Rearrangement of \(CCND1\) (BCL1/PRADI) 3' Untranslated Region in Mantle-Cell Lymphomas and t(11q13)-Associated Leukemias

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Rearrangement and overexpression of \(CCND1\) (BCL1/PRADI), a member of the cyclin G, gene family, are consistent features of t(11q13)-bearing B-lymphoid tumors (particularly mantle-cell lymphoma [MCL]). Its deregulation is thought to perturb the G1-S transition of the cell cycle and thereby to contribute to tumor development. As suggested by previously published studies, rearrangement of the 3' untranslated region (3' UTR) of \(CCND1\) may contribute to its activation in some lymphoid tumors. To define further the prevalence of such rearrangements, we report here the result of the molecular study of 34 MCL and six t(11q13)-associated leukemias using a set of probes specific to the different parts of the \(CCND1\) transcript. We also sequenced the entire cDNA of the overexpressed \(CCND1\) transcripts in a t(11q13)-associated leukemia. DNA from four of these 40 patients showed rearrangement of the 3' UTR coexisting with major translocation cluster (MTC) rearrangement. Southern blot and sequence analyses showed that, as a result of these rearrangements, the 3' AU-rich region containing sequences involved in mRNA stability and in translational control is eliminated. Moreover, the finding that the \(CCND1\) mRNA half-life was greater than 3 hours (normal tissues, 0.5 hours) in these t(11q13)-associated cell lines stresses the importance of posttranscriptional rearrangement in the activation of \(CCND1\). Finally, we did not observe any mutation in the coding frame of the \(CCND1\) cDNA analyzed.

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A MAJORITY OF HUMAN hematopoietic malignancies carry nonrandom chromosomal alterations; experimental evidence indicates that genes located at recurring chromosomal breakpoints are directly involved in tumor pathogenesis. The t(11;14)(q13;q32) translocation and its molecular counterpart, bcl-1 rearrangement, are consistent features of the subtype of non-Hodgkin’s lymphoma designated centrocytic lymphoma or the similar intermediate lymphocytic lymphoma, now referred to as mantle-cell lymphoma (MCL). As a result of this translocation, the putative \(BCLI/PRADI\) proto-oncogene, on chromosome 11, is juxtaposed to an IgH-enhancer sequence located on chromosome 14. The \(BCLI/PRADI\) gene is known under different names (PRADI, cyclin D1, \(BCLI\), D11S287E). We will refer to it as \(CCND1\), in accordance with the official nomenclature. Chromosomal breakpoints are widely scattered on chromosome 11q13, but three hot spots have been individuated: the major translocation cluster (MTC) lying approximately 110 kb centromeric of the \(CCND1\) gene, and two minor translocation clusters (mTCs), which are less frequently involved: mTC1 and mTC2. mTC1 is localized approximately 22 kb telomeric of MTC, and mTC2, which has been recently identified, maps to the 5' flanking region of the \(CCND1\) gene (probe B as described by Williams et al). \(CCND1\) is a member of the cyclin G, family; its deregulation is thought to perturb the G1-S transition of the cell cycle and thereby to contribute to human tumor development. This hypothesis is in agreement with the finding that \(CCND1\) is overexpressed in the vast majority of the MCL and t(11q13)-associated leukemias analyzed so far.

With regard to the mechanisms of activation of \(CCND1\) in lymphoid tumors, one can consider several possibilities. It has been first postulated that activation of \(CCND1\) in t(11;14)-carrying tumors is a consequence of its juxtaposition to an immunoglobulin cis-acting sequence. According to another hypothesis, \(CCND1\) activation might occur at the postranscriptional level through rearrangement of its 3' untranslated region (3' UTR). In fact, in primary tumors and in cell lines with chromosome 11q13 structural abnormalities, a 1.5-kb mRNA can be detected in addition to the normal 4.5-kb mRNA. Sequencing of \(CCND1\) cDNA in a few cell lines has shown that the smaller transcript corresponds to a shortened form of the normal 4.5-kb transcript as a result of the use of different polyadenylation signals or of deletions of the 3' end of the gene. These data suggested that, in some cases, activation of \(CCND1\) might result from the loss of regulatory sequences, which are known to be implicated in mRNA stability and in translational control. Finally, sequencing analysis of the \(CCND1\) coding region in primary human tumors has shown that amino acid substitutions are not required for \(CCND1\)'s oncogenic effects.

