Independent and Cooperative Activation of Chromosomal c-fos Promoter by STAT3*

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The c-fos gene was one of the earliest vertebrate genes shown to be transcriptionally induced by growth factors. Intensive study of the promoter of c-fos (−325 to −80) by transient or permanent transfections of synthetic DNA constructs has repeatedly shown the importance of several sequence elements and the resident nuclear proteins that bind them (e.g. ternary complex factor/ELK1; serum response factor, cAMP response element-binding protein/amino-terminal fragment/AP-1). However these studies have left unanswered numerous questions about the role of these proteins in the regulation of the native chromosomal gene. In particular, the role of a site in this enhancer that binds STATs has been controversial. We present evidence here that STAT3 and not STAT1 accumulates on the chromosomal c-fos promoter and provides a boost to transcription without the activation of resident nuclear proteins through serine kinases. Also, when resident nuclear proteins such as ELK1 are activated by varying extents by mitogen-activated protein kinase pathways, STAT3 activation provides a 2-fold boost regardless of the final level of activated transcription. Thus the several proteins that interact with the c-fos enhancer apparently can act either in a cooperative or independent manner to achieve very different levels of transcription.

The c-fos proto-oncogene encodes a basic leucine zipper transcription factor, the gene of which is activated transcriptionally in response to a wide range of extracellular stimuli including mitogenic growth factors (1, 2). c-fos was one of the founding members of the “immediate early” response genes and was shown by run-on transcription analysis to be stimulated promptly but briefly at the transcriptional level (1, 3). Because of this initial characterization, the c-fos promoter has been extensively studied, and binding sites for several DNA binding factors have been determined to lie between −325 and −60 upstream of the c-fos start site (4). Of particular note, the transfection of wild type and mutant c-fos promoter constructs has demonstrated the critical importance of the Ets and serum response elements at −320 (see Fig. 1). The Ets site is bound by ternary complex factors (TCFs),† Ets family members (i.e. ELK1, SAP1a/b, or SAP2) that are subject to inducible serine phosphorylation (4–7). In the case of ELK1, extracellular ligands stimulate mitogen-activated protein kinase phosphorylation of serine 383, leading to tighter association with serum response factor homodimers constitutively bound to the serum response element and to increased rates of transcription (8–10).

This basic framework was expanded by the discovery of several other binding sites, some of which participate in the regulation of the transactivated c-fos promoter through other signaling mechanisms. These mechanisms include a direct repeat element, a sis-inducible element (SIE) that can bind to the STATs, two TFII-I sites, and at least two cAMP-response element/AP-1-type sites that effect responses to extracellular signaling proteins through serine phosphorylation cascades (11–14). Histone modification of the chromatin substrate for chromosomal c-fos activation has been described recently (15, 16), but the assembly of resident nuclear proteins on the c-fos promoter during gene activation has not.

No firm conclusion has been reached about the importance of the SIE to the regulation of the chromosomal c-fos locus, which raises doubts about any role of the STATs in regulating c-fos transcription. On the one hand, the SIE is conserved across species (17), and in vivo footprinting has demonstrated SIE protection within 20 min of epidermal growth factor (EGF) stimulation (10). In an electromophoretic mobility shift assay (EMSA), the SIE site can clearly bind to STAT proteins that have been activated by treatment with platelet-derived growth factor and EGF, among other cytokines (18, 19), and reporter constructs bearing the SIE confer transient platelet-derived growth factor inducibility in the absence of the serum response element (13, 18). Also, mutations of this site in transiently expressed as well as stably integrated reporter constructs impair transcriptional responses not only to sis/platelet-derived growth factor but also to TPA and serum (4, 20).

However, other investigators have discounted the importance of STAT regulation. For example, deletion of the SIE from a luciferase construct including the TCF/serum response element/AP-1 sites failed to have any impact on EGF inducibility during the transfection of cultured HeLa cells (21). In addition, the discovery of an overlapping TFII-I site that is required for serum induction of c-fos (Fig. 1) has raised some doubts about whether the previously characterized mutations in the SIE site were the result of a loss of STAT or TFII-I function (14). Moreover the SIE does not resemble an optimal STAT-binding site (13, 22, 23). However, all of these transcription studies were not definitive for the native chromosomal
c-fos gene. Also, the stimuli used (e.g. growth hormone or EGF) have a very significant MAP kinase component that is known to be a potent stimulus on its own (e.g. TPA treatment) 

Therefore the extent to which STAT activity alone or in combination contributes to the regulation of the chromosomal gene has remained unclear.

