Poly(ADP-ribose) polymerase-1 (PARP-1) catalyzes the rapid and extensive poly(ADP-ribosylation) of nuclear proteins in response to DNA strand breaks, and its expression, although ubiquitous, is modulated from tissue to tissue and during cellular differentiation. PARP-1 gene promoters from human, rat, and mouse have been cloned, and they share a structure common to housekeeping genes, as they lack a functional TATA box and contain multiple GC boxes, which bind the transcriptional activator Sp1. We have previously shown that, although Sp1 is important for rat PARP1 (rPARP) promoter activity, its finely tuned modulation is likely dependent on other transcription factors that bind the rPARP proximal promoter in vitro. In this study, we identified one such factor as NF1-L, a rat liver isoform of the nuclear factor 1 family of transcription factors. The NF1-L site on the rPARP promoter overlaps one of the Sp1 binding sites previously identified, and we demonstrated that binding of both factors to this composite element is mutually exclusive. Furthermore, we provide evidence that NF1-L has no effect by itself on rPARP promoter activity, but rather down-regulates the Sp1 activity by interfering with its ability to bind the rPARP promoter in order to modulate transcription of the rPARP gene.

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Marc-André Laniel‡‡§, Guy G. Poirier‡‡§, and Sylvain L. Guérin‡¶

From the ‡Oncology and Molecular Endocrinology Research Center and the ¶Unit of Health and Environment, CHUL Research Center, Ste-Foy, Quebec G1V 4G2, Canada

Poly(ADP-ribose) polymerase-1 (PARP-1) is a nuclear enzyme which catalyzes the addition of ADP-ribose units from nicotinamide adenine dinucleotide (NAD⁺) onto itself and other nuclear proteins such as histones and topoisomerases (reviewed in Refs. 1 and 2). It is made up of three functional domains, namely the amino-terminal DNA-binding domain, the central automodification domain, and the carboxyl-termi-
**EXPERIMENTAL PROCEDURES**

**Plasmid Constructs**—The rPARP promoter fragment pCR3 (Fig. 1), spanning region -103 to +13 relative to the mRNA start site, and its Sp1 triple-mutant derivative pCR3/F2-F3-F4m, have been described previously (36). The site-directed mutant pCR3-L3m was produced by the polymerase chain reaction (PCR), using pCR3 as template and the synthetic oligonucleotides L3m (5'-CAGTTCTCCGAGGCTGGCTAATAAAA-

-TACCCCTGCA-3') (see above), the high affinity binding site for Sp1 (5'-GATCATATCTG-

-GGGGGGAGACAGACAG-3') (44), the PARP-1 promoter initiator sequence (5'-GATTCGGGGCCAGCATCAGACATCGTCC-3'), the pCR3 probe (5'-GTCTGG-3'), and 3'-end-labeled as described above. The NF1-L-DNA complex was then visualized by native polyacrylamide gel electrophoresis (4% for the pCR3 region, which was performed using 5 μl of the NF1-L-containing CM-Sepharose fraction. Briefly, after pCR5 was 5'-end-labeled on the top strand, 3 x 10⁶ cpm labeled probe was incubated for 10 min at room temperature with the protein extract and treated with DNase I (Worthington, Freehold, NJ) as described previously (45). Digestion products were resolved by electrophoresis on a 5% polyacryl-

amide sequencing gel.

For dimethylsulfate (DMS) methylation interference, the 140-bp HindIII-XbaI pCR3 fragment was 5'-end-labeled on the top strand and partially methylated with DMS essentially as described (46). Once methylated, 6 x 10⁶ cpm labeled probe was incubated with 10 μl of the NF1-L-containing CM-Sepharose fraction in buffer D and DNA-protein complexes were separated by native polyacrylamide gel electrophoresis as described above. The NF1-L-DNA complex was then visualized by autoradiography and isolated by electroelution (47). The isolated la-

beled DNA was finally treated with piperidine (46) and further ana-

lyzed on a 8% sequencing gel.