The aim of the present study was to determine the incidence and the consequences on the transcription rate of rearrangement of the 3' UTR of \(CCND1\) in primary human tumors. For this purpose, we first sequenced the coding region and the 3' UTR of the overexpressed \(CCND1\) transcripts in one t(11q13)-associated leukemia. We next analyzed breakpoints that map to the \(CCND1\) 3' UTR in a large series of MCL and t(11q13)-associated leukemias by using a set

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of probes specific to the different parts of the CCND1 transcript. The results of MTC, mtTC1, and mtTC2 rearrangement analysis of most of the samples presented here have been previously reported. Finally, when material was available, CCND1 protein level was assessed in these tumors by Western blot analysis.

MATERIALS AND METHODS

Tissue samples and cell lines. Thirty-three cases of MCL with available frozen material were analyzed (cases no. 1 to 33). Cytogenetic data were not available for any of these MCL cases. Each case was classified by using histologic criteria previously described. We also analyzed four cases of B-cell chronic lymphocytic leukemia (B-CLL) with a t(11;14)(q13;q32) (cases no. 34 to 38), and one case of B-CLL, one case of plasma-cell leukemia carrying a t(11;19)(q13;q13) translocation (case no. 39). All cases (no. 1 to 39) were included in a previous report.

Cell-suspension and frozen-section immunophenotypic studies were performed as previously reported. The following markers were used in this study: IgG, IgM, IgD, IgA,κ, λ light chains, B1 (CD20), B4 (CD19), Leu-14 (CD22), T101 (CD5), OKT3 (CD3), Leu-2 (CD7), and J5 (CD10). All MCL cases were monoclonal B cells; 24 of the 30 tested showed CD5 expression and CD10 was positive in only seven of the 31 cases tested. All B-cell leukemias expressed monoclonal immunoglobulin and were positive for markers of the B-cell lineage. The Gob. cell line was derived from the leukemic cells of patient no. 39. Malignant cells continued to proliferate in RPMI 1640 with 20% fetal calf serum only in the presence of recombinant human interleukin-2 (rIL-2, 20 to 30 IU/mL; Boehringer Mannheim, Mannheim, Germany). After 3 months of culture, rIL-2 was no longer necessary for the cells to proliferate. It is likely that, as a consequence of its mitogenic effect, rIL-2 favored the occurrence of secondary genetic changes leading to growth factor–independence. Cells from the original culture have now been growing continuously for nearly 1 year. Immunophenotype and karyotype were identical to those seen during the initial examination.

Two cell lines carrying a t(11;14)(q13;q32) translocation: Rec-1 (referred to as case 40) established from a MCL, and XG5, a human myeloma cell line; Ramos, a Burkitt’s lymphoma cell line; reactive lymph nodes, normal tonsils, and human fibroblasts were also used in this study.

DNA and RNA isolation and analysis. High–molecular weight DNA was extracted from fresh cells or from frozen material following standard procedures. After digestion with appropriate endonucleases as recommended by the suppliers (Boehringer Mannheim), DNA fragments were electrophoresed on 6.8% agarose gels and transferred onto nylon filters. Total cellular RNA was isolated from cultured cell lines or from frozen samples by the acid guanidium thiocyanate-phenol-chloroform method. For Northern blot analysis, poly(A)+ or total RNA was size fractionated in formaldehyde-1.2% agarose gels and transferred onto nylon filters.