In this series of experiments, we have examined chromosomal c-fos transcription by STAT3 in the absence of detectable STAT1 or MAP kinase activity. We find that STAT3 activation alone induces c-fos mRNA accumulation. Chromatin immunoprecipitation shows that STAT3 but not STAT1 can accumulate at the c-fos promoter. This selectivity in chromatin accumulation is not the result of differences in DNA-binding preferences that are evident in vitro DNA-binding assays, and it is presumably the result of STAT3 interaction with other nuclear proteins that are known to be on the promoter. Finally, we show that although the STAT3-associated induction of c-fos in response to human interleukin-6 (IL-6) is much weaker on its own than when induction is brought about by TPA or EGF stimulation, it maximizes the transcriptional response to either of these stimuli.

EXPERIMENTAL PROCEDURES

Cell Culture and Antibodies—HepG2 cells were obtained from ATCC and grown in Eagle’s modified essential medium (with nonessential amino acids, Earle’s salts, 2 mM l-glutamine, 1.5 g/liter sodium bicarbonate, and 1 mM sodium pyruvate) supplemented with penicillin/streptomycin (Invitrogen) and 10% fetal bovine serum (HyClone). Before all experiments, cells were serum-starved overnight with minimum Eagle’s medium containing 0.2% fetal bovine serum. Whole and fractionated cell extracts were prepared as described previously (24). Unless otherwise stated, recombinant IL-6 (R&D Systems) was used at a concentration of 2.5 ng/ml final concentration. 12-O-tetradecanoylphorbol-13-ace (TPA, Sigma) was resuspended in Me2SO and used at a concentration of 15 ng/ml final concentration. Recombinant human epidermal growth factor (EGF, Calbiochem) was used at a concentration of 50 ng/ml final concentration. Kinase inhibitors were used at 50 μM for PD098059 (MEK1 inhibitor) and 2 μM for SB203580 (p38 inhibitor). Inhibitors were added 10–15 min before stimulation with cytokine or TPA. Durations of treatments were as stated in the text. Phosphospecific antibodies for pT180/pY182-p38, pT202/pY204-ERK1/2, pY705-STAT3, pT202/pY204-JNK, and pT185-JNK, and pT180/pY182-p38 were obtained from Cell Signaling and used at a 1:1000 dilution for Western blotting. Antibodies to the STAT1 C terminus, STAT3 C terminus, ELK1, and pS383-ELK1 were obtained from Santa Cruz Biotechnology.

Electrophoretic Mobility Shift Assay—EMSA was performed as described previously (24, 25). Blunt-ended EMSA probes were phosphorylated by polynucleotide kinase in the presence of [γ-32P]ATP to approximately the same specific activity. The sequences for the oligonucleotide probes were (sense strand): SIE, 5′-GAGCAATTTCCGTCAGTCCT-3′; m67, 5′-GAGCAATTTCCCGTCAATCCCT-3′.

Chromatin Immunoprecipitation—Formaldehyde fixation, chromatin breakage, antibody precipitation protocols, and PCR conditions were described previously (25). The following antibodies were used for pre-
Mitogen-activated Protein Kinases and STATs Can Be Activated Separately in HepG2 Cells—Previous studies of STAT activation of the c-fos promoter have often made use of ligands for receptor tyrosine kinases that activate several signaling pathways in addition to the STATs (1–7; see the Introduction). Therefore the strong activation of the c-fos promoter by MAP kinases might obscure the impact of the STATs on the regulation of this locus. Furthermore, many ligands activate both STAT1 and STAT3. We dissected the contribution of different STATs from each other and from MAP kinases by using IL-6 at low concentrations that activated STAT3 preferentially to STAT1 (Fig. 2A); 2.5 ng/ml IL-6 affords near maximal activation of STAT3 with only a trace of activated STAT1. Because in some cell types IL-6 activates MAP kinase signaling (27) and might contribute to c-fos activation through this route, we determined the extent of MAP kinase activation in HepG2 cells under conditions of low-dose IL-6 treatment. Western blotting with phosphospecific antibodies to various MAP kinases and ELK1 established that the level of IL-6 treatment used does not lead to detectable MAP kinase activity (Fig. 2B, lanes 1–3). Likewise, treatment with TPA, which stimulates various serine kinases, did not lead to tyrosine phosphorylation of STAT3 (Fig. 2B, lanes 4 and 5). Thus the two activators, IL-6 and TPA, apparently act through different signaling pathways under these conditions. As reported previously, simultaneous cotreatment with TPA blocks IL-6-mediated tyrosine phosphorylation of STAT3 (28). STAT3 serine phosphorylation was found to be sensitive to application of the MEK1 inhibitor PD098059 (Fig. 2B, lanes 7–12), thereby precluding the use of MAP kinase inhibitors to completely remove the possibility of low level activation. In all cases in Fig. 2, equal loading was confirmed by stripping the Western blots and probing for equal STAT3 or ELK1 immunoreactivity (data not shown).