**Cell Culture, Transient Transfection, and CAT Assay—** Rat GH4C1 cells were grown in Ham’s F-10 medium (Sigma-Aldrich, Oakville, Ontario, Canada) supplemented with 10% fetal bovine serum (Life Technologies, Inc., Burlington, Ontario, Canada) and 20 μg/ml genta-

mycin, under 5% CO₂ at 37 °C. The GH4C1 protein extract was incubated with the labeled probe in the case where the expression vectors NF1-L/pSI (kindly provided by Dr. Winnie Ekiold, Institute of Medical Biochemistry, University of Oslo, Oslo, Norway) or NF1-XpIDNA3 (kindly provided by Dr. Bin Gao, Medical College of Virginia, Richmond, VA) were added, GH4C1 cells were transfected withGeneSHUTTLE-20 cationic liposome (Quantum Biotechnologies, Montréal, Quebec, Canada), using 1 μg of test plasmid, 0.5 μg of pXGH5, and the expression vectors as described in the caption to Fig. 5B. The SL2 cells were transfected by the calcium phosphate precipitation method, using 15 μg of test plasmid and 5 μg of the human growth hormone (hGH) gene-encoding plasmid pXGH5 (49). In the case where the expression vectors NF1-L/pSI (kindly provided by Dr. Winnie Ekiold, Institute of Medical Biochemistry, University of Oslo, Oslo, Norway) or NF1-XpIDNA3 (kindly provided by Dr. Bin Gao, Medical College of Virginia, Richmond, VA) were added, GH4C1 cells were transfected withGeneSHUTTLE-20 cationic liposome (Quantum Biotechnologies, Montréal, Quebec, Canada), using 1 μg of test plasmid, 0.5 μg of pXGH5, and the expression vectors as described in the caption to Fig. 5B. The SL2 cells were transfected by the calcium phosphate precipitation method, using 15 μg of test plasmid, 5 μg of the β-galac-

tosidase (lacZ) gene-encoding plasmid pAKc5-V3-His/LacZ (Invitrogen, Carlsbad, CA), and the pPacSp1 or pSpAC-F1-L expression vectors as described in the legend to Fig. 6A. CAT activities were measured as described previously (50) and normalized to either hGH secreted into the culture medium (for GH4C1), which was assayed using a radioimmunoassay kit (Medicorp, Montréal, Quebec, Canada), or lacZ produced in the cells (for SL2), which was measured as described (51). Each single transfection experiment was repeated with at least two independent transfection experiments performed in triplicate. Standard deviation for the CAT assay is provided for each transfected plasmid and for each cell type. Only values three times greater than the background level caused by the reaction mixture alone (usually corresponding to ~0.15% chloramphenicol conversion) were considered significant.
RESULTS

Rat NF1-L Binds the rPARP Promoter in Vitro at a Site Overlapping an Sp1 Binding Site—We have previously demonstrated that, although Sp1 specifically binds to (Fig. 2, A and B) and strongly transactivates the GC-rich rPARP promoter, it is not sufficient to account for all of its transcriptional activity (36). Furthermore, a nuclear protein likely belonging to the NF1 family of transcription factors was shown to bind to the rPARP minimal promoter region, which extends from –103 to +13 (pCR3, see Fig. 1 and Ref. 37). In fact, EMSA analysis, using a heparin-Sepharose- and CM-Sepharose-enriched rat liver nuclear extract, revealed the specific binding of a protein that is clearly distinct from Sp1 (Fig. 1A). The interaction of this rat liver DNA-binding protein with the rPARP promoter likely occurs through a putative NF1 binding site (L3) previously identified on the pCR3 fragment (36, 37), since formation of the DNA-protein complex was completely abolished by competition with an excess of unlabeled oligonucleotide bearing the target sequence for human CTF/NF-I (42) (Fig. 2A). In contrast, competition using unlabeled oligonucleotides bearing unrelated sequences such as that for Sp1 or the initiator sequence from the PARP promoter had no effect on pCR3-rat liver protein complex formation (Fig. 2A). However, when using a crude nuclear protein extract from rat pituitary GH4C1 cells, only Sp1 forms a complex with the pCR3 fragment, since its formation is prevented by an Sp1-specific antiserum but not by a pre-immune or an NF1-1-specific antiserum (Fig. 2B).