DNA probes and hybridization procedures. A 2.3-kb SacI fragment representing the MTC on chromosome 11q13 was a gift from Y. Tsurimoto (Philadelphia, PA). Probes “A” and “E” are polymerase chain reaction (PCR)-amplified DNA fragments encompassing nucleotides 148 to 310 and 2,856 to 3,091, respectively, on the human PRAD1 cDNA sequence. Probes “B,” “C,” and “D” correspond to CCND1 cDNA subclones (Fig 1). MYC exon 3 probe was a gift from D. Stiehl (Lille, France). Alpha-32P-labeling, prehybridization, hybridization, washing, and washing were performed as previously described.

Preparation and analysis of cDNA library. Poly(A)+ RNA extracted from case no. 39 was used to construct an oligo-dT–primed human cDNA library in the lambda gtl vector as recommended by the supplier (Pharmacia, Uppsala, Sweden).

Sequencing procedure and sequence analysis. Overlapping deletions of CCND1 cDNA cloned into Bluescript. SK+ (Stratagene, La Jolla, CA) were obtained by the unidirectional exonuclease III digestion method (Erase-a-Base System; Promega, Madison, WI). Deletion clones were sized on agarose gels, and the inserts of the selected clones were sequenced using the double-stranded DNA sequencing technique (dideoxy chain termination procedure) with Sequenase II (USB, Cleveland, OH) as described by the manufacturer.

Study of CCND1 mRNA stability. Exponentially growing cells (Rec-1, XG5, and Gob, cell lines) were treated with 10 µg/mL of actinomycin D (Sigma Chemical, St Louis, MO). CCND1 mRNA level was then assessed by Northern blot analysis at various times after addition of actinomycin D. The Northern blot was sequentially hybridized to a CCND1 probe and to a MYC exon 3 probe as a control.

Western blot analysis. For Western blot analysis, proteins from the pathological samples were solubilized in lysis buffer (150 mmol/L NaCl, 50 mmol/L Tris-HCL, pH 8. 0.5% sodium deoxycholate, 1% Triton ×100). Proteins (30 µg) from each sample were then separated by sodium dodecyl sulfate 10% polyacrylamide slab gel electrophoresis and electrophoretically transferred onto nitrocellulose filters. For immunodetection, the filters were incubated with a 1:750 dilution of a polyclonal rabbit anti-cyclin D antibody (UBI, New York, NY) at room temperature. After washing, fixation of the antibody was shown by using a blotting detection kit for rabbit antibodies (Amersham, Uppsala, Sweden). The polyclonal antibody used in this study was raised against a peptide contained in the C-terminal domain of the protein (residues 208 to 295).

RESULTS

In a previous study, we showed that in MCL and t(11q13)-associated leukemias, the steady-state level of CCND1 transcript is dramatically elevated relative to any other lymphoid tissues and that a 1.5-kb mRNA is predominantly expressed. One case of t(11;19)-associated leukemia (case no. 39) expressed, in addition to the 1.5-kb transcript, two aberrant transcripts of 2 and 3 kb, indicating that the CCND1 mRNA may be altered in this tumor (Fig 2). To characterize further the CCND1 transcripts in this lymphoid malignancy, a cDNA library was made from fresh tumor cells. Screening of this library with probe A allowed us to isolate 12 positive clones. Eleven clones covering less than 1,500 bp may correspond to the 1.5-kb transcript. The longest of them was entirely sequenced; it is almost identical to the region encompassing nucleotides 1 to 1346 on the PRAD1 cDNA sequence, except for two base changes: (1) a G is present at nucleotide 870 instead of an A in the coding sequence; (2) a C is present at nucleotide 1100 instead of an A in the 3’ UTR. None of the base changes observed altered the amino acid sequence of the protein. There is no recognizable polyadenylation sequence (AATAAA) anywhere within the sequence of the 11 clones analyzed, and none of them contains a poly(A) tail. However, the corresponding transcripts are polyadenylated, since poly(A)+ selection increased the signal obtained on Northern blot (Fig 2). It is likely that, in this oligo-dT-
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Fig 1. Comparison of the restriction maps of the 3' end of CCND1 with those of the normal 4.5-kb CCND1 cDNA and of two cDNA clones isolated from case no. 39. Black boxes indicate the coding region; dotted line represents the MER11 sequence; double-headed arrow corresponds to the CCND1 last exon; slided-horizontal lines indicate the position of the probes used in this study. CEN, centromere; TEL, telomere, X, Xbd; E, EcoRI; H, HindIII; P, PstI; B, BamHI; Bg, BglII; S, SacI.

