Expression of p27\textsuperscript{Kip1} and c-Jun Activation Binding Protein 1 Are Inversely Correlated in Systemic Anaplastic Large Cell Lymphoma\textsuperscript{1}

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ABSTRACT

Purpose: p27\textsuperscript{Kip1} (p27) is a universal cyclin-dependent kinase inhibitor that inhibits cell cycle transition from G\textsubscript{1} to S phase and is primarily regulated at the post-transcriptional level via the ubiquitin-proteasome pathway. In vitro data suggest that p27 degradation may be accelerated by the c-Jun activation domain binding protein-1 (JAB1), originally identified as a coactivator of the gene regulatory AP-1 proteins. We assessed p27 and JAB1 in systemic anaplastic large cell lymphoma (ALCL), a group of tumors in which a substantial subset overexpresses anaplastic lymphoma kinase (ALK).

Experimental Design: The study included 5 ALK-positive ALCL cell lines, namely Karpas 299, JB-6, SR-786, SU-DHL1, and TG-S1, and 66 ALCL tumors (24 ALK positive and 42 ALK negative). The cell lines were analyzed by Western blot methods, and the tumors were assessed immunohistochemically.

Results: SU-DHL1 and TG-S1 cells were positive for p27 and negative for JAB1, whereas SR-786 and JB-6 cells were positive for JAB1 but negative for p27. Karpas 299 expressed p27 at relatively low levels and JAB1 at high levels. Using a 10\% cutoff, p27 was positive in 12 of 66 (18.2\%) ALCL tumors (5 ALK positive and 7 ALK negative), whereas JAB1 was detected in 47 of 53 (88.7\%) tumors (15 ALK positive and 32 ALK negative) assessed. p27 and JAB1 expression were inversely correlated (Spearman $r = -0.27, P = 0.03$). For 54 ALCL patients with complete follow-up, and in separate analyses of patients with ALK-positive or -negative tumors, p27 expression correlated with poorer prognosis.

Conclusions: p27 is absent or expressed at low levels in most ALCL tumors and inversely correlates with JAB1. These findings suggest that JAB1-mediated degradation of p27, allowing cell cycle progression, may play a role in the pathogenesis of ALCL.

INTRODUCTION

Diverse mechanisms regulating the cell cycle have been involved in human tumorigenesis (1). Among other mechanisms, cell cycle progression is controlled by activation of complexes composed of cyclins and CDKs.\textsuperscript{3} The activity of CDKs is regulated by CDK inhibitors that can be classified in two different groups. The INK family includes p16\textsuperscript{INK4A}, p15\textsuperscript{INK4B}, p18\textsuperscript{INK4C}, and p14\textsuperscript{ARF} (the human homologue of p19\textsuperscript{INK4D}), and these proteins function as inhibitors of CDK4 and CDK6, competing with cyclins. The Cip/Kip family includes p21\textsuperscript{WAF1/Cip1}, p27\textsuperscript{Kip1}, and p57\textsuperscript{kip2} that act as universal CDK inhibitors of the G\textsubscript{1} phase of the cell cycle (2).

The p27 gene is located on chromosome 12p13, and its product p27\textsuperscript{Kip1} (p27) is an important negative regulator of transition from G\textsubscript{1} to S phase of the cell cycle (3, 4). p27 interacts with cyclin-CDK complexes through a conserved domain that contains both cyclin and CDK binding sites. Binding of p27 to cyclin-CDK complexes inhibits their activity, thus preventing phosphorylation of retinoblastoma protein, which is important for progression from G\textsubscript{1} to S phase (1). The expression of p27 seems to be high in quiescent cells and declines as cells enter S phase. The cellular abundance of p27 is regulated primarily at the post-transcriptional level by the ubiquitin-proteasome pathway (5). Phosphorylation of p27 at T187, by the cyclin E/CDK2 complex, is required for p27 degradation (6–8).

The human JAB1 was originally identified as a coactivator of the gene regulatory AP-1 proteins (Jun/Fos proto-oncogenes) involved in the control of cell proliferation (9). Recent evidence suggests that JAB1 (JAB1/CSN5) is the fifth component of the COP9 signalosome (CSN) complex (reviewed by Chamovitz et al. (11)). Tomoda \textit{et al.} (11) have identified a mouse JAB1\textsuperscript{p38} that interacts specifically with p27 protein.