Using DNase I and DMS methylation interference footprinting, we precisely mapped the binding site of the NF1-like protein to the L3 region of the rPARP proximal promoter (Fig. 3, A and B), which we had previously identified (37) as a potential NF1 target site due to its similarity both to the consensus sequence recognized by members of the NF1 family (42) and to the proximal silencer-1 element from the rat growth hormone gene (52). Interestingly, the footprinted L3 region completely overlaps the F2 region (see Figs. 1 and 3), which was shown to bind Sp1 (36).

In order to unequivocally identify the rat liver L3-binding protein as a genuine member of the NF1 family, we performed supershift experiments using an antiserum specific to the rat liver form of NF1 known as NF1-L (38). As shown in Fig. 4A, the rat liver DNA-binding protein formed a complex (NF1-L) of similar electrophoretic mobility using either the NF1 consensus binding site or the L3 sequence as the labeled probe, and this complex was efficiently supershifted by the anti-NF1-L antiserum (C1). As shown in Fig. 4B, the same rat liver protein bound the pCR3 DNA fragment to form a specific complex (NF1-L), which was supershifted by the anti-NF1-L antiserum (C1), but not by the pre-immune rabbit serum (PS) or by an anti-Sp1 antibody (Sp1Ab). We therefore conclude that the rat liver protein that binds to the rPARP proximal promoter region is NF1-L.

Members of the NF1 Family Indirectly Down-regulate the rPARP Promoter Activity—To characterize in more detail the effect of NF1 on the rPARP promoter, the L3 element was mutated at positions critical for its recognition by NF1 (Fig. 3 and Ref. 37) in order to yield the mutant derivative pCR3-L3m. This mutated L3 sequence was previously shown to abolish NF1 binding (37) and thus would give valuable information in assessing the functional role of NF1 on rPARP promoter transcriptional activity. When the mutated pCR3-L3m construct was transiently transfected into rat pituitary GH4C1 cells, its activity was similar to that directed by mutant pCR3 (Fig. 5A), suggesting that NF1 had no obvious effect on rPARP transcription. This is consistent with previous observations using the mutant derivative pCR3/F2-F3-F4m, in which all three Sp1 binding sites (F2, F3, and F4; see Fig. 1) were mutated (36). This mutated construct had practically no tran-
transcriptional activity when transiently transfected into GH4C1 cells (36) despite the fact that GH4C1 cells displayed efficient NF1 binding activity on the pCR3/F2-F3-F4m DNA fragment (Fig. 5B). Indeed, binding of an NF1 protein from GH4C1 cells to labeled pCR3/F2-F3-F4m was efficiently competed by ex-

FIG. 3. Footprinting analysis of NF1-L binding to the rPARP promoter. A, a 282-bp HindIII-XbaI obtained from the recombinant plasmid pCR5 (36) was 5' end-labeled at its HindIII site and incubated with the CM-Sepharose-enriched preparation of NF1-L and then subjected to DNase I digestion. A control sample treated with DNase I but with no protein added (U) and a DNA “G” sequencing reaction performed on the same probe (G) were also included. The DNA sequence of the L3 protected region is indicated along with its positioning relative to the rPARP mRNA start site. B, the 140-bp HindIII-XbaI pCR3 fragment used in Fig. 2 was 5'-end-labeled on the top strand, partially methylated with DMS and incubated with CM-Sepharose-enriched NF1-L. The NF1-L/pCR3 complex (C) was resolved by EMSA and isolated by electroelution, along with the free probe (U). The labeled DNA from the complex was then treated with piperidine and further analyzed on a sequencing gel. The position of the two G residues whose methylation by DMS interferes with binding of NF1-L is shown, along with the surrounding rPARP promoter sequence.