Fig 2. Northern blot analysis of CCND1 expression in MCL or leukemia with rearrangement of the CCND1 3' UTR. (Left) 10 µg of total RNA from each sample was processed for Northern blot analysis as described in the Methods and the filter was hybridized to a CCND1 probe (probe A). (Right) 5 µg of poly(A) RNA (A) and 5 µg of total RNA from case no. 39 were blotted and hybridized to probe A.

primed library, all the cDNA clones were initiated from the numerous poly(A) stretches present within the 3' end of the CCND1 mRNA.

We also isolated a 3,013-nucleotide long cDNA clone representative of the 3-kb aberrant transcript. The first 2,275 nucleotides of this clone are identical to nucleotides 2 to 2276 of the PRADI cDNA sequence, with the same base changes at positions 870 and 1100, and are followed by a sequence (nucleotides 2276 to 3013) unrelated to the CCND1/PRADI gene. Comparison of this sequence with those in data bases (EMBL data base) showed that it corresponds to a new member of the MER11 sequences family. In fact, this region has greater than 90% similarity with two members (HUMP45C17, HUMSIGG3) of this family of medium reiteration frequency repetitive sequences.

It should be noted that in all the analyzed cDNA clones, the CCND1 coding frame is retained and that the mRNA destabilizing signals AUUUA present in the normal transcript are eliminated. In case no. 39, PCR amplification of genomic DNA with primers flanking the CCND1/MER11 junction (nucleotides 2090 to 2465) yielded a 375-bp fragment whose sequence matched perfectly that of the 3-kb aberrant transcript (data not shown), demonstrating that the rearrangement occurred at the genomic level and was not the result of a cloning artifact. The fact that the same base changes was observed in the two groups of cDNA suggests that the 1.5-kb transcript represents an alternatively processed form of the 3-kb mRNA and that they both originate from the same allele.

On Southern blots containing BamHI and HindIII-cleaved DNA from case no. 39, probes D and E detected two different rearranged bands in addition to the same germline band (Fig 4). The first explanation of this result is that rearrangement of the 3' end of CCND1 corresponds to an insertion of the MER11 sequence at this site. However, as case no. 39 is associated with a variant t(11;19)(q13;q13) translocation, we cannot rule out the possibility that the MER11 sequence originates from chromosome 19 and that the rearranged band detected by probe E corresponds to the der(19) chromosome. In Fig 4, case no. 39, the intensity of the rearranged bands differs considerably as compared with the residual germline band. This pattern was not observed when using probes A, B, and E (data not shown). This indicates that on the der(11) chromosome, the 3' CCND1 UTR corresponding to probe D was amplified during the translocation process.

This observation and a previously published study showing that the 3' end of CCND1 was rearranged in one case of lymphoma suggested that, in some tumors, its deregulation might occur at the posttranscriptional level. To test this hypothesis, we have analyzed a large series of MCL and t(11q13)-associated leukemias using probes specific to the different parts of the CCND1 transcript (Fig 1). Three of the 40 tumors (cases no. 4, 34, and 40; case no. 39 not included) showed rearrangement of the 3' end of CCND1. Southern blot analysis using probes B or C detected a rearranged fragment in BamHI- and SacI-cleaved DNA (Fig 5).
of the rearranged bands cohybridized to the immunoglobulin JH probe (data not shown). Probes D and E did not detect any rearranged fragment in these cases, although they detected the same germine bands, as did probes B and C in *Bam*HI- and *Sai*I-cleaved DNA. This led us to postulate that, in these cases, the genomic region corresponding between the stop codon and the AUG initiation codon (Fig 6), each rearrangement being identified on two alleles. Conversely, the two bands cohybridized to the immunoglobulin sequence is in italics. *Position of the two breaks occurred on one or on both alleles.*

