Histone Deacetylase 3 Binds to and Regulates the Multifunctional Transcription Factor TFII-I

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Histone deacetylase 3 (HDAC3) is one of four members of the human class I histone deacetylases that are implicated in transcriptional repression through deacetylation of acetyllysines in amino-terminal tails of core histones. In an immunoaffinity purification using anti-HDAC3, transcription factor TFII-I copurified with HDAC3. Specificity of the HDAC3-TFII-I interaction was confirmed by coimmunoprecipitation of epitope-tagged proteins, GST pull-down assays, and protein colocalization with indirect immunofluorescence. An anti-TFII-I immunoprecipitate contained histone deacetylase enzymatic activity. Mutational analyses revealed that the carboxyl-terminal domain of HDAC3 (residues 373–401) and residues 363–606 of TFII-I were required for the HDAC3-TFII-I interaction. Transcriptional activation by TFII-I was severely reduced by overexpression of HDAC3. These results suggest that HDAC3 modulates some of the functions of TFII-I and provides a link between histone deacetylase and a multifunctional transcriptional activator.

The organization of chromatin structure is a fundamental, yet extremely critical, component of gene regulation in all eukaryotic cells. Whether chromatin is transcriptionally active or repressed is determined, at least in part, by the modification of nucleosomal histones. Of the many possible post-translational modifications of histones, the most common are acetylation and methylation of amino-terminal tails. Of intact histone deacetylase (HDAC) enzymes have been identified whose functions are primarily to regulate the acetylation status of histones and maintain regions of chromatin in transcriptionally inactive states. The first human histone deacetylase, HDAC1, was cloned by Schreiber and colleagues (1) using a deacetylase inhibitor affinity matrix. The second human histone deacetylase, HDAC2, was identified in our laboratory in a yeast two-hybrid experiment with the YY1 transcription factor as bait (2). HDAC1 and HDAC2 each have a high degree of sequence homology to the yeast protein RPD3, and both enzymes primarily exist in the same complex proteins.

The third human histone deacetylase, HDAC3, was cloned

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§ The abbreviations used are: HDAC, histone deacetylase; HLH, helix-loop-helix; GST, glutathione S-transferase; PBS, phosphate-buffered saline; HA, hemagglutinin; TSA, Trichostatin A; TF, transcription factor.

Plasmids—The following plasmids have previously been described: pGal4-VP16 (2), pGST-HDAC3 (3), expression plasmids for HDAC3 deletion mutants (12), expression plasmids for various FLAG-HDACs (9, 18), pEDG and pEDG-TFII-I (19), pGal4TK-Luc (9), c-fos- and Vβ-luciferase reporters (20), and pMcsrc (21).
pcDNA3-HA-TFII-I was constructed by subcloning TFII-I cDNA downstream of the cytomegalovirus promoter and in-frame with the HA sequence in pcDNA3.1 (Invitrogen). Plasmids that express HA-TFII-I deletions were constructed by digestion of pcDNA3-HA-TFII-I with various restriction enzymes, followed by religation. The plasmid expressing an enzymatic-deficient HDAC3 mutant (H134Q/H135A/A136S) was generated using the Kunkel mutagenesis procedure as outlined in the Muta-Gene system (Bio-Rad). All constructs were verified by DNA sequencing.

Immunochemical Reagents and Techniques—Polyclonal anti-TFII-I antibody has been described (22). Monoclonal anti-FLAG M2, monoclonal anti-GST, and polyclonal anti-HA antibodies were obtained from Sigma.

Immunoprecipitations were performed in a solution of PBS containing 0.1% Nonidet P-40 and protease inhibitors as previously described (23). Immunocomplexes were washed six times with the same buffer, and immunoprecipitated proteins were removed from protein A beads by either boiling in gel loading buffer or by elution with excess peptide antigens. For Western blot analyses, proteins were resolved on SDS-polyacrylamide gels and transferred to polyvinylidene difluoride membranes. After blocking with nonfat dried milk, the membranes were treated with diluted primary antibodies, followed by diluted alkaline phosphatase-conjugated secondary IgG. The blots were then developed using 5-bromo-4-chloro-3-indolyl phosphate and nitro blue tetrazolium.

