Mammalian ribonucleotide reductase shows S-phase specific expression and consists of two non-identical subunits, proteins R1 (large subunit) and R2 (small subunit). A comparison between the human and mouse TATA-less R1 gene promoters revealed four highly conserved DNA regions, while the remaining sequence showed a low degree of conservation. Two regions, α and β, were earlier identified as protein binding regions in the mouse R1 promoter by using DNase footprinting technique. The two new regions are located to the transcription start and to a DNA sequence about 40 base pairs downstream from the start. Gel shift assays using TFII-I antibodies and competition with an oligonucleotide representing the terminal deoxynucleotidyl transferase initiator element identified the start region as a TFII-I binding initiator element. The conserved downstream region, called γ, also formed specific DNA-protein complexes in gel shift assays. Functional studies, using synchronized cells stably transformed by R1 promoter-luciferase reporter gene constructs, indicated that the initiator and the γ elements together were necessary for cell cycle-regulated R1 promoter activity. Earlier published data, indicating Sp1 binding to the R1 α/β regions, could not be confirmed, suggesting that the R1 initiator element may function independent of Sp1.

Ribonucleotide reductase is a key enzyme in the synthesis of DNA precursors, catalyzing the reduction of the four ribonucleotides to their corresponding deoxyribonucleotides. The mammalian enzyme belongs to the class I ribonucleotide reductases (1, 2). In this class, the active enzyme consists of two nonidentical homodimeric subunits, proteins R1 and R2, each inactive alone. The large subunit (R1) binds the ribonucleoside diphosphate substrates and the nucleoside triphosphate allosteric effectors as well as harboring the active site, containing redox-active cysteine residues. The small subunit (R2) contains binuclear non-heme iron centers, which generate a tyrosyl free radical required for catalysis. The crystal structures of the corresponding Escherichia coli proteins were recently published (3, 4).

Ribonucleotide reductase activity is cell cycle regulated showing maximal levels during the S-phase. This regulation is imposed by de novo synthesis and breakdown of the R2 protein while the R1 protein is present in constant and excess amounts during the cell cycle (5, 6).

The levels of R1 and R2 mRNA in serum-synchronized cells and in elutriated cells vary in parallel with undetectable levels in G0/G1 cells and maximal values in S-phase cells (7, 8).

In mouse cells, the R1 gene is localized to chromosome 7 (9) and the active R2 gene to chromosome 12 (10). The mouse R1 gene covers 26 kilobases and contains 19 exons. In contrast to the R2 promoter, the R1 promoter lacks a TATA box. DNase I footprinting assays identified two protein-binding regions in the mouse R1 promoter, α (nt 98 to 76) and β (nt 189 to 167), that are identical except for one base pair. Three protein complexes bound to each 23-mer, and one showed S-phase specific binding (11). The sequence of the human R1 gene promoter was recently published (12).

In common promoter factors the TATA box is the binding site for the general transcription factor TBP, which in turn promotes the assembly of the transcription initiation complex (13, 14). Other promoters lack TATA box and instead contain an initiator element at the transcription start. This element directs the transcription start to a certain nucleotide, as in the case of the thymidylate synthase gene, lacking both a TATA box and an initiator element, has a region that displays a random start of transcription. However, the insertion of a TdT initiator element in the thymidylate synthase promoter will direct the start of transcription to a major start site (16). Finally, there are promoters that contain both a TATA box and an initiator element, e.g. the adenovirus-major late promoter (Ad-ML). A model has been presented, based on the Ad-ML promoter, suggesting different pathways for the formation of the preinitiation complex (17). The pathway of choice is decided by the presence or absence of a TATA box or an Inr element.

The transcription factor TFII-I, a 120-kDa polypeptide, binds to the initiator elements of the Ad-ML promoter, the TdT promoter, and the human immunodeficiency virus-1 promoter (HIV-1) (18). TFII-I, in combination with other proteins, has shown to promote the assembly of a transcription initiation complex containing TBP on the Ad-ML initiator element (17). In this paper, we present data showing that the TATA-less mouse ribonucleotide reductase R1 gene promoter contains an initiator element of the TdT type. The initiator binding protein TFII-I binds to the R1 initiator element. We also show that the R1 initiator element is important for the regulation of promoter activity.

**MATERIALS AND METHODS**

Construction of R1 Promoter-Luciferase Reporter Gene Plasmids—The plasmid p19LucR1.1.0 (Fig. 1) was created by amplifying a region of the 5’-end of the R1 gene with the primers 5’-TCCCCAGCTTGAGGTT-3’ and 5’-GCTTGAAGAGCTCTGCT-3’.