When material was available, Western blot analysis using a polyclonal rabbit anti-cyclin D antibody confirmed, at the protein level, that cyclin D. It is to be noted that the steady-state level of the transcripts is dramatically elevated in the 3' UTR is not an aberrant transcript observed in case no. 39. The 295-amino acid coding is shown. The MER1 transcript was detected in cases no. 39 and 40 and in normal human fibroblasts used as positive control. The mRNA half-life is 0.5 hours."

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**Fig 4.** Southern blot analysis of CCND1 3' end rearrangement in case no. 39. DNA from case no. 39 and from normal peripheral blood leukocytes (C) was digested with the indicated enzyme (B, BamHI; H, HindIII), and processed for Southern blot analysis as described in the Methods. The filters were hybridized to probe D and E. The scale is in kilobases.

**Fig 5.** Southern blot analysis of rearrangement of the CCND1 3' end in MCL and t(11q13)-associated leukemias. DNA, extracted from the pathological samples and from normal peripheral blood leukocytes (C), was digested with the indicated enzymes (S, SacI; B, BamHI) and processed for Southern blot analysis as described in the Methods. The filters were hybridized to probes C and B. The scale is in kilobases.

**Fig 6.** MTC rearrangement in MCL or leukemias with a break in the 3' end of CCND1. DNA extracted from the pathological samples and from normal peripheral blood leukocytes (C) was digested with BamHI endonuclease and processed for Southern blot analysis as described in the Methods. The filter was hybridized to a MTC probe. The scale is in kilobases.

**Fig 7.** Western blot analysis of the CCND1 protein in MCL and t(11q13)-associated leukemias. Proteins were extracted from pathological samples, normal tonsil (T), reactive lymph node (L), Ramos cell line (R), and normal human fibroblasts (F). Immunodetection of the CCND1 protein was performed as described in the Methods.

In XG5, the half-lives of the 1.5- and 4.5-kb transcripts are approximately 3 hours each; in Rec-1 and Gob., the short transcripts appeared to be even more stable, with a half-life greater than 5 hours (Fig 8). Indeed, no comparison can be made with normal B-lymphoid tissues, which do not express CCND1. This showed that increase in mRNA stability could constitute one of the mechanisms by which CCND1 is deregulated in MCL and t(11q13)-associated leukemias.

**DISCUSSION**

The results presented here constitute additional elements in favor of the role of CCND1 in lymphoid neoplasia and provide some clues with regard to its activation mechanisms.

Cloning and sequence analysis of CCND1 cDNAs in a case of B-CLL showed that the coding frame was retained and that the different sizes of CCND1 mRNA resulted from different 3' untranslated structures. In this leukemia, the CCND1 gene was expressed primarily as a 1.5-kb transcript, but two aberrant transcripts of 2 and 3 kb were also detected. The absence of a recognizable polyadenylation site and of a poly(A) tail in the sequence of 11 cDNA clones covering less than 1,500 bp did not allow us to specify the nature of the shortest transcript. It may correspond, as it has been previously reported, to a truncated form of the normal 4.5-kb mRNA through the use of different polyadenylation signals. Sequence analysis showed that the 3-kb aberrant transcript results from the juxtaposition of a repetitive sequence of the MER11 family to the CCND1 coding sequence. This might first represent an example of insertional mutagenesis leading to gene deregulation, as it has been
were sequentially hybridized to a probe (probe A) and to a 1.5-kb transcript. The size of CCND1 transcripts is in kilobases.