For intracellular localization of HDAC3 and TFII-I, COS1 cells were grown on acid-etched coverslips in 100-mm tissue culture plates for about 24 h and transfected with 0.5 μg of pFLAG-HDAC plasmid as described below. Two days after transfection, the cells were washed with ice-cold PBS, fixed in 4% paraformaldehyde for 15 min, and permeabilized overnight in PBS containing 1% glycine and 0.1% Triton X-100. Cells were incubated for 30 min at room temperature with anti-FLAG coupled with fluorescein isothiocyanate (Upstate) and anti-TFII-I antibodies. After washing with PBS, the cells were incubated with diluted goat anti-rabbit IgG conjugated to tetramethyl rhodamine (Sigma). The cells were then washed extensively with PBS, and coverslips were applied with 40% glycerol before analyzing under a Carl Zeiss confocal microscope.

GST Pull-down Assays—GST and GST-HDAC3 were expressed and purified as described (3). 35S-TFII-I was prepared using the coupled

![Fig. 1. Physical interaction between HDAC3 and TFII-I.](image-url)

A, HeLa cells were transfected with plasmids encoding the indicated proteins. Cell extracts were immunoprecipitated with an anti-FLAG antibody and immunoblotted with an anti-HA antibody (top left panel), an anti-GST antibody (top right panel), or an anti-FLAG antibody (middle panel). Total extracts were immunoblotted with an anti-HA antibody (bottom panel). B, autoradiogram of in vitro-translated TFII-I protein captured by a GST-HDAC3 fusion protein (top panel). The input lane was loaded with one-tenth the amount of 35S-labeled protein used in the binding reactions. The gel was stained with Coomassie Blue before autoradiography to ensure that GST-HDAC3 was not overloaded compared with GST (bottom panel).

Table I

| Sequence of tryptic fragments of p130 (TFII-I) |
|---------------------------------------------|
| FAQALGLTAVEK                                 |
| DQSAVVQGLPEGAVFK                             |
| TPTQNGSNVPFPR                                 |
| APSYLEISSRM                                  |
| GPVTIPPLFQSHVEDLYVEGLPEGIPFR                 |
| FEAPHNLDLYEGLPFENIPFR                        |
| SIFTFGGIPR                                   |
| EFSPEAWNNAK                                   |
| SSPSYHGIPR                                   |
| EQVNDLFSR                                    |
| VPVPPENSPEFLYVEGLPEGIPFR                     |
| RPFLEPK                                      |
| WILENK                                       |
| HPENYDLATLK                                   |
transcription-translation rabbit reticulocyte lysate system (Promega). Equal molar quantities of GST and GST-HDAC3, both conjugated to glutathione-Sepharose beads, were incubated with radiolabeled TFII-I. Binding reactions, washing conditions, and analysis by electrophoresis and subsequent autoradiography were performed as previously described (3).

**Histone Deacetylase Assay**—Deacetylase activity was determined using hyperacetylated core histones purified from HeLa cells (24, 25). Briefly, each immunoprecipitated sample was mixed with 5000 cpm of [3H]acetate-labeled core histones. After incubation at room temperature overnight, the reactions were quenched with 1 M HCl and 0.16 M acetic acid (50 μl in each sample). Released [3H]acetate was extracted with 600 μl of ethyl acetate by vortexing and centrifugation (5 min at 14,000 rpm). The ethyl acetate supernatants (250 μl from each sample) were quantified by scintillation counting.

**Transfection and Luciferase Assay**—COS1 cells were cotransfected with plasmids directing the synthesis of various effector proteins and a luciferase reporter using the FuGene 6 transfection reagent (Roche). Each transfection contained 0.5 μg each of effector and reporter DNAs, and all transfections were normalized to equal amounts of DNA with parental expression vectors. For the c-fos-luciferase assay, cells were refed with medium containing 10% serum 24 h after transfection. Twelve hours later, the cells were stimulated with 25 ng/ml recombinant human epidermal growth factor (Sigma). Epidermal growth factor treatment was not necessary for the Vβ-luciferase assay. Cells were collected and luciferase activity was determined using the dual luciferase reporter assay system (Promega).

