RNA polymerase III transcription is down-regulated when F9 embryonal carcinoma cells differentiate into parietal endoderm. This reflects a decrease in the activity of TFIIIB, a multisubunit complex that is required for all class III gene expression. Two essential components of TFIIIB are the TATA-binding protein (TBP) and an associated polypeptide called BRF that is specific to this complex. The abundance of both TBP and BRF decreases during F9 cell differentiation. Whereas the amount of TBP assembled into TFIIIB is down-regulated, this is not the case for all TBP-containing complexes. BRF levels show a more dramatic decline that appears sufficient to account for the overall change in transcriptional activity. Developmental regulation of a specific class of genes may therefore be achieved through changes in the availability of a TBP-associated factor.

The rapidly changing patterns of gene expression required for early development demand tight transcriptional control. In situ hybridization has revealed that RNA polymerase (pol) III transcription is regulated strongly during mouse embryogenesis (1). After fertilization, the steady-state levels of pol III transcripts increase severalfold, and labeling is seen in the pronuclei and polar bodies, consistent with de novo transcription (1). Indeed, microinjection experiments using single cell embryos have demonstrated that the pol III machinery is active even before cell cleavage (2). The blastomeres of two- and four-cell morulae and of eight-cell blastocysts are heavily labeled (1). Hybridization decreases in the trophectoderm cells of expanding blastocysts but remains strong in the inner cell mass (1). By the late primitive streak stage, high expression is restricted to the ectoderm and mesoderm but has decreased substantially in the embryonic and extra-embryonic endoderm (1).

The decrease in pol III activity during differentiation into endoderm can be reproduced accurately using embryonal carcinoma (EC) cells, which mimic events within the early embryo (3-5). For example, pol III transcription decreases substantially both in vitro and in intact nuclei when F9 EC cells differentiate into parietal endoderm (PE) (4, 5). Crude fractions containing the general pol III factor TFIIIB are sufficient to restore expression in PE cell extracts to undifferentiated levels (4). This suggested that the down-regulation of pol III during PE formation is achieved by a specific decrease in the availability of active TFIIIB (4). However, the molecular details of this event remain to be determined, since TFIIIB was largely uncharacterized at the time of the previous study.

It has since become clear that TFIIIB is a multisubunit complex that contains the TATA-binding protein TBP and at least two TBP-associated factors (TAFs) (reviewed in Refs. 6-8). One of these TAFs is related in both structure and function to the general pol II factor TAFII (9-14). This TAF has been variously named TDS4, PCF4, BRF, and TFIIIB90, but we shall refer to it as BRF, an acronym for TFIIB-related factor. Although yeast TFIIIB has been reconstituted using recombinant components (15-17), the mammalian factor is much less well characterized (reviewed in Refs. 6-8). This is partly because of the instability of TFIIIB, which tends to dissociate during purification (18-21). Although several groups have identified polypeptides as candidate TAFs for human TFIIIB, there is little consensus as yet (13, 14, 18-21). To date, BRF is the only component of mammalian TFIIIB that has had its gene cloned and its function established unequivocally (13, 14).

Although TFIIIB in higher organisms remains incompletely characterized, the identification of TBP and BRF as essential components has provided the opportunity to investigate regulatory events using molecular probes and affinity-purified fractions. We have therefore returned to the F9 system to investigate in more detail the mechanism(s) responsible for regulating pol III transcription during differentiation. We have confirmed the previous observation that TFIIIB activity decreases specifically when F9 cells differentiate. We demonstrate that this is associated with the down-regulation of one or more TAFs, and that TAF availability is limiting for pol III transcription in PE extracts. We have raised antibodies that recognize murine BRF and used these to demonstrate that BRF levels decrease substantially during F9 cell differentiation. The decrease in abundance of this essential TAF seems sufficient to account for the down-regulation of class III gene expression that accompanies PE formation.