Fig 8. Study of CCND1 mRNA stability in t(11q13)-bearing cell line: Rec. (R), Gob. (G), and XGS (X) cell lines. Total RNA was extracted at the indicated times after addition of actinomycin D and processed for Northern blot analysis as described in the Methods. The filters were sequentially hybridized to a CCND1 probe (probe A) and to a MYC exon 3 probe. The size of CCND1 transcripts is in kilobases.

0 1 2 3 4 5
Hours
~ 3 kb
~ 2 kb
~ 1.5 kb
CCND1: G
MYC: G
~ 1.5 kb
CCND1: R
MYC: R
~ 4.5 kb
CCND1: X
MYC: X
~ 3 kb

The finding that the half-life of CCND1 mRNA is increased in three cell lines carrying a t(11q13) translocation stresses the importance of posttranscriptional derangement in activation of CCND1. The fact that in the XGS cell line the half-lives of the 4.5-kb and 1.5-kb CCND1 mRNAs are identical allows us to rule out the hypothesis that the AU-rich region contained in the 3' UTR, and deleted in some tumors, is responsible for the greater stability of the truncated messages. However, it must be pointed out that the half-life of the CCND1 short mRNA is significantly longer in tumors with 3' UTR rearrangement and, thus, that these rearrangements may alter RNA stability. There exist other situations where certain genes implicated in the control of cell proliferation are deregulated through stabilization of their transcripts. So, the inappropriate expression of the MYC proto-oncogene in Burkitt’s lymphoma can result from an increase of the half-life of its transcript.22,23 However, in this case, the sequences implicated in the control of the mRNA stability are not only localized in the 3' UTR, but also in the 5' region encompassing the first exon of MYC. It has also been reported that the mRNA stability of different cytokines and cyclins G1 is increased in some hematopoietic and solid tumors without gross genetic abnormalities of the transcripts. From these data, it appears that the AU-rich sequences present in the 3' UTR of certain genes are not always implicated in mRNA stability and that other mechanisms should exist. Their nature remains to be determined. Comparison of the sequences of the rearranged 3' UTR with those of the short 1.5-kb transcripts observed in most of the MCLs and of the normal 4.5-kb mRNA should provide data information with regard to the regions putatively involved in mRNA stability.

AUUUA motifs in the 3' UTR of RNAs can also help to modulate the efficient translation of these transcripts. In particular, cytokine-derived UA-rich sequence can be responsible for a translational blockade in vitro.37,38 Consistent with this hypothesis is the finding that in two cases of tumors (cases no. 39 and 40) with deletion of the CCND1 mRNA AU-rich regions, the CCND1 protein is expressed at a high level. Finally, the fact that in most of the MCL and t(11q13)-associated leukemias analyzed, CCND1 is primarily expressed as a 1.5-kb transcript prompts us to pinpoint the importance of the translational control of CCND1 expression in the pathogenesis of these tumors. It remained to be determined why a short transcript is also produced in some tumors without detectable rearrangement of the CCND1 3' UTR.

All cases presented here demonstrated rearrangement of both the MTC region and the CCND1 3' UTR. This observation indicates that, in some cases, activation of CCND1 may be the consequence of two independent genetic events, namely, the juxtaposition of the CCND1 promoting region to IgH enhancer in the t(11;14) translocation and the loss of 3' end regulatory sequences. Nucleotide changes leading to amino acid substitutions in
the sequence of the CCND1 protein have been described in one cell line. The present report and the finding that in two primary human tumors the CCND1 coding sequence is normal suggest that amino acid changes are not required for CCND1 to develop oncogenic properties in primary human tumors.

The results of this study also provide the first evidence that deregulation of CCND1 in MCLs and t(11q13)-associated leukemias leads to the accumulation of abnormally high levels of a normal 35-kD CCND1 protein, which we did not find expressed in normal lymphoid tissues and in three follicular lymphomas (Fig 7). The normal size of the CCND1 protein in two cases of tumor (cases no. 39 and 40) with a break in the 3' UTR confirms that the rearrangement did not alter the CCND1 coding frame.

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