As judged by RT-PCR assays of mRNA concentration (Fig. 2C), TPA treatment led to a very large induction of the chromosomal c-fos gene, whereas a much smaller induction (∼5%) of the c-fos gene followed IL-6 treatment (Fig. 2C). Similar patterns were also observed for junB, an immediate early gene also thought to be subject to regulation by STAT3 (29) (Fig. 3). The IL-6-mediated stimulation of the c-fos and junB genes was attenuated by the addition of the kinase inhibitor PD098059, suggesting potential sensitivity of these promoters to STAT3 serine phosphorylation, a modification known to be required for maximal STAT3 transcriptional activity (30). This sensitivity to PD098059 was also observed for SOCS3, a target gene insensitive to TPA stimulation alone (data not shown).

Although the data shown in Fig. 2 suggested that IL-6-dependent STAT3 activation of c-fos transcription is possible, definitive proof required more sensitive examination of MAP kinase activity and direct evidence for binding to the chromosomal c-fos promoter by STAT3. We therefore sought a highly sensitive indicator of MAP kinase activity in HepG2 cells. With two c-fos copies per cell, we reasoned that c-fos promoter-bound phosphorylated ELK1, the terminal substrate of the various MAP kinases, should provide a sensitive marker for p38, ERK1/2, or c-Jun NH2-terminal kinase activity (31). Chromatin immunoprecipitation with anti-pS383-ELK1 antibodies showed the presence of serine phosphorylated ELK1 on the promoter after 30 min of TPA treatment but not after IL-6 treatment (Fig. 4A, lanes 6–8), suggesting again that IL-6 does not activate a serine kinase cascade that reaches the c-fos promoter. Therefore the IL-6 activation of the chromosomal c-fos gene is most likely to occur through STAT3.
STAT3 but Not STAT1 Is Present at the c-fos Promoter in Vivo—We then turned to the importance of STAT3 compared with STAT1 as an activator of c-fos by doing chromatin precipitation with various antibodies both on the c-fos promoter and the IRF-1 promoter, which is a gene activated by IFNγ through the activation of STAT1. RT-PCR demonstrated that IL-6 treatment leads to c-fos mRNA accumulation with minimal or no IRF-1 accumulation, and IFNγ leads to accumulation of IRF-1 mRNA but not c-fos mRNA (Fig. 3). We then performed chromatin immunoprecipitation experiments of the c-fos and IRF promoters. The anti-STAT3 antibody precipitated both c-fos and IRF-1 promoter DNA after 30 min of IL-6 treatment (Fig. 4A, lanes 1–3). On the other hand, activation for 30 min with the STAT1-specific cytokine IFNγ led to STAT1 accumulation at the IRF-1 promoter but not the c-fos promoter (Fig. 4A, lanes 4 and 5). As a control, precipitation of an internal segment of the c-fos coding region was found not to precipitate with either antibody (data not shown). Thus STAT3 accumulates at the c-fos promoter after IL-6 treatment, but STAT1 does not, which indicates a specificity for STAT3 over STAT1. On the other hand, both STAT3 and STAT1 accumulate on the IRF-1 promoter, but only STAT1 accumulation correlates with actual transcriptional activation (Fig. 3).