**RESULTS**

**Physical Interaction of TFII-I and HDAC3**—We previously purified an endogenous HDAC3 complex from a total extract prepared from HeLa cells using an anti-HDAC3 immunoaffinity column (9). We found that in addition to HDAC3, eight proteins (p215, p205, p195, p130, p125, p54, p52, and p35) specifically co-eluted with histone deacetylase activity. When the 215K, 205K, and 195K polypeptides were subjected to in-gel tryptic digestion followed by sequencing by microcapillary HPLC ion trap mass spectrometry, the resulting peptide sequences were shown to be derivatives of the nuclear receptor co-repressors, NCoR and SMRT (9). We have now shown that protein microsequencing of p130 has identified this HDAC3-associated polypeptide as the transcription factor TFII-I (Table I).

To ensure that the co-purification of TFII-I with anti-HDAC3 was not a result of antibody cross-reactivity, we transfected HeLa cells with plasmids expressing either HA-TFII-I or GST-TFII-I and FLAG-HDAC fusion proteins. Extracts prepared from transfected cells were then immunoprecipitated with an anti-FLAG or anti-GST antibody and immunoblotted with an anti-HA antibody. As shown in Fig. 1A, top panel, FLAG-HDAC3 interacted with HA-TFII-I and GST-TFII-I (lanes 3 and 8), whereas FLAG alone, FLAG-HDAC4, FLAG-HDAC5, and FLAG-HDAC8 did not (lanes 1, 4–6, 9–11). Interestingly, HA-TFII-I or GST-TFII-I also bound, to a limited extent, both FLAG-HDAC1 and FLAG-HDAC2 (lanes 2 and 7).

To support the observation that HDAC3 and TFII-I interact, we tested whether a GST-HDAC3 affinity matrix would capture TFII-I. Bacterially expressed GST-HDAC3 was bound to glutathione-Sepharose beads and incubated with 35S-labeled TFII-I produced by *in vitro* translation in a reticulocyte lysate. The beads were then washed and boiled in sample buffer, and the proteins released from the beads were analyzed by electrophoresis in a SDS-polyacrylamide gel. TFII-I was captured by the GST-HDAC3 fusion protein (Fig. 1B, lane 3) but not by the GST polypeptide alone (lane 2).
Colocalization studies were performed to confirm the HDAC3-TFII-I interaction in mammalian cells. COS1 cells were transiently transfected with plasmids expressing FLAG-HDAC3, fixed with paraformaldehyde, and immunostained with an anti-FLAG antibody. Consistent with our previous findings, images obtained with a confocal laser scanning system showed that HDAC3 was present in both the nucleus and cytoplasm (Fig. 2). TFII-I was regionally dispersed throughout the nuclei of COS1 cells. Importantly, numerous distinct nuclear regions in which TFII-I and HDAC3 colocalized were identified (middle panel), in agreement with the observation that the two proteins physically interact in vivo. As expected, TFII-I also colocalized with HDAC1 (left panel). In contrast, HDAC5 did not colocalize with TFII-I, acting as a negative control (right panel).

Residues 373–401 of HDAC3 Are Necessary for the HDAC3-TFII-I Interaction—To identify the domain of HDAC3 that interacts with TFII-I, we coprecipitated HeLa cells transfected with a plasmid expressing HA-TFII-I with plasmids expressing FLAG fused to full-length HDAC3 or various C-terminal truncated forms of HDAC3. As shown in Fig. 3, A and B, full-length HDAC3 (1–428) and HDAC3 (1–401) clearly bound TFII-I (Fig. 3B, lanes 1 and 2), whereas fragments corresponding to HDAC3 residues 1–373, 1–313, 1–265, and 1–180 did not bind TFII-I (lanes 3–6). These data suggest that residues 401–428 of HDAC3 are not necessary for HDAC3-TFII-I association and that the minimal interaction region is located in residues 373–401.

Residues 363–606 of TFII-I Are Required for the HDAC3-TFII-I Interaction—In a reciprocal experiment, we identified the region of TFII-I that interacts with HDAC3. C-terminal deletions of TFII-I (1–781 and 1–606) bound HDAC3 (Fig. 4A; Fig. 4B, lanes 1 and 2), suggesting that residues 606–958 of TFII-I are not important for HDAC3-TFII-I interaction. In contrast, TFII-I (1–363) did not associate with HDAC3 (lane 3). Further deletion analyses show that TFII-I (133–958 and 133–781) interacted with HDAC3, whereas TFII-I (133–363) did not (lanes 4–6). Taken together, these results suggest that the minimal HDAC3-binding domain is located between residues 363–606 of TFII-I but that the interaction domain may extend from residues 133 to 606.

