory domains are a critical determinant of tissue and hormone specificity of gene responsiveness. Such mechanisms could also play important roles in development and homeostasis by enforcing specificity of action among members of transcription factor families that have similar DNA recognition properties.

There are many examples where chromatin architecture has been implicated in determining whether a gene is expressed. Notable examples under active investigation include position effect variegation in Drosophila and gene silencing near telomeres in yeast. Although mammalian examples are less tractable experimentally, certainly X chromosome inactivation and parental imprinting have received considerable attention. The results of the present work imply that controls more subtle than a simple on or off decision are at work, identifying a novel mechanism for differential regulation of gene expression. It will be important to identify additional examples. One possibility is the recent report of a stably transfected MMTV-CAT gene inducible by glucocorticoids but refractory to mineralocorticoids (15).

Chromatin architecture may also influence the modulation of steroid-mediated induction by cellular signal transduction pathways. The hormonal activation of the MMTV promoter has been reported to be potentiated by cAMP in transient chromatin but inhibited in stable chromatin (35). However, inhibition is not a universal finding. Both GR and PR action on stably integrated MMTV promoters can be potentiated in fibroblasts and mammary carcinoma cell lines, including T47D(A1–2) (36–39). Although it is difficult to compare results between different cell lines, these data may suggest that the response of the steroid induction to cAMP elevation may differ at different chromosomal locations. Together with the present data, these findings provide support for the concept of chromatin architecture imposing constraints that can confer differential transcriptional responses.

Acknowledgments—We thank Dr. Mariel Garcia and the University of Colorado Health Sciences Center Cytogenetics core laboratory for help with the FISH analysis; T. Archer for helpful discussions; and S. Martin, T. Blumenthal, and J. Jaehning for critically reading the manuscript.

REFERENCES

1. Chandler, V. L., Maler, B. A., and Yamamoto, K. R. (1983) Cell 33, 489–499
2. Scheideriet, C., and Beato, M. (1984) Proc. Natl. Acad. Sci. U. S. A. 81, 5329–5333
3. Majors, J., and Varmus, H. E. (1983) Proc. Natl. Acad. Sci. U. S. A. 80, 5866–5870
4. Cato, A. C. B., Mikol, R., Shutz, G., Arnemann, J., and Beato, M. (1986) EMBO J. 5, 2237–2240
5. Darbre, P. D., Page, M., and King, R. J. B. (1986) Mol. Cell. Biol. 6, 2847–2854
6. Cato, A. C. B., Henderson, D., and Punta, H. (1987) EMBO J. 6, 363–368
7. Arriza, J. L., Weinberger, C., Cerelli, G., Glaser, T. M., Handel, B. L., Housman, D. E., and Evans, R. M. (1987) Science 237, 268–275
8. Ham, J., Thompson, A., Needham, M., Webb, P., and Parker, M. (1988) Nucleic Acids Res. 16, 5263–5267
9. Richard-Foy, H., and Hager, G. L. (1987) EMBO J. 6, 2321–2328
10. Truss, M., Bartsch, J., Schelbhart, A., Hache, R. J. G., and Beato, M. (1995) EMBO J. 14, 1737–1751
11. Archer, T. R., Lefebvre, P., Woldfogel, R. F., and Hager, G. L. (1992) Science 255, 1573–1576
12. Archer, T. R., Zaniekiewski, E., Moyer, M. L., and Nordeen, S. K. (1994) Mol. Endocrinol. 8, 1154–1162
13. Wigler, M., Pellier, A., Silverstein, S., Axel, R., Urlaub, G., and Chasin, L. (1979) Proc. Natl. Acad. Sci. U. S. A. 76, 1373–1376
14. Affolger, C. R., Zweidler, A., Mahowald, A., and Cohen, L. H. (1974) J. Biol. Chem. 249, 3729–3736
15. Bonovitch, M. T., List, H. J., Zhang, S., Danilewski, M., and Riegel, A. T. (1998) J. R. Lambert and S. K. Nordeen, unpublished observations.