Selectivity of STAT Accumulation at the c-fos Promoter Is Not Because of Differences in DNA Binding Properties—Both STAT3 and STAT1 are known to bind to the SIE site in EMSA DNA binding assays (18, 32). Therefore the discovery of selective STAT3 retention at the c-fos locus during transcriptional activation raises two possibilities. One possibility is that STAT3 has decreased kinetics of DNA dissociation compared with STAT1 with similar Kd. For a previously reported STAT1 linker mutant, this sort of change in kinetics compared with wild type led to impaired chromatin accumulation and transcriptional inactivity (25). A second possibility is that STAT3 interacts with other proteins present at the c-fos promoter that serve to retain it.

We therefore repeated the observation that STAT1 and STAT3 bind approximately equally (18) in EMSA analysis with either the SIE from the c-fos gene (Fig. 5A, left) or a mutated version of this site (variously termed m67 or hSIE) that has increased binding for the STATs (Fig. 5A, right). We then examined the off-rate of DNA binding by exposure of the DNA–protein complex to unlabeled probe for the SIE site (m67 provided as reference) (Fig. 5B). The SIE exhibits rapid and equal protein-DNA dissociation kinetics for both STAT1 and STAT3. Therefore STAT3-specific accumulation on the c-fos promoter (see Fig. 4A) does not rely on a markedly different dissociation rate of STAT3 compared with STAT1, which strongly suggests protein interaction between STAT3 and other proteins on the promoter as the basis for stable STAT3 binding and chromatin accumulation.

Maximal Transcriptional Activation by the c-fos Promoter Requires Both Activated STAT3 and MAP Kinase Activity—Given the weak induction of the c-fos gene by IL-6 alone, we examined the effect of IL-6 treatment after co-treatment with TPA or the natural polypeptide activator, EGF. As mentioned earlier, TPA treatment has the effect of blocking STAT3 phosphorylation in HepG2 cells. To achieve near simultaneous activation of STAT3 and proteins activated by TPA/EGF, we pretreated cells with IL-6 for 5–30 min before a 30-min TPA or EGF treatment and then examined c-fos mRNA accumulation (Fig. 6). Although both TPA and EGF result in much stronger c-fos mRNA accumulation, the IL-6 pretreatment resulted in an –2-fold boost to the large TPA or EGF inductions. (To demonstrate this difference the RT-PCR reaction was carried out under non-saturating conditions.)

We also carried out a transfection experiment to examine the supplemental effect of IL-6 on TPA-induced transcription (Fig. 7) using a luciferase reporter assay. Once again, under conditions of acute transfection there was an –2-fold boost in signal by IL-6 compared with TPA alone. This effect required an intact SIE site indicating the critical importance of STAT3 binding to the IL-6 supplementation.
DISCUSSION

This work addresses several different questions about activation of the chromosomal c-fos promoter. First, it has been concluded from many transfection (permanent and transient) experiments that the serum response factor-ELK1 complex, likely also including the nearby AP-1 proteins, is required for the optimal transcriptional response to growth factors and to phorbol esters (TPA). Yet there was also evidence from transfections that a STAT site (SIE) had a role in the regulation of c-fos. Whether activity of the chromosomal gene depended on this latter element was not settled. In these studies, we examined the role of the SIE in the regulation of the endogenous c-fos locus.

We first uncoupled stimulation of the STAT proteins from the MAP kinase induction of the chromosomal gene by using low levels of IL-6. IL-6 treatment leads to STAT3 activation with little STAT1 activation, and IL-6 does not induce phosphorylation of ELK1 at the c-fos locus as does TPA, as measured by chromatin immunoprecipitation. Thus we conclude that IL-6 treatment alone induces c-fos gene transcription in the absence of demonstrable MAP kinase activation. Further, chromatin immunoprecipitation established that IL-6 stimulation correlates with binding by STAT3. Even though the IL-6 induction of c-fos was ~20-fold less than that stimulated by TPA or EGF, it is clear that IL-6 treatment augments by 2–3-fold either TPA or EGF stimulation of c-fos transcription.