TFII-I Associates with Histone Deacetylase Activity—To determine whether the HDAC3-TFII-I interaction results in the recruitment of HDAC enzymatic activity by TFII-I, we expressed GST-TFII-I in COS1 cells, prepared immunoprecipitates from extracts using an anti-GST antibody, and assayed for HDAC activity. On average, HDAC activity was nearly 50-fold higher in immunocomplexes containing GST-TFII-I when compared with GST alone (Fig. 5). The TFII-I-associated HDAC activity was greatly reduced by Trichostatin A (TSA), a specific inhibitor of deacetylases. Although we cannot exclude the possibility that HDAC1/2 (in addition to HDAC3) may contribute to the HDAC activity associated with TFII-I, this result unequivocally confirms that TFII-I interacts with HDACs.
HDAC3 inhibits the activity of TFII-I. Expression plasmids for TFII-I, HDAC3, various HDAC3 mutants, c-Src, HDAC6, or Gal4-VP16 were transfected into COS1 cells together with a reporter construct as indicated. Luciferase activities are the averages ± S.D. from three separate experiments. An anti-TFII-I Western blot was performed to ensure that HDAC3 did not significantly reduce the expression of TFII-I (A, right panel).
HDAC3 Regulates the Transcriptional Activity of TFII-I—To determine whether HDAC3 affects the transcriptional activity of TFII-I, we examined its effect on the activity of the c-fos promoter, which is regulated by TFII-I (20). As predicted, overexpression of TFII-I significantly activated the c-fos promoter (Fig. 6A). More importantly, overexpression of HDAC3 substantially inhibited the activation of the c-fos promoter by TFII-I, consistent with the premise that HDAC3 can modulate the activity of TFII-I. The expression of TFII-I was not affected by HDAC3 (Fig. 6A, right panel), ruling out the possibility that HDAC3 down-regulates the human EF-1α promoter used to express TFII-I. Activation of the c-fos promoter by TFII-I was not affected by an HDAC3 mutant (H134Q/H135A/A136S) lacking deacetylase activity or by HDAC3 mutants that do not bind TFII-I (1–373, 1–313, 1–265, 1–180) (Fig. 6, A and B).

Recently, it was found that TFII-I can activate the c-fos promoter through a Src-dependent mechanism (26). To determine whether HDAC3 represses Src-dependent TFII-I activation, we expressed TFII-I and c-Src, together with HDAC3, in the presence of the c-fos reporter. As shown in Fig. 6C, activation of c-fos by TFII-I plus c-Src was completely abolished by HDAC3.

In addition to c-fos, TFII-I is required for the transcription of the naturally TATA-less but initiator-containing Vβ promoter (19, 27). In separate experiments, HDAC3 inhibited the ability of TFII-I to activate the Vβ promoter (Fig. 6D). However, neither the HDAC3 mutant (H134Q/H135A/A136S) nor HDAC6 had an effect on the activation of the Vβ promoter by TFII-I.

Taken together, these results unambiguously show that the transcriptional activity of TFII-I is modulated by interaction with the HDAC3 protein.

To confirm that the inhibition of activation by the TFII-I protein is not due to a general inhibitory effect of HDAC3 overexpression, we transfected cells with pGal4-VP16 and pGal4-TKLuc. As shown, overexpression of HDAC3 did not affect transcriptional activation of the Gal4-TK promoter by the Gal4-VP16 protein (Fig. 6E). Thus, our data strongly suggest that HDAC3 is not a general cytoxic protein but rather is a specific cellular inhibitor of TFII-I.

**DISCUSSION**

The two best studied human histone deacetylases, HDAC1 and HDAC2, regulate gene expression, at least in part, by forming complexes with other cellular factors. To obtain a greater mechanistic and functional understanding of HDAC3, we previously purified and attempted to identify proteins capable of forming heterologous complexes with HDAC3 (9). Here, we identify one of the previously isolated HDAC3-binding proteins as the transcription factor, TFII-I.