NF1 interferes with Sp1 binding on the rat PARP promoter. A, a 282-bp HindIII-XbaI obtained from the recombinant plasmid pCR5 (36) was 5' end-labeled at its HindIII site and incubated with the CM-Sepharose-enriched preparation of NF1-L and then subjected to DNase I digestion. A control sample treated with DNase I but with no protein added (U) and a DNA “G” sequencing reaction performed on the same probe (G) were also included. The DNA sequence of the L3 protected region is indicated along with its positioning relative to the rPARP mRNA start site. B, the 140-bp HindIII-XbaI pCR3 fragment used in Fig. 2 was 5'-end-labeled on the top strand, partially methylated with DMS and incubated with CM-Sepharose-enriched NF1-L. The NF1-L/pCR3 complex (C) was resolved by EMSA and isolated by electroelution, along with the free probe (U). The labeled DNA from the complex was then treated with piperidine and further analyzed on a sequencing gel. The position of the two G residues whose methylation by DMS interferes with binding of NF1-L is shown, along with the surrounding rPARP promoter sequence.

FIG. 4. Binding of NF1-L to the rPARP promoter as revealed by supershift analyses in EMSA. A, CM-Sepharose-enriched NF1-L (CM-Sep) was incubated in the presence of a 5' end-labeled double-stranded oligonucleotide bearing either the sequence of the high affinity CTF/NF-I consensus binding site (NF1) or that of the rPARP L3 element (L3). The binding reaction was performed in either the absence or the presence of a polyclonal antibody directed against rat liver NF1-L (NF1Ab). Formation of DNA-protein complexes was then monitored by EMSA as in Fig. 2. The position of both the NF1-L and a supershifted complex (C1) resulting from the binding of the NF1Ab to the NF1-L-labeled probe complex is indicated, along with that of a nonspecific signal (NS) that often appears in EMSA. U, unbound fraction of the labeled probes. B, the 140-bp HindIII-XbaI pCR3 labeled probe used in Fig. 2 was incubated with the CM-Sepharose-enriched preparation of NF1-L either alone or in the presence of antibodies directed against either NF1-L (NF1Ab) or Sp1 (Sp1Ab). As a negative control, incubation was also performed in the presence of pre-immune serum (PS). The position of both the NF1-L/pCR3 complex (NF1-L) and its corresponding supershifted counterpart (C1) is provided, along with that of the free probe (U).

NF1 interferes with Sp1 binding on the rat PARP promoter.
NF1 Interferes with Sp1 Binding on the Rat PARP Promoter

We then used the pCR3 fragment and its Sp1 mutant derivative pCR3/F2-F3-F4m labeled probes in EMSA with the NF1-L-enriched rat liver protein extract and the GH4C1 nuclear protein extract, which supports strong Sp1 binding to the pCR3 probe (see Fig. 2A and Ref. 36). When the pCR3 probe was incubated with a constant amount of NF1-L and increasing amounts of GH4C1 extract, NF1-L binding to pCR3 was abolished by the increasing amounts of Sp1 (Fig. 7A, left panel). On the other hand, NF1-L binding to the Sp1 mutant probe was expectedly unaffected by increasing amounts of GH4C1 nuclear extract (Fig. 7A, right panel). The reverse is also true, i.e., increasing amounts of NF1-L abolished Sp1 binding to pCR3 (Fig. 7B, left panel), suggesting that binding of NF1-L and Sp1 to the rPARP promoter is mutually exclusive. This and the SL2 transfection experiments show that NF1-L acts indirectly on rPARP promoter transcriptional activity by preventing Sp1 from binding to its target and therefore leads to decreased transcriptional activation of the rPARP promoter.