\textsuperscript{1}The abbreviations used are: CDK, cyclin-dependent kinase; T187, threonine residue 187; PI, proliferation index; PFS, progression-free survival; ALK, anaplastic lymphoma kinase; DAB, 3,3'-diaminobenzidine; ALCL, anaplastic large cell lymphoma; JAB1, c-Jun activation binding protein 1.

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causes translocation of p27 from the nucleus to the cytoplasm, and decreases the amount of p27 in the cell by accelerating its degradation via the ubiquitin-proteasome pathway (11). JAB1 seems to interact with p27 in the nucleus because fusion analysis with a nuclear export signal has shown that cytoplasmic translocation per se is not sufficient for p27 to be degraded (11). The expression patterns of JAB1 in lymphoid tissues are undefined.

Although p27 expression has been assessed in a number of human cancers (reviewed by Slingerland and Pagano in Ref. 12), including some lymphoid neoplasms (12–15), no previous study has investigated p27 expression in systemic ALCL (16), a group of tumors in which a substantial subset overexpresses ALK (17, 18), which is associated with more favorable clinical outcome (19, 20). In this study, we assessed p27 expression in a series of ALCL cases and correlated the findings with ALK and clinical outcome. On the basis of our preliminary data that showed a lack of p27 in a subset of ALCL cell lines and most ALCL tumors, we hypothesized that JAB1-mediated degradation of p27 may be the mechanism responsible for p27 down-regulation in ALCL. We therefore also assessed expression levels of JAB1 in ALCL cell lines and tumors.

MATERIALS AND METHODS

Cell Lines. The panel of ALK-positive ALCL cell lines included Karpas 299 (a gift from Dr. M. Kadin, Boston, MA), SR-786, SU-DHL-1 (both from DSMZ, Braunschweig, Germany), JB-6, and TS-G1 (a gift from Dr. D. Jones, Houston, TX). All cell lines carry the t(2;5) and overexpress ALK protein. The cell lines were maintained in RPMI 1640 supplemented with 1% nonessential amino acids, 10% FCS (Invitrogen Corp., Grand Island, NY), and 1% streptomycin-penicillin. Cells were incubated at 37°C in a humidified atmosphere containing 5% CO2.

Protein Extraction and Western Blot Analysis. Cells in log phase growth were collected, washed twice in cold PBS, and lysed at 4°C in lysis buffer composed of 25 mM HEPES (pH 7.7), 400 mM NaCl, 0.5% Triton X-100, 1.5 mM MgCl2, 2 mM EDTA, 2 mM DTT, 0.1 mM phenylmethylsulfonyl fluoride, protease inhibitors (10 μg/ml leupeptin, 2 μg/ml pepstatin, 50 μg/ml antipain, 2 μg/ml aprotinin, 20 μg/ml chymostatin, and 2 μg/ml benzamidine), and phosphatase inhibitors (2 mM NaF, 1 mM Na3VO4, and 20 μM β-glycerophosphate). Aliquots of cell lysates (70 μg of protein) resolved in 10% SDS-PAGE were transferred to nitrocellulose polyvinylidene difluoride membranes and probed with primary antibodies as follows: (a) p27 (polyclonal; BD Biosciences PharMingen, San Diego, CA); (b) JAB-1 (monoclonal; Zymed, South San Francisco, CA); and (c) p21 (monoclonal; Oncogene, La Jolla, CA). Reactions were visualized with secondary antibody conjugated with horseradish peroxidase (Bio-Rad, Hercules, CA) using enhanced chemiluminescence reagents (Amersham Pharmacia, Piscataway, NJ). β-Actin (Sigma, St. Louis, MO) served as internal positive control for all Western blots.

ALCL Tumors. This group included 66 cases of systemic ALCL accessioned at The University of Texas M. D. Anderson Cancer Center. The clinicopathological features of the affected patients were reported previously (21). The median age of patients with ALK-positive tumors was 35 years compared with 49 years for patients with ALK-negative tumors (P = 0.005 by Mann-Whitney t test). All other clinical parameters were comparable.