**EXPERIMENTAL PROCEDURES**

**Cell Culture—**F9 cells were cultured and differentiated as described previously (4).

**Preparation of Extracts and Protein Fractions—**Whole cell extracts were prepared according to the method of Manley et al. (22) and also by a more direct freeze-thaw procedure (23). Both approaches yielded similar results.

Phosphocellulose chromatography, heparin chromatography of TFIIIC, DNA affinity purification of TFIIIC, Mono Q purification of TFIIIB, preparation of recombinant TBP, and TBP affinity purification of TFIIIB TAFs were carried out as described previously (23). TFIIIB was also partially purified from EC and PE extract phosphocellulose (PC)-B fractions using Macro-Prep Q (Bio-Rad) and a protocol...
modified from Meyers and Sharp (24). PC-B was loaded onto Q columns in buffer A (20 mM Hepes (pH 7.9), 20% glycerol, 1 mM EDTA) containing 50 mM KCl. After washing with buffer A containing 200 mM KCl, TFIIIB was eluted using buffer A containing 600 mM KCl.

Transcription Assays—Transcription reactions were carried out as previously (4), except that pBR 322 was not included, and the incubations were for 60 min at 30 °C.

Antibodies and Western Blotting—Anti-BRF antibody 128 was raised by immunizing rabbits with synthetic peptide KISSKINYSVLRLGS (human BRF residues 533–547) coupled to keyhole limpet hemocyanin. Anti-TFIIIC antibody 481 was raised by immunizing rabbits with synthetic peptide ICYAEASVEMSLPG (human TFIIIC residues 41–55) coupled to keyhole limpet hemocyanin. Anti-TFIIIC antibody Ab2 (25) was a generous gift from Yuhong Shen and Arnold Berk. Western immunoblot analysis was performed as described previously (23).

RESULTS

F9 Cell Differentiation Is Accompanied by a Specific Decrease in TFIIIB Activity—Whole cell extracts were prepared from undifferentiated F9 EC cells and from cells that had been induced to differentiate into parietal endoderm by culture in the presence of retinoic acid and dibutyryl cAMP. Extracts of PE cells were found to transcribe the VA gene much less efficiently than extracts prepared in parallel from EC cells (Fig. 1A). This was consistently the case using several sets of extracts, two different extraction procedures, and PE cells harvested after 5, 7, or 9 days of differentiation.2 We conclude that these cell-free systems accurately reproduce the down-regulation of pol III transcription that occurs in vivo.

Fractions containing partially purified TFIIIB were prepared from the F9 EC and PE extracts by sequential chromatography on phosphocellulose and MacroPrep-Q. These were then tested for their ability to reconstitute VA transcription in the presence of a complementing PC-C fraction containing TFIIIC and pol III. TFIIIB activity was consistently found to be significantly reduced in the fractions prepared from PE extracts (Fig. 1B). Quantitation of six independent comparisons showed that, on average, the PE fractions had 6-fold lower TFIIIB activity than the corresponding EC fractions.

Complementation assays were also used to compare the TFIIIC activities of EC and PE extracts after chromatography on phosphocellulose. PC-C fractions from PE extracts were found to be at least as active as the equivalent fractions from EC extracts in reconstituting VA expression (Fig. 1C). The observed decrease in TFIIIB activity is therefore a specific event.

TFIIIB Activity Limits the Rate of pol III Transcription in F9 PE Extracts—Add-back experiments were carried out to determine which factor is limiting for pol III transcription in differentiated F9 cell extracts. VA expression was stimulated by the addition of PC-B but not by PC-C or affinity-purified TFIIIC fractions (Fig. 2A). Indeed, the affinity-purified TFIIIC depressed the level of transcription; such over-titration effects may reflect the ability of excess TFIIIC to sequester limiting TFIIIB away from promoter sites. Since TFIIIB is the only known pol III factor that is specific to PC-B, these observations suggest that TFIIIB activity is limiting in the PE extracts. However, we cannot exclude the possibility of unknown class

fractions both have protein concentrations of ~70 ng/ml. C. TFIIIC activity is not decreased after F9 cell differentiation. pVA template (250 ng) was transcribed using 2 μl of HeLa PC-B fraction alone (lanes 2 and 5) or in the presence of 2 μl of HeLa PC-C (lane 1), 4 or 6 μl of EC PC-C (lanes 3 and 4, respectively), and 4 or 6 μl of PE PC-C (lanes 6 and 7, respectively). The EC and PE PC-C fractions both have protein concentrations of ~0.6 mg/ml.