Our experiments also shed light on mechanisms for inducing STAT1- or STAT3-specific activation of chromosomal genes. For a number of years, it has been clear that STAT3 and STAT1 have opposing roles in growth control; STAT3 is activated in proliferative states and STAT1 in growth arrest (33). However, the virtually identical DNA binding specificities of these two STATs have raised the question of how these opposing signals are interpreted at the DNA level (34). Using the c-fos and IRF-1 genes, we demonstrate two ways that such a conundrum can be resolved. In the case of c-fos, both STAT3 and STAT1 bind weakly to the nonoptimal SIE site, but only STAT3 is retained at the promoter, presumably because of protein contacts made by STAT3 that are not made by STAT1 (Fig. 4). Thus, IL-6 activates transcription of the c-fos gene and IFNγ does not. In the case of IRF-1, a perfect STAT site is present in the promoter ~150 bp from the start site, and both activated STAT3 and STAT1 bind to the chromatin at this site. However, only IFNγ (through STAT1) leads to strong induction of the IRF-1 promoter. Although both STATs are retained on the chromatin, only STAT1 activates transcription. It should also be noted that these specificities of transcriptional regulation make physiological sense, because c-fos is a proto-oncogene and IRF-1 is a proapoptosis gene, which fits the consensus for roles of STAT3 and STAT1 (2, 35).

Therefore STAT specificity at the promoter level can be determined by selective factor retention or selective factor activity. We speculate that other transcriptionally active proteins bound to adjacent sites on these two promoters may govern this selective accumulation and activity of the STAT1 and STAT3 molecules. For example, c-Jun, which interacts more strongly with STAT3 than STAT1 (36), could be constitutively present on the AP-1 site(s) in the c-fos promoter and may help immobilize STAT3.

How do these findings affect thinking about the enhanceosome concept popularized by studies on the IFNβ and TCRα gene promoters (37)? In those two cases, multiple proteins are bound to short DNA segments and apparently physically interact with high spatial specificity in order for fulsome transcriptional activation of the two genes. Previous work with stably integrated c-fos reporter constructs suggested that a productive transcriptional response from c-fos requires the SIE, AP-1, and serum response element to work in concert in a manner similar to the IFNβ and TCRα gene enhanceosomes (20). In our experiments, there may be protein-protein interaction on the c-fos promoter between activated STAT3 and other constitutively bound proteins. But the activation by serine phosphorylation of ELK1, a necessary event in TPA and EGF stimulation of transcription, does not have to occur in STAT3-driven transcription.

**Fig. 7. Luciferase reporter gene analysis of the c-fos promoter.** A, starved HepG2 cells were transfected as described under “Experimental Procedures” and then assayed for luciferase activity. SIE-KO and AP1-KO mutations were described in Fig. 1. Upper panel, normalized luciferase values. Lower panel, -fold inductions. Error bars represent one-half of the difference between duplicate experiments. B, further luciferase studies. M67/TFII-I-KO mutation is as described in the legend for Fig. 1.
of c-fos. (Figs. 3 and 4). Nonetheless, simultaneous action of STAT3 and phospho-ELK1 (plus perhaps other serine phosphorylations) does appear to maximize the transcriptional output of STAT3. This arrangement seems appropriate, because many growth factors which activate MAP kinases are also sources of STAT3 activation (38).