The abbreviations used are: nt, nucleotide; TdT, terminal deoxynucleotidyl transferase; Ad-ML, adenovirus-major late promoter; HIV-1, human immunodeficiency virus-1 promoter.
GCTGCCTTATGCTCAAG-3' (P1) and 5'-GAAGGCCTTCCGCCGCTA-GAAGCTGAAG-3' (P2). The fragment, starting at nt -812 and ending at nt -242 relative to the major transcription start, was digested with HindIII and StuI (underlined in P1 and P2) and ligated into the HindIII and SmaI sites of the previously described luciferase plasmid p19luc (19).

The plasmids p19lucR1 0.49 and p19lucR1 0.30 were created by digesting p19lucR1 1.0 with, respectively, EcoRV and AccI (AccI filled in by the Klenow fragment of DNA polymerase 1) together with SpI (in the luciferase gene). The resulting fragments were ligated into p19luc opened with HindIII (filled in by the Klenow fragment of DNA polymerase 1) and SpI (in the luciferase gene). The promoter fragments in p19lucR1 0.49 and p19lucR1 0.30 started at nt -241 and nt -53, respectively, and both ended at nt -421.

Overlap extension polymerase chain reaction (20) was used to create the mutations of the Inr and γ regions in the two constructs p19lucR1 0.30-Inr and p19lucR1 0.30-γ. Briefly, to construct p19lucR1 0.30-Inr, we first amplified the region upstream from the Inr, from nt -53 to -8, with the oligonucleotides 5'-TCCCAAGTTGGCTATCTGT-CAGTTCGCCGC-3' (P3) and 5'-AACACAGATACCGAACAACAGACGGTT-TCAACGGCCTGGGAGGTTTGGGATATCCAGAACATGCAGAGCAACGCGACGGAC-3' (P4). The same primer set was used for the construction of p19lucR1 0.30-γ (GATCGGGGCGGGGCGAGC-3') and 5'-TTGCCCACACTCAATATGCGG-3', and 3'-AACGGGTGTGGGTTATACCGCCG-5'.

Promoter regions in the two constructs p19lucR1 0.30-Inr and p19lucR1 0.30-γ were used instead of primers P4 and P5. The same region that replaced the Inr in the previous construct had now replaced the region (nt -34 to nt +59).

All constructs were verified by restriction enzyme analysis or dideoxyribonucleotide sequencing.

Transformation of Cells and Determination of Luciferase Activity—To study the activity of different R1 promoter constructs, BALB/3T3 cells were stably transformed by electroporation as described previously (21). Several independent clones containing different constructs were synchronized by serum starvation as described earlier (7). At different time points after serum readdition, cells were harvested and assayed for luciferase activity as described (21). The levels of luciferase activity were normalized against protein concentration measured by the Bradford method (22). At each time point, an aliquot of cells was analyzed by flow cytometry to determine the distribution of cells in the different cell cycle phases (6).

Electrophoretic Mobility Shift Assays—Nuclear extracts were prepared from BALB/3T3 cells as described (23). The protein concentration was measured by the Bradford method (22).

A typical reaction mixture included 1.4 fmol end-labeled oligonucleotide (7100 cpm/mmol), 0.78 μg of poly(dI-dC), 10% glycerol, 10 μM Hepes (pH 7.9), 60 μM KCl, 1 mM dithiothreitol, 4.5 μg of bovine serum albumin, and 10 μg of nuclear extract in a volume of 15 μl (24). In competition experiments, unlabeled oligonucleotides were added to the reaction mixes at different concentrations prior to the addition of nuclear extract. A 15-min incubation of the mixture at 30 °C was followed by separation on a 4% native low-ionic strength polyacrylamide gel, which was dried and autoradiographed on Kodak X-Omat AR film (11)