2 H. Alzuherri and R. J. White, unpublished data.

![Image](http://www.jbc.org/)

Fig. 1. PE extracts are deficient in TFIIIB but not TFIIIC activity. A, EC extracts have higher pol III transcriptional activity than PE extracts. pVA template (250 ng) was transcribed using 11.2 μg (lanes 1 and 3) or 16.8 μg (lanes 2 and 4) of F9 EC (lanes 1 and 2) or PE (lanes 3 and 4) whole cell extract. B, TFIIIB activity decreases during F9 cell differentiation. pVA template (250 ng) was transcribed using 2 μl of HeLa PC-C fraction alone (lane 1) or in the presence of 1 μl (lanes 2 and 4) or 2 μl (lanes 3 and 5) of MacroPrep Q-purified TFIIIB from EC (lanes 2 and 3) or PE (lanes 4 and 5) extracts. The EC and PE TFIIIB fractions both have protein concentrations of ~70 ng/ml. C. TFIIIC activity is not decreased after F9 cell differentiation. pVA template (250 ng) was transcribed using 2 μl of HeLa PC-B fraction alone (lanes 2 and 5) or in the presence of 2 μl of HeLa PC-C (lane 1), 4 or 6 μl of EC PC-C (lanes 3 and 4, respectively), and 4 or 6 μl of PE PC-C (lanes 6 and 7, respectively). The EC and PE PC-C fractions both have protein concentrations of ~0.6 mg/ml.

[2 H. Alzuherri and R. J. White, unpublished data.]
III factors that might also elute specifically in the PC-B. To reduce the possibility of such uncharacterized contaminants, we purified TFIIIB further by gradient chromatography on Mono Q. The resultant TFIIIB fraction was found to be extremely efficient at activating VAI transcription when added to PE extract (Fig. 2B). Indeed, this fraction was able to restore levels of expression in the PE extract to those obtained using an equal amount of EC extract. It is therefore likely that the expression of class III genes in differentiated F9 cell extracts is limited by the availability of active TFIIIB.

**F9 Cell Differentiation Is Accompanied by a Decrease in the Activity of One or More TFIIIB TAFs**—Since TFIIIB is a complex containing both TBP and TAFs, we tested which of these components is limiting for pol III transcription in PE extracts. Fractions containing TFIIIB TAFs were prepared from PC-B by affinity chromatography on columns carrying immobilized TBP. Such fractions are capable of reconstituting transcription in the presence of PC-C and recombinant TBP (23). Expression of the VAI gene in a PE extract was increased by up to 5-fold after the addition of affinity-purified TFIIIB TAFs (Fig. 3). In contrast, recombinant TBP produced no stimulation. These results suggest that it is the TAF component of TFIIIB that limits the rate of pol III transcription in extracts prepared from differentiated F9 cells.

We have previously devised a complementation assay that allows the direct comparison of TFIIIB TAF activity between unfractionated extracts (23). This assay exploits the fact that heating an extract at 47 °C for 15 min inactivates endogenous TBP and TFIIIC but leaves the pol III TAFs unaffected (23, 26–30). The activity of the TAF components of TFIIIB can then be measured by adding the heat-treated extract to a complementation reaction containing TBP, TFIIIC, and pol III but no TFIIIB (23, 31, 32). Fig. 4 shows that Mono Q-purified TFIIIB will reconstitute transcription in such a system after it has been heated in this way (lanes 10–12). Using this assay, it was found that F9 EC extracts are substantially more active than PE extracts (lanes 1–9). Twenty µg of PE extract are required to produce a signal in this assay that is comparable with that produced by 2.5 µg of EC extract (compare lane 2 with lane 9). This dramatic decrease in TFIIIB TAF activity appears sufficient to account for the down-regulation of pol III transcription that accompanies F9 cell differentiation.