DISCUSSION

Poly(ADP-ribosyl)ation is a major post-translational modification potentially involved in chromatin architecture (1) and likely to affect important nuclear functions such as DNA repair, recombination, replication, and transcription. Although PARP-1, the main poly(ADP-ribosyl)ating enzyme (2), is expressed in a variety of cells and organs, its transcriptional regulation during cell cycle progression, cell proliferation, and differentiation is likely to impact on the timing and extent of PARP-1 activity and function. Indeed, it has been shown that PARP-1 mRNA levels increase just before maximal enzymatic activity during thymocyte proliferation (22), astrocyte proliferation and differentiation (25), and lymphocyte activation (28). Furthermore, elevated levels of PARP-1 mRNA apparently account for the enhanced poly(ADP-ribosyl)ation observed in Ewing's sarcoma cells (24).

In this study of the rPARP proximal promoter, we investigated the regulatory mechanisms involved in its expression and have highlighted the roles of both Sp1 and NF1 in fine-tuning rPARP gene transcription. Whereas Sp1 clearly up-regulated rPARP transcription (Ref. 36 and Fig. 6B), the role of NF1 appeared more ambiguous; although mutation of the NF1 binding site in the rPARP fragment pCR3 had no effect on its transcriptional activity in rat pituitary GH4C1 cells (Fig. 5A), overexpression of NF1-L or NF1-X in the same cells down-regulated pCR3 activity (Fig. 6A and data not shown). In Dro-
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Fig. 6. Co-transfection experiments in rat GH4C1 and Drosophila SL2 cells. A, both the wild-type rPARP promoter-bearing plasmid pCR3 (black columns) and its mutated derivative pCR3-L3m (white columns) were transiently transfected into GH4C1 cells along with the NF1-L expression plasmid (0.5 or 1 μg). As a negative control, pCR3 was also cotransfected along with the empty vector pSI (which was used for constructing the NF1-L expression plasmid). CAT activities were measured and normalized as detailed under “Experimental Procedures.” Values are expressed as percentage of CAT activity relative to the level directed by either pCR3 and pCR3-L3m when cotransfected with the control plasmid pSI. Standard deviation is provided for each value shown. B, the rPARP promotor-bearing plasmid pCR3 was transfected into Drosophila SL2 cells along with the empty vector pPac, or with expression plasmids encoding either NF1-L (0.2, 0.5, or 1 μg) or Sp1 (1 μg), either individually or in combination. CAT activities were measured and normalized to β-galactosidase as described under “Experimental Procedures.” Standard deviation is provided for each selected condition.

Disruption of the Sp1 gene has revealed that, although important for embryonic development, it is dispensable for cell growth and differentiation (58), suggesting that it may not be relevant to differentiation- and cell cycle-related PARP-1 transcription. On the other hand, Sp1 is one of at least 16 members of the Sp/XKLF family of transcription factors able to bind GC or GT boxes (59), and it is therefore plausible that other members of this family take over Sp1 function in Sp1-deficient cells. Nevertheless, a number of genes have been shown to rely on Sp1 for either cell cycle-regulated expression, including thymidine kinase (60) and dihydrofolate reductase (61), or differentiation-associated expression, such as acetylcholine receptor ε (62) and keratin K3 (63). Interestingly, these Sp1-related events are dependent upon modification of Sp1 activity, either by its association with other regulators such as cell cycle-related transcription factor E2F (60, 61), by its phosphorylation (62) or by its competition with other transcription factors such as AP-2 (63). The analysis of the keratin K3 promoter (63) is particularly relevant to the present study, in that the ratio between Sp1 and AP-2, rather than actual regulation of Sp1, seems to be critical to the modulation of keratin K3 expression.