Oligonucleotides Used in Electrophoretic Mobility Shift Assays—The following oligonucleotides were used in the assays. R1 γ footprint (11), 5'-TTGCCACACTCAATATGCGG-3' and 3'-AACGGGTGTGGGTTATACCGCCG-5'; R1 β footprint (11), 5'-TTGCCACACTCAATATGCGG-3' and 3'-AACGGGTGTGGGTTATACCGCCG-5'; R1 initiator element, 5'-GAAGACGTCTATTTCAATGCGG-3' and 3'-TTCTTG-CAGTAAACCTTAAAGGACG-5'; R1 γ region, 5'-GCTCAGGGGCACCACCCACCACCTCGCCCTTTCCG-3'; The terminal deoxynucleotidyl transferase initiator element (15), 5'-AGAGCCCTCTATTCTGGAGACACCAC-3' and 3'-TCTCGGAGAATGACCTCTTGGTGGT-5'; Sp1 consensus element (25), 5'-ATTCCAGTCAATTTACCTGCTCCG-3' and 3'-TTCTTG-CAGTAAACCTTAAAGGACG-5'; R1 γ region, 5'-GCTCAGGGGCACCACCCACCACCTCGCCCTTTCCG-3'; AP-1 consensus element (26), 5'-CGCTTGTAGTACGCGCCG-3' and 3'-CCGAACTACTCAGTGCGCCCTTTCCG-3'.

Antibodies Used in Electrophoretic Mobility Shift Assays—Affinity-purified antibodies against TFII-I and p50 subunits (a kind gift from A. L. Roy) were added as recommended by A. L. Roy. Antibodies against Sp1, USF, Y1 (Santa Cruz Biotechnology), were added as recommended by the manufacturer. The samples were incubated 1–5 h on ice before the 15-min incubation at 30 °C.

RESULTS

Sequence Comparison between the Mouse and Human R1 Promoter—Two protein binding regions in DNA, α and β, were earlier identified in the mouse R1 promoter (11). To identify elements that could be important for promoter activation, we searched for conserved DNA sequences in the R1 promoters of mouse and human. Sequence comparisons between the mouse and human R1 promoters showed four regions of high homology (Fig. 2A). The α and β regions showed 91 and 78% identity between mouse and human. Furthermore, we identified a highly conserved region at the transcription start, which we provisionally named Inr (initiator element). The Inr region showed a 90% identity between mouse and human, over a region of 20 base pairs. The fourth conserved region, termed γ, started 34 nucleotides downstream from the transcription start. It showed a 96% identity over a region of 26 base pairs. The conserved regions had the same distribution and approximately the same distance between each other in the two promoters, while the remaining sequence only showed a low degree of conservation (40%).

The strong homology between the human and mouse R1 genes at the transcription start suggested the presence of an initiator element, directing the start of transcription. A com-
A

\[ \begin{array}{c}
\text{mouse R1} \\
\alpha \quad \beta \\
\text{human R1} \\
\gamma
\end{array} \]

 Comparison between the mouse and human R1 promoters. The arrows indicate the transcription start. The conserved regions are boxed, and the small letters indicate non-conserved nucleotides. The mouse and human sequences are published (11, 12). B, comparison between the nucleotide sequence around the R1 transcription start and the published sequence of some initiator elements (18). The transcription start is underlined.

parison of the R1 Inr with known initiator elements (Fig. 2B) showed some homology to the initiator element of the mouse TdT gene (15), where six nucleotides at the transcription start were identical to the R1 Inr element.

An Oligonucleotide Corresponding to the Conserved Region of the R1 Gene Transcription Start Forms Specific DNA-Protein Complexes—Gel shift assays with an end-labeled oligonucleotide corresponding to the R1 transcription start identified one DNA-protein complex (Fig. 3). This complex was competed by the unlabeled oligonucleotide corresponding to the R1 transcription start (lanes 3-5) but not by an unrelated unlabeled oligonucleotide containing a consensus binding site for Sp1 (lane 9), indicating a specific DNA-protein interaction. The DNA-protein complex was also competed by an unlabeled oligonucleotide corresponding to the TdT Inr element (lanes 6-8), although less efficient than the R1 transcription start oligonucleotide. An end-labeled oligonucleotide corresponding to the TdT Inr formed two complexes that were both specific, since they were competed by the unlabeled TdT Inr oligonucleotide (Fig. 4, lanes 3-5). Major complex binding to the TdT Inr was also competed by the R1 Inr oligonucleotide (lanes 6-8). Unrelated, unlabeled oligonucleotides containing consensus binding sites for Sp1 or AP-1 proteins showed no competition when added at a 500 and 1000 molar excess (Fig. 4, lanes 9 and 10). The mobilities of the major DNA-protein complexes formed by the TdT Inr oligonucleotide and the R1 transcription start oligonucleotide were identical (data not shown).