**The Abundance of BRF Decreases Substantially When F9 Cells Differentiate**—We carried out immunoblot analyses to look for qualitative or quantitative changes in the TFIIIB-specific TAF BRF. Available antisera against BRF were found to react poorly with murine extracts, giving a weak signal with
multiple bands.\textsuperscript{2} As the mouse gene for BRF had not been reported, we examined the available BRF sequences for regions that have been especially conserved through evolution. We have identified recently the gene for BRF from Caenorhabditis elegans (33). Comparison of this sequence with that of human and three different yeasts allowed us to identify a region near the C terminus of BRF that is particularly well conserved. We therefore raised an antiserum against a 15-residue epitope from this region. Western blot analysis revealed that this antiserum, named 128, recognizes human BRF that has been purified with little or no change after differentiation. The TBP present in PC-C and PC-D is associated with the complexes SNAPc, TFIID, and SL1/TIF-IB (6). Thus, the reduced TBP levels found in PE extracts are specific to a particular TBP-containing complex.

Although F9 cell differentiation is accompanied by a decrease in the abundance of both BRF and TBP, this is not the case for all components of the transcription apparatus. We have already shown by complementation assays that TFIIC activity is not reduced in PE cell extracts. Western blot analysis reinforces this result, since we observe no change in the abundance of the \( \beta \) or \( \alpha \) subunits of TFIIC after F9 cell differentiation (Figs. 6, A and B, respectively). These data have been confirmed using alternative antisera against TFIIC.\textsuperscript{7} It is therefore clear that the down-regulation of TFIIBB is a specific regulatory event.

**DISCUSSION**

The results presented in this manuscript indicate that F9 cell differentiation is accompanied by a substantial decrease in the activity of TFIIBB, a general factor that is required for all pol III transcription. This is a specific phenomenon, since TFIIC activity is not reduced in PE extracts. Indeed, TFIIBB seems to be the only general pol III factor that is deficient in differentiated F9 cells, since it is possible to restore VA\(_{A}\) transcription to EC levels simply by adding TFIIBB to a PE extract. Direct assays and add-back experiments indicate that the loss of TFIIBB activity during differentiation reflects the down-regulation of one or more pol III TAFs, which become limiting for VA\(_{A}\) expression. This conclusion is substantiated by Western blot analyses, which demonstrate a large decrease in the abundance of the essential TAF BRF.

Meij\"{e}ner et al. have also investigated the regulation of pol III transcription during F9 cell differentiation (5). These workers chromatographed EC and PE extracts on phosphocellulose and Q-Sepharose and then carried out complementation assays to compare the activities of TFIIBB and TFIIC (5). They found that under some assay conditions TFIIBB fractions from PE extracts were substantially less active than those from EC extracts (5), as we have observed. However, such differences were reported to be inconsistent and dependent on the reaction conditions (5). In contrast, a PC-C fraction from PE cells was described as being “virtually unable to reconstitute transcription” in the presence of PC-B (5). Although this experiment was not quantitated, no detectable signal was obtained with the PE PC-C, whereas the EC PC-C fraction was active in the same assay (5). The almost complete inactivity of the PE PC-C fraction was especially striking, since the unfractonated PE starting material used in that study was only 5-fold less active than the EC extract (5). Meij\"{e}ner et al. concluded that F9 cell differentiation is accompanied by a substantial reduction in TFIIC with little or no change in TFIIBB activity (5).