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REFERENCES

1. Greenberg, M. E., and Ziff, E. B. (1984) Nature 311, 433–438
2. Karin, M., Liu, Z., and Zandi, E. (1997) Curr. Opin. Cell Biol. 9, 240–246
3. Lau, L. F., and Nathans, D. (1987) Proc. Natl. Acad. Sci. U. S. A. 84, 1182–1186
4. Hill, C. S., and Treisman, R. (1995) EMBO J. 14, 5037–5047
5. Gille, H., Sharrocks, A. D., and Shaw, P. E. (1992) Nature 358, 414–417
6. Treisman, R. (1995) EMBO J. 14, 4905–4913
7. Whitmarsh, A. J., Yang, S. H., Su, M. S., Sharrocks, A. D., and Davis, R. J. (1997) Mol. Cell. Biol. 17, 2360–2371
8. Marais, R., Wynne, J., and Treisman, R. (1993) Cell 73, 381–393
9. Gille, H., Kortenjann, M., Thomae, O., Moomaw, C., Slaughtuer, C., Cobb, M. H., and Shaw, P. E. (1995) EMBO J. 14, 951–962
10. Ferrara, R. E., Shaw, P. E., and Nordheim, A. (1989) Nature 340, 68–70
11. Fisch, T. M., Pryce, R., and Roeder, R. G. (1987) Mol. Cell. Biol. 7, 3490–3502
12. Fisch, T. M., Pryce, R., Simon, M. C., and Roeder, R. G. (1989) Genes Dev. 3, 396–411
13. Wanner, G. J., Hayes, T. E., Hoban, C. J., and Cochran, B. H. (1990) EMBO J. 9, 4477–4484
14. Kim, D.W., Cheriyath, V., Roy, A. L., and Cochran, B. H. (1998) Mol. Cell. Biol. 18, 3310–3320
15. Cheung, P., Tanner, K. G., Cheung, W. L., Sassone-Corsi, P., Denu, J. M., and Allis, C. D. (2000) Mol. Cell 5, 905–915
16. Thomson, S., Clayton, A. L., and Mahadevan, L. C. (2001) Mol. Cell 8, 1231–1241
17. Treisman, R. (1985) Cell 42, 889–902
18. Zhang, Z., Wen, Z., and Darnell, J. E., Jr. (1994) Science 264, 95–98
19. Goumans, A. M., Zhang, Z., Wen, Z., Thomas, M. J., Darnell, J. E., Jr., and Rutwein, P. (1995) Mol. Endocrinol. 9, 171–177
20. Robertson, L. M., Kerpola, T. K., Vendrell, M., Luk, D., Smenye, R. J., Bocchiaro, C., Morgan, J. I., and Curran, T. (1995) Neuron 14, 241–252
21. Leaman, D. W., Pichardsoy, S., Flickinger, T. W., Connemese, M. A., Schlesinger, J., Kerr, J. M., Levy, D. E., and Stark, G. R. (1996) Mol. Cell. Biol. 16, 369–375
22. Hodges, C., Lin, J., Stofega, M., Guan, K., Carter-Su, C., and Schwartz, J. (1998) J. Biol. Chem. 273, 31327–31336
23. Meraz, M. A., White, J. M., Sheehan, K. C., Bach, E. A., Dighe, A. S., Kaplan, D. H., Riley, J. K., Greenlund, A. C., Campbell, D. Carver-More, K., Dubeis, R. N., Clark, R., Aguet, M., and Schreiber, R. D. (1996) Cell 84, 431–442
24. Yang, E., Wen, Z., Haspel, R. L., Zhang, J. J., and Darnell, J. E., Jr. (1999) Mol. Cell. Biol. 19, 5106–5112
25. Yang, E., Henriksen, M. A., Schofer, O., Zakharev, R., and Darnell, J. E., Jr. (2002) J. Biol. Chem. 277, 13455–13462
26. Schonhatal, A., Herrlich, P., Rahmsdorf, H. J., and Ponta, H. (1988) Cell 54, 325–334
27. Hirot, T. (1998) in The Cytokine Handbook (Thomson, A. W., ed) pp. 197–228, Academic Press, San Diego, CA
28. Sengupta, T. K., Talbot, E. S., Scherle, P. A., and Ivashkiv, L. B. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 11107–11112
29. Coffer, P., Buttack, C., van Puijenbroeck, A., Kleo-de Jonge, M., Horn, F., and Kruiper, W. (1995) Oncogene 10, 965–994
30. Wen, Z., Zhong, Z., and Darnell, J. E., Jr. (1995) Cell 82, 241–250
31. Whitmarsh, A. J., Shore, P., Sharrocks, A. D., and Davis, R. J. (1995) Science 269, 403–407
32. Sadowski, H. B., Shuai, K., Darnell, J. E., Jr., and Gilman, M. Z. (1993) Science 261, 1739–1744
33. Bremberg, J., and Darnell, J. E., Jr. (2000) Oncogene 19, 2468–2473
34. Horvath, C. M., Wen, Z., and Darnell, J. E., Jr. (1999) Genes Dev. 13, 984–994
35. Tanaka, N., Ishihara, M., Kitagawa, M., Harada, H., Kimura, T., Matsuoyama, T., Lamphey, M. S., Aizawa, S., Mak, T. W., and Taniguchi, T. (1994) Cell 77, 829–839
36. Zhang, X., Weisz, S., Hovath, C. M., and Darnell, J. E., Jr. (1999) Mol. Cell. Biol. 19, 7138–7146
37. Carey, M. (1998) Cell 92, 5–8
38. Darnell, J. E. (1997) Science 277, 1630–1635

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