Transcription Factor TFII-I Binds to the R1 Transcription Start—Affinity-purified antibodies against human TFII-I (27) bind TFII-I and prevent it from binding to DNA. In our hands, the TFII-I polyclonal antibodies prevented formation of DNA-protein complexes when using either the TdT initiator oligonucleotide or the R1 Inr oligonucleotide and a crude nuclear extract from mouse fibroblasts (Fig. 5, lanes 4-6, and Fig. 6, lanes 4 and 5). The preimmune serum did not affect formation of the DNA-protein complexes. This is strong indication that TFII-I binds specifically to the transcription start of the R1 gene. The transcription factor USF has been shown to interact with the initiator elements of the HIV-1 and the Ad-ML promoters (18, 28). The transcription factor YY1 has also been shown to interact with an initiator element (29). However, supershift antibodies to USF or YY1 did not alter the mobility of the DNA-protein complex formed by the R1 initiator element (Fig. 5, lanes 7 and 8). The presence of USF in the nuclear extract was verified using an E-box element oligonucleotide (30) (data not shown).

Protein Binding to the γ Region of the Mouse R1 Promoter—Gel shift assays with an oligonucleotide corresponding to the γ region showed formation of several DNA-protein complexes (Fig. 7). Competition with unlabeled γ oligonucleotide (lanes 3-5) or unlabeled R1 β footprint oligonucleotide (lanes 6-8) showed that at least the complex with the highest mobility was specific (indicated by an arrow in Fig. 7). TFII-I antibodies did not interfere with the formation of this complex, and it was not supershifted by the USF antibodies (data not shown).

Protein Binding to the α and β Footprint of the Mouse R1
Promoter—The nucleotide sequences of the α and β footprint are identical except for one nucleotide (11). Gel shift assays with α or β footprint oligonucleotides gave the same pattern of three DNA-protein complexes (Fig. 8 and data not shown). Several TATA-less promoters, including the TdT promoter, contain Sp1 binding sites that greatly stimulate transcription from the Inr (14). Earlier UV cross-linking experiments suggested that Sp1 binds to the β footprint and not to the putative Sp1 site in the mouse R1 promoter (11). We have now studied this interaction in more detail with supershift antibodies raised against Sp1 and recombinant Sp1 protein (Promega). Gel shift assays using an Sp1 consensus oligonucleotide clearly demonstrated the presence of Sp1 in our nuclear extract (Fig. 8, compare lanes 5–7 to lanes 8–9). However, Sp1 did not bind to the R1 β oligonucleotide since no supershift was observed with the Sp1 antibodies (Fig. 8, lanes 3 and 4). Furthermore, the supershifted Sp1-DNA complex showed a lower mobility than any of the DNA-protein complexes formed using a nuclear extract and the α oligonucleotide (Fig. 8, lane 4 and lanes 5 and 6). Similar results were obtained with the β oligonucleotide (data not shown).

Cell Cycle Regulation of R1 Promoter Activity—To study if the conserved protein binding regions in the R1 promoter are involved in the cell cycle regulation of R1 promoter activity, we made a number of promoter-luciferase reporter gene constructs (Fig. 1). The constructs were used to stably transform BALB/3T3 cells that were subsequentially synchronized by serum starvation and assayed for luciferase activity. At least three clones containing each construct were assayed. All three constructs, p19lacR1 1.0 (data not shown), p19lacR1 0.49, and p19lacR1 0.30, showed a similar biphasic expression pattern when cells were stimulated to proliferate from quiescence (Fig. 9, A and B). There was a minor peak 4 h after stimulation, while the major increase of activity appeared about 18 h after serum readdition. In contrast, the p19lacR1 0.30-Inr and p19lacR1 0.30-γ constructs, lacking the Inr element and γ region, respectively, both seemed to have lost the latter activation (Fig. 9, C and D).

Protein Binding to the R1 Inr Element and to the γ Region during the Cell Cycle—The results with the p19lacR1 0.30 reporter gene construct showed that the R1 Inr element and γ element together were necessary for cell cycle-regulated transcription. Therefore, we used gel shift assays in an attempt to demonstrate a correlation between specific binding to the Inr element or the γ region and transcriptional regulation. However, nuclear extracts from synchronized BALB/3T3 cells failed...
DISCUSSION

The conserved R1 promoter initiator element binds TFII-I specifically but does not fully conform to the pyrimidine-rich Inr consensus YYAN(T/A)YY (31). Furthermore, the TdT, the Ad-ML, and the HIV-1 promoters all contain two initiator elements, one located around the transcription start and the other about 40 base pairs downstream from the first one (28). The position of the conserved R1 γ region fits the position of a second Inr element, but the γ region is purine rich and has no sequence similarity to the R1 Inr element.