We cannot reconcile this report with our current and earlier results. The results presented in this manuscript indicate that F9 cell differentiation is accompanied by a substantial decrease in the activity of TFIIBB, a general factor that is required for all pol III transcription. This is a specific phenomenon, since TFIIC activity is not reduced in PE cell extracts. Indeed, TFIIBB seems to be the only general pol III factor that is deficient in differentiated F9 cells, since it is possible to restore VA\(_{A}\) transcription to EC levels simply by adding TFIIBB to a PE extract. Direct assays and add-back experiments indicate that the loss of TFIIBB activity during differentiation reflects the down-regulation of one or more pol III TAFs, which become limiting for VA\(_{A}\) expression. This conclusion is substantiated by Western blot analyses, which demonstrate a large decrease in the abundance of the essential TAF BRF.

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findings (4). Meißner et al. (5) have relied solely on complementation assays using fractionated factors. As the authors pointed out, such an approach is vulnerable to the possibilities of differential recovery or inactivation during chromatography. Although we have employed the same approach, we have also provided a variety of additional independent lines of evidence in order to reduce the danger of artifacts. Our conclusions are further strengthened by the use of affinity-purified reagents and molecular probes, none of which were used in the previous study. Our evidence that TFIIIC is not substantially deficient in F9 PE extracts is as follows. 1) Band shift assays using as probe {\textit{VA1}} and B2 gene fragments or a B-block oligonucleotide demonstrated previously that the DNA binding activity of TFIIIC does not decrease when F9 cells differentiate (4). 2) Titration of transcription activity using a B-block oligonucleotide demonstrated that TFIIIC levels are similar in EC and PE extracts (4). 3) Mono Q-purified TFIIIB is sufficient to restore TFIIIC levels during F9 cell differentiation. A, antibody 128 recognizes both human and mouse BRF. pVA1 template (500 ng) was transcribed using 4 \( \mu \)l of HeLa (lanes 1–3) or F9 EC (lanes 4–6) cell extract that had been immunodepleted using either protein A-Sepharose alone (lanes 1 and 4), protein A-Sepharose prebound to anti-BRF antibody 128 (lanes 2 and 5), or protein A-Sepharose prebound to preimmune serum 128 (lanes 3 and 6). PI, preimmune B, PE extracts contain less BRF than EC extracts. 56 \( \mu \)g of EC (lane 1) or PE (lane 2) whole cell extract and 1.75 \( \mu \)g of phosphocellulose and Macro-Prep Q-purified TFIIIB from EC (lane 3) or PE (lane 4) extract were resolved on an SDS-7.8% polyacrylamide gel and then analyzed by Western immunoblotting with anti-BRF antibody 128. B, BC fractions from EC extracts contain more BRF and TBP than PC-B fractions from PE extracts. 22 \( \mu \)g of PC-A (lanes 1 and 2), 22 \( \mu \)g of PC-B (lanes 3 and 4), 12 \( \mu \)g of PC-C (lanes 5 and 6), and 5.6 \( \mu \)g of PC-D (lanes 7 and 8) fractions from EC (lanes 1, 3, 5, and 7) or PE (lanes 2, 4, 6, and 8) extract were resolved on an SDS-7.8% polyacrylamide gel and then analyzed by Western immunoblotting with anti-BRF antibody 128 (top panel) and anti-TBP antibody SI-1 (Santa Cruz) (bottom panel). The extra band running above TBP in the PC-C fractions is not recognized by other anti-TBP antibodies and is therefore presumed to be unrelated to TBP.