Three lines of evidence confirmed that TFII-I is a genuine HDAC3-associated protein. First, coimmunoprecipitation experiments showed that TFII-I interacts with HDAC3 but not HDAC-4, -5 or -6. Second, using a GST-HDAC3 fusion protein, biochemical evidence was obtained indicating that HDAC3 and TFII-I interact in vitro. Finally, immunocytochemical methods revealed a similar subcellular distribution of HDAC3 and TFII-I in mammalian cells. Although the present experiments rely on overexpression of HDAC3 or TFII-I, we believe that they accurately reflect true in vivo interactions, in part because TFII-I copurifies with HDAC3 in an anti-HDAC3 immunofluorescence column using a whole cell extract without overexpression of either protein (9).

In addition to its interaction with HDAC3, TFII-I also interacts very weakly with HDAC1 and HDAC2 in coprecipitation experiments. Although this observation is not surprising considering that several proteins that bind HDAC1/2 also partner with HDAC3 (3, 9, 28–31), it is conceivable that there are multiple affinity levels of interaction, with HDAC3-TFII-I forming the most stable complex. Also, at least four isoforms of TFII-I exist (15), and at this time, our protein microsequencing data do not exclude the possibility that HDAC3 binds more than one isoform of TFII-I.

Analysis of HDAC3 deletion mutants revealed that residues 373–401 of HDAC3 are required for the HDAC3-TFII-I interaction. Although the importance of this region with respect to mechanisms and functions of HDAC3 is unknown at this time, this area is known to be outside both the HDAC3 nuclear export sequence and the oligomerization domain and contributes to the deacetylase and transcriptional activity of HDAC3 (12). In future studies, it will be important to determine whether this TFII-I-interacting domain binds other cellular factors or associates with TFII-I exclusively.

An unusual feature of the TFII-I protein is the presence of six highly conserved 90-residue repeats (R1-R6), and a striking feature of these repeats is the presence of HLH motifs, which have been implicated in protein-protein interactions. Our deletion mutational studies indicate that residues 363–606 of TFII-I are essential for the HDAC3-TFII-I interaction. This region encompasses a portion of R2 and nearly the entire R3 and R4 I-repeats. Although hetero- and homo-dimerization mediated through HLH motifs is a well-known phenomenon, it is presently unclear how the HLH domain of TFII-I forms a complex with HDAC3, which does not appear to contain an HLH domain. It is possible that HDAC3 and TFII-I interact via a third protein that contains both an HLH motif and an HDAC3 interaction domain. Further experiments using highly purified HDAC3 and TFII-I will resolve this issue.

The biological and functional significance of the HDAC3-TFII-I interaction remains in question. One possibility is that, in addition to its many other functions, TFII-I also recruits HDAC activity to promoters containing TFII-I binding sites. By doing so, it may help modulate the overall transcriptional activity from TFII-I-regulated promoters. If so, TFII-I then joins a rapidly growing list of sequence-specific DNA-binding transcription factors that regulate transcription by recruitment of HDAC activity. In support of this model, we show that TFII-I immunoprecipitates contain HDAC activity and that HDAC3 inhibits the activity of the c-fos and Vβ promoters. The crucial question that needs to be addressed now is whether the recruitment of HDAC3 by TFII-I is a regulated process and, if so, how to identify the signal involved. It is also conceivable that HDAC3 blocks the ability of TFII-I to activate transcription without tethering itself to the transcription complex. Finally, the possibility that TFII-I may be a substrate for HDAC3, and possibly for HDAC1/2 as well, cannot yet be ruled out. Experiments designed to explore each of these possibilities are now in progress.