Many Inr-containing promoters bind Sp1, which greatly stimulates transcription from the Inr (14). For example, it was shown that Sp1 stimulated a synthetic promoter that only contained an Inr more effectively than a promoter that only contained a TATA box (32). There is one putative Sp1 binding element in reverse orientation in the mouse R1 promoter (nt 238 to 233), but no Sp1 binding could be demonstrated by using DNase I footprinting experiments (11). In contrast, earlier UV cross-linking experiments suggested that Sp1 binds to the β footprint (11). However, our gel shift assays in this paper with Sp1 supershift antibodies did not reveal any interaction between Sp1 and the α/β footprints. Therefore, the transcription from the R1 Inr element seems to be regulated independently of Sp1, in contrast to the earlier described pyrimidine-rich Inr elements.

TFII-I stimulates Inr element-dependent transcription from the Ad-ML promoter in a cell-free system (17). We now demonstrate that the TFII-I binding R1 Inr element is important for R1 promoter activity. Earlier results had demonstrated that a protein binds specifically to the conserved α/β footprints when cells enter S-phase (11). Two additional DNA-protein complexes bind to the α/β footprints, but this binding was constant during the cell cycle. The two cell cycle-invariant DNA-protein complexes contained different proteins since they precipitate at different ammonium sulfate concentrations (data not shown).

Unexpectedly, our R1 promoter-reporter gene constructs showed a very similar cell cycle-dependent pattern of luciferase expression when the α/β footprints were present and when they were absent. Therefore, the region nt −53 to +242, containing the Inr element plus the γ element, appears to be sufficient for a cell cycle-regulated activation of the R1 promoter. In our experiments using synchronized clones of stably transformed cells, it is difficult to compare absolute promoter strength due to variations in levels of synchrony and positional effects.

Protein binding to the α/β footprints may increase the expression seen with the Inr and γ elements alone. We hope to be able to measure this using in vitro transcription assays.

In promoters containing a TATA box, it has been shown that TBP binds to the TATA box. TBP stabilizes the formation of a functional preinitiation complex in vitro (cf. 14), but to mediate an activation of transcription from upstream elements, the TBP-associated factors are required (33). TATA-less promoters have also been shown to be dependent on TBP for the formation of the preinitiation complex (cf. 34). However, it is still unclear how the components of this complex are recruited to a TATA-less promoter. One idea is that an initiator binding protein (i.e. TFII-I (18), YY1 (29), HIP-1 (35), USF (18, 28, 30)), with spec-

FIG. 9. Upper panel, luciferase activity in serum-synchronized BALB/3T3 cells stably transformed with R1 promoter-luciferase gene constructs. The luciferase activity in each time point has been divided by the luciferase activity in extracts from the quiescent cells (O h). The values for quiescent cells varied from 13 to 187 light units/μg protein in the different experiments. Lower panel, cell cycle phase composition, determined by DNA flow cytometry. ●, G0-phase cells; ○, S-phase cells; ■, G2 + M-phase cells. A represents a clone containing the construct p19ucR1 0.49, B represents a clone containing the construct p19ucR1 0.30, C represents a clone containing the construct p19ucR1 0.30-Inr, and D represents a clone containing the construct p19ucR1 0.30-γ.
ficity for a certain type of initiator element first recruits TBP and then other proteins to the preinitiation complex (17). However, sequence analyses of synthetic Inr-containing promoters downstream from Sp1 sites suggested that a universal protein should recognize all initiator sequences (31).

Recent data from experiments with the TATA-less TdT promoter suggested an alternative pathway for preinitiation complex formation involving TATA-less, Inr-containing promoters where TBP-associated factors participate in TBP recruitment. In this reaction the TATA binding activity of TBP is not required (34). It has also been reported that RNA polymerase II has some affinity for sequences around the transcription start (36). Our data give no information about additional proteins binding to the R1 Inr, but our gel shift experiments indicate that if more proteins are involved, they are dependent on TFII-I.

We cannot explain why the major rise in luciferase activity in our p19luc R1 1.0/0.49/0.30 constructs appears first in late S-phase and not in early S-phase as the R1 mRNA. This may indicate that we still have not identified all elements required for correct cell cycle-regulated R1 gene expression. Further-

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The TATA-less Promoter of Mouse Ribonucleotide Reductase R1 Gene Contains a TFII-I Binding Initiator Element Essential for Cell Cycle-regulated Transcription

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