FIG. 6. The abundance of TFIIIC does not change significantly when F9 cells differentiate (A) EC, and PE extracts contain similar levels of the TFIIIC\( \beta \) subunit (B). Whole cell extract (56 \( \mu \)g) from EC (lane 1) or PE (lane 2) cells and a TFIIIC fraction (9 \( \mu \)g) prepared by PC and heparin chromatography of a HeLa cell extract (lane 3) were resolved on an SDS-7.8% polyacrylamide gel and then analyzed by Western immunoblotting with anti-TFIIIC\( \beta \) antibody 481. B, EC and PE extracts contain similar levels of the TFIIIC\( \alpha \) subunit. The TFIIIC fraction (9 \( \mu \)g) prepared by PC and heparin chromatography of a HeLa cell extract (lane 1) and whole cell extract (56 \( \mu \)g) from EC (lane 2) or PE (lane 3) cells were resolved on an SDS-6% polyacrylamide gel and then analyzed by Western immunoblotting with anti-TFIIIC\( \alpha \) antibody Ab2. C, PC-B fractions from EC extracts contain more BRF and TBP than PC-B fractions from PE extracts. 22 \( \mu \)g of PC-A (lanes 1 and 2), 22 \( \mu \)g of PC-B (lanes 3 and 4), 12 \( \mu \)g of PC-C (lanes 5 and 6), and 5.6 \( \mu \)g of PC-D (lanes 7 and 8) fractions from EC (lanes 1, 3, 5, and 7) or PE (lanes 2, 4, 6, and 8) extract were resolved on an SDS-7.8% polyacrylamide gel and then analyzed by Western immunoblotting with anti-BRF antibody 128 (top panel) and anti-TBP antibody SI-1 (Santa Cruz) (bottom panel). The extra band running above TBP in the PC-C fractions is not recognized by other anti-TBP antibodies and is therefore presumed to be unrelated to TBP.
pol III transcription in PE extracts, which would not be possible if TFIIIC were deficient. 4) The addition of PC-C or affinity-purified TFIIIC fractions does not stimulate transcription in a PE extract. 5) Complementation assays with PC-C fractions reveal no decrease in TFIIIC activity after F9 cell differentiation. 6) Western analysis reveals no change in the abundance of the α or β subunits of TFIIIC. Our contention that TFIIIB is down-regulated during PE formation is based on the following lines of evidence. 1) PC-B and Mono Q-purified TFIIIB fractions are sufficient to raise pol III transcription in PE extracts to levels occurring in EC extracts. 2) VA₆ expression in PE extracts is activated by the addition of affinity-purified TFIIIB TAF fractions, which contain BRF². 3) Complementation assays with unfraccionated extracts demonstrate a dramatic change in TFIIIB activity. 4) Complementation assays after fractionation on phosphocellulose and MacroPrep-Q show that much less TFIIIB activity is recovered from PE extracts than from EC extracts. 5) Western blotting demonstrates directly that the essential pol III TAF BRF becomes much less abundant when F9 cells differentiate. 6) TBP levels in the TFIIIB fractions also decrease during differentiation.

The observed decline in BRF levels seems sufficient to account for the down-regulation in TFIIIB. Although the decrease in BRF levels seems sufficient to account for the down-regulation of pol III transcription during F9 cell differentiation, we cannot at this stage conclude that it is the primary cause for the decrease in TFIIIB activity. It is entirely possible that a decrease in the synthesis of another pol III TAF reduces the opportunity for BRF to be assembled into complete TFIIIB complexes. Any surplus unassembled BRF may then be targeted for degradation, thereby leading to the observed decrease in abundance. A similar consideration applies to TBP; there may be less TBP assembled into TFIIIB as observed decrease in abundance. A similar consideration applies if TFIIIB complexes in PE cells. Definitive resolution of this question will require the identification of the remaining mammalian pol III TAF(s) and the generation of molecular probes.

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The coregulation of batteries of genes involved in producing a shared phenotypic goal must be essential for normal development. One mechanism by which this could be achieved is through changes in the activity of specific TAFs. Although a cell type-specific TAF has been described (34), this study provides, to our knowledge, the first documented example in which the regulation of a TAF has been shown to accompany a specific event that occurs during early embryogenesis. The decrease in abundance of BRF during PE formation is likely to account, at least in part, for the general decline in transcription of all pol III templates tested. This may provide a paradigm for a mechanism that allows the complex and rapidly changing patterns of developmental gene expression to be achieved in a coordinated fashion.

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Regulation of a TATA-binding Protein-associated Factor during Cellular Differentiation
Hadi M. Alzuherri and Robert J. White

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