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REFERENCES
1. Taunton, J., Hassig, C. A., and Schreiber, S. L. (1996) Science 272, 408–411
2. Yang, W. M., Inouye, C., Zeng, Y., Bearss, D., and Seto, E. (1996) Proc. Natl. Acad. Sci. U. S. A. 93, 12845–12850
3. Yang, W. M., Yao, Y. L., Sun, J. M., Davie, J. R., and Seto, E. (1997) J. Biol. Chem. 272, 28001–28007
4. Dangond, F., Hafer, D. A., Tong, J. K., Randall, J., Kujima, R., Utku, N., and Gullans, S. R. (1998) Biochem. Biophys. Res. Commun. 242, 646–652
5. Emiliani, S., Fischle, W., Van, L. C., Al, A. Y., and Verdin, E. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 2795–2800
6. Guenther, M. G., Lane, W. S., Fischle, W., Verdin, E., Lazar, M. A., and Shiekhattar, R. (2000) Genes Dev. 14, 1048–1057
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7. Li, J., Wang, J., Nawaz, Z., Liu, J. M., Qin, J., and Wong, J. (2000) EMBO J. 19, 4342–4350
8. Urnov, F. D., Yee, J., Sachs, L., Collingwood, T. N., Bauer, A., Beug, H., Shi, Y. B., and Wolfe, A. P. (2000) EMBO J. 19, 4074–4090
9. Wen, Y. D., Perisic, V., Staszewski, L. M., Yang, W. M., Krones, A., Glass, C. K., Rosenfeld, M. G., and Seto, E. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 7202–7207
10. McKinsey, T. A., Zhang, C. L., Lu, J., and Olson, E. N. (2000) Nature 408, 106–111
11. Takami, Y., and Nakayama, T. (2000) J. Biol. Chem. 275, 16191–16201
12. Yang, W. M., Tsai, S. C., Wen, Y. D., Fejer, G., and Seto, E. (2002) J. Biol. Chem. 277, 9447–9454
13. Underhill, C., Qutob, M. S., Yee, S. P., and Torchia, J. (2000) J. Biol. Chem. 275, 40463–40470
14. Roy, A. L., Du, H., Gregor, P. D., Novina, C. D., Martinez, E., and Roeder, R. G. (1997) EMBO J. 16, 7091–7104
15. Cheriyath, V., and Roy, A. L. (2000) J. Biol. Chem. 275, 26300–26308
16. Roy, A. L., Meisterernst, M., Pognonec, P., and Roeder, R. G. (1991) Nature 354, 245–248
17. Roy, A. L. (2001) Gene 274, 1–13
18. Grunzinger, C. M., Hassig, C. A., and Schreiber, S. L. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 4868–4873
19. Cheriyath, V., Novina, C. D., and Roy, A. L. (1998) Mol. Cell. Biol. 18, 4444–4454
20. Kim, D. W., Cheriyath, V., Roy, A. L., and Cochran, B. H. (1998) Mol. Cell. Biol. 18, 3310–3320
21. Luttrell, D. K., Luttrell, L. M., and Parsons, S. J. (1988) Mol. Cell. Biol. 8, 497–501
22. Novina, C. D., Cheriyath, V., Denis, M. C., and Roy, A. L. (1997) Methods 12, 254–263
23. Laherty, C. D., Yang, W. M., Sun, J. M., Davie, J. R., Seto, E., and Eisenman, R. N. (1997) Cell 89, 349–356
24. Zhang, Y., LeRoy, G., Seelig, H.-P., Lane, W. S., and Reinberg, D. (1998) Cell 95, 279–289
25. Hassig, C. A., Tong, J. K., Fleischer, T. C., Owa, T., Grable, P. G., Ayer, D. E., and Schreiber, S. L. (1998) Proc. Natl. Acad. Sci. U. S. A. 95, 3519–3524
26. Cheriyath, V., Desgranges, Z. P., and Roy, A. L. (2002) J. Biol. Chem. 277, 22796–22805
27. Manzano-Winkler, B., Novina, C. D., and Roy, A. L. (1996) J. Biol. Chem. 271, 12076–12081
28. Lai, A., Lee, J. M., Yang, W. M., DeCaprio, J. A., Kaelin, W. G., Jr., Seto, E., and Branton, P. E. (1999) Mol. Cell. Biol. 19, 6632–6641
29. Johnson, C. A., White, D. A., Lavender, J. S., O'Neill, I. P., and Turner, B. M. (2002) J. Biol. Chem. 277, 9580–9587
30. Nicolas, E., Ait-Si-Ali, S., and Trouche, D. (2001) Nucleic Acids Res. 29, 3131–3136
31. Vaute, O., Nicolas, E., Vandele, L., and Trouche, D. (2002) Nucleic Acids Res. 30, 475–481