The NF1 family is composed of four members encoded by distinct genes, NF1-A, -B, -C, and -X (53), producing distinct protein products, which can form homo- or heterodimers (64). In addition, all four NF1 mRNAs can be differentially spliced to yield a multitude of proteins with subtle differences in their transactivation capacities (58, 65). Disruption of the NF1-A gene leads to severe neurological defects, with the majority of mice dying perinatally, yet other organs seem to develop normally (66). As in the case of the Sp1 knockout study, other members of the NF1 family may compensate for the absence of...
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NF1-A. Nevertheless, proteins of the NF1 family have been implicated in adipocyte differentiation (67) and in liver regeneration (68). In adipocytes, the adipocyte p2 gene expression, which is dependent on NF1, is induced upon differentiation (67), as is expression of PARP-1 (13), even though Sp1 expression is down-regulated in the early stages of adipocyte differentiation (69). On the other hand, in liver regeneration, NF1 concentration decreases (68) whereas PARP-1 expression increases (20), which is consistent with Sp1 activity being more prominent (70). That NF1 proteins exhibit stimulatory activity in one case (i.e. adipocyte p2 gene expression) and inhibitory activity in the other (i.e. the rPARP promoter) has been previously observed and shown to be dependent on the promoter or the cell type (71).

Some correlation is observed between the level of PARP-1 mRNA in mouse organs (15) and that of Sp1 (72), although it is not complete. Indeed, mouse thymus and testis express nearly as much PARP-1 (15) despite that Sp1 levels are 8 times higher (70) compared to PARP-1 levels (15), thereby confirming that Sp1 is an important but not the only transcription factor involved in PARP-1 gene expression. Interestingly, NF1 proteins are also highly expressed in the lung (65) and, in light of the present study, may contribute to down-regulation of PARP-1 expression in the lung.

Composite elements are transcriptionally active DNA sequences, which bind two or more transcriptional regulators, and have been found in many vertebrate gene promoters (73). They provide an efficient way of fine-tuning gene expression in different cellular situations, by exploiting either the synergistic or antagonistic effects of the transcription factors they bind to respectively overactivate or down-regulate transcription. In the present study, we provide evidence that the rPARP gene promoter is regulated by the antagonistic effect of NF1 over Sp1 transactivation on a composite element. Both of these transcription factors have been found in composite elements on other gene promoters. Antagonistic binding of Sp1 has been reported with erythroid cell-specific factor NF-E1 on the human $\zeta$-globin promoter (74), where it may account for tissue-specific expression, with AP-2 on the rabbit K3 keratin promoter (63), where it is associated with differentiation-specific expression, and with NF-xB on the human fas promoter (75), where it is involved in lymphocyte activation-related up-regulation. In the case of NF1, its mutually exclusive binding has been reported with AP-2 on the hGH promoter (76), but also, and consistent with our results, with Sp1, on the rat liver-type arginase promoter (77), on the murine collagen $\alpha(1)$ promoter (78), and on the rat $\alpha_{1B}$ adrenergic receptor gene promoter (79). In the latter two studies, mutually exclusive binding of Sp1 and NF1 has been suggested to confer an important mechanism of tissue-specific expression. Interestingly, and in contrast to the results presented here on the rPARP promoter, Sp1 actually down-regulates NF1-mediated activation of the collagen $\alpha(1)$ (1) promoter (78).

We have shown that Sp1-activated transcription of the rPARP gene promoter is susceptible to subtle regulation via the mutually exclusive binding of NF1-L. As Sp1 and NF1-L are both individual members of extended families of transcription factors, it is expected that transcriptional regulation through a composite Sp1/NF1 element, such as those reported here on the rPARP promoter, on the rat liver-type arginase promoter (77), the murine collagen $\alpha(1)$ (1) promoter (78), or the rat $\alpha_{1B}$ adrenergic receptor gene promoter (79), will lead to complex patterns of activation/down-regulation depending on the cell type or the cellular situation analyzed, as members of both families may be differentially expressed in such instances.

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