Steroid-selective Chromatin Remodeling

32713

by guest on July 24, 2018http://www.jbc.org/Downloaded from
Steroid-selective Chromatin Remodeling

16. Gass, E. K., Leonhardt, S. A., Nordeen, S. K., and Edwards, D. P. (1998) Endocrinology 139, 1905–1919
17. Yoshinaga, S. K., Peterson, C. L., Herskowitz, I., and Yamamoto, K. R. (1992) Science 258, 1598–1604
18. Chiba, H., Muramatsu, M., Nomoto, A., and Kato, H. (1994) Nucleic Acids Res. 22, 1815–1820
19. Khavari, P. A., Peterson, C. L., Tamkun, J. W., Mendel, D. B., and Crabtree, G. R. (1995) Nature 366, 170–174
20. Muchardt, C., and Yaniv, M. (1993) EMBO J. 12, 4279–4280
21. Ostlund Farrants, A-K., Blomquist, P., Kwon, H., and Wrange, O. (1997) Mol. Cell. Biol. 17, 895–905
22. Nordeen, S. K. (1988) BioTechniques 6, 454–458
23. Gardiner, K. (1995) Curr. Opin. Genet. Dev. 5, 315–322
24. Spencer, T. E., Jenster, G., Burcin, M. M., Allis, C. D., Zhou, J., Mizzen, C. A., McKenna, N. J., Onate, S. A., Tsai, S. Y., Tsai, M. J., and O’Malley, B. W. (1997) Nature 389, 194–198
25. Nagy, L., Kao, H. Y., Chakravarti, D., Lin, R. J., Hassig, C. A., Ayer, D. E., Screiber, S. L., and Evans, R. M. (1997) Cell 89, 373–380
26. Torchia, J., Rose, D. W., Inostroza, J., Kamei, Y., Westin, S., Glass, C. K., and Rosenfeld, M. G. (1997) Nature 387, 677–684
27. Chen, H., Lin, R. J., Schiltz, R. L., Chakravarti, D., Nash, A., Nagy, L., Privalsky, M. L., Nakatani, Y., and Evans, R. M. (1997) Cell 89, 569–580
28. Bartsch, J., Truss, M., Bode, J., and Beato, M. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 10741–10746
29. Bresnick, E., John, S., Berard, D. S., Lefebvre, P., and Hager, G. L. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 9183–9187
30. Fryer, C. J., and Archer, T. K. (1998) Nature 393, 88–91
31. Bresnick, E. H., Rories, C., and Hager, G. L. (1992) Nucleic Acids Res. 20, 865–870
32. Miesfeld, R. L. (1989) Crit. Rev. Biochem. Mol. Biol. 24, 101–117
33. Lieberman, B. A., Bona, B. J., Edwards, D. P., and Nordeen, S. K. (1993) Mol. Endocrinol. 7, 515–527
34. Nordeen, S. K., Suh, B. J., Kuhnel, B., and Hutchison, C. A., III (1996) Mol. Endocrinol. 4, 1866–1873
35. Pennie, W. D., Hager, G. L., and Smith, C. L. (1995) Mol. Cell. Biol. 15, 2125–2134
36. Nordeen, S. K., Moyer, M. L., and Bona, B. J. (1994) Endocrinology 134, 1723–1732
37. Beck, C. A., Weigel, N. L., Moyer, M. L., Nordeen, S. K., and Edwards, D. P. (1993) Proc. Natl. Acad. Sci. U. S. A. 90, 4441–4445
38. Nordeen, S. K., Bona B. J., and Moyer, M. L. (1993) Mol. Endocrinol. 7, 731–742
39. Moyer, M. L., Borror, K. C., Bona, B. J., DeFranco D. B., and Nordeen, S. K. (1993) J. Biol. Chem. 268, 22933–22940
Steroid-selective Initiation of Chromatin Remodeling and Transcriptional Activation of the Mouse Mammary Tumor Virus Promoter Is Controlled by the Site of Promoter Integration

James R. Lambert and Steven K. Nordeen

J. Biol. Chem. 1998, 273:32708-32714.
doi: 10.1074/jbc.273.49.32708

Access the most updated version of this article at http://www.jbc.org/content/273/49/32708

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 39 references, 14 of which can be accessed free at http://www.jbc.org/content/273/49/32708.full.html#ref-list-1