The diagnosis of ALCL was based on morphological and immunohistologic criteria as specified by the WHO classification (16). All ALCLs expressed CD30 and T cell-associated antigens (CD3, CD5, CD43, or CD45RO) and were negative for B-cell antigens (CD20 or CD79a). Tumors negative for CD3 and CD5 and positive for CD43 or CD45RO were considered to be of T-cell lineage in this study, but null cell lineage cannot be excluded as CD43 and CD45RO react with histiocytes. Null cases were negative for all T-cell antigens. ALK was assessed using the ALK-1 antibody (1:30; DAKO Corp., Carpinteria, CA) and was positive in 24 cases.

Design and Construction of the Tissue Array. Tissue sections, 5-μm thick, were cut from a tissue array that included triplicate tumor cores from all ALCL tumors and two reactive lymph nodes. A manual tissue arrayer (Beecher Instruments, Silver Spring, MD) was used to construct the tissue array as has been described (22).

Immunohistochemical Methods. The immunohistochemical methods used have been described previously (21). For all antibodies, heat-induced epitope retrieval was performed. The following panel of monoclonal antibodies was used: (a) p27 (1:200; DAKO); (b) phosphorylated p27 (1:200) and JAB1 (both from Zymed); and (c) MIB-1 (1:120; Immunotech, Westbrook, ME; Ref. 23).

The specificity of the JAB1 antibody was tested in a competition study, using a specific JAB1 peptide at a concentration of 100 μM, as well as an unrelated peptide to stain full tissue sections of two normal tonsils and reactive lymph nodes each. The specific JAB1 peptide was identical to the one used for the production of the corresponding monoclonal antibody (Zymed). Competition of JAB1-specific peptide with the JAB1 antibody resulted in a lack of JAB1 immunostaining in control slides (see “Results”). A similar competition study using human tonsil tissues was performed to test the specificity of phosphorylated p27 using a 22 amino acid p27 fragment (specific peptide) containing the phosphorylated T197 residue, as described previously (24).

The slides were incubated with the monoclonal antibody at room temperature for 60 min. Detection of the immunoreaction was performed using the LSAB+ kit (DAKO), which contains a secondary biotinylated antibody and streptavidin/horseradish peroxidase complex.

Tissue sections from normal tonsil were used as external positive controls for p27, phosphorylated p27, JAB1, and MIB-1 immunostaining. In addition, reactive small lymphocytes in all tissue sections served as internal positive controls for each antibody. Slides stained with normal rabbit serum (DAKO) without primary antibody were used as negative controls.

Any staining of ALCL cells was considered positive, irrespective of intensity. Only nuclear immunostaining of p27 was considered positive. Expression levels for p27, phosphorylated p27, and JAB1 were determined by counting ≥1000 tumor cells in each case. p27 and JAB1 expression appeared to be continuous variables. However, based on the distribution of data and for the purpose of statistical analysis, we used a 10% cutoff for p27 and JAB1 expression. Other cutoffs also were used for...
survival analysis. PI was designated as the percentage of MIB1-positive nuclei.

**Statistical Analysis.** The nonparametric Spearman’s rank correlation coefficient was applied to evaluate the strength of the relationship between p27, JAB1, and other variables. The $\chi^2$ and Fisher’s exact tests were used to compare the expression of all proteins as groups (positive versus negative) with various clinicopathological parameters. The Mann-Whitney $U$ test was chosen for the nonparametric correlation of p27 and JAB1 between ALK-positive and -negative ALCL. PFS was defined as time from initiation of therapy to last follow-up, primary treatment failure, or relapse. For overall survival, only patient deaths attributable to the disease were considered as events. Survival analysis was based on the method of Kaplan and Meier. All computations were carried out using the StatView statistical program (Abacus Concepts, Inc., Berkeley, CA).

**RESULTS**

**Cell Lines.** Immunoblots showed that expression of p27 was inversely related with that of JAB1 in four ALCL cell lines; SU-DHL1 and TG-S1 were positive for p27 and negative for JAB1, whereas SR-786 and JB-6 were positive for JAB1 but negative for p27 (Fig. 1). The Karpas 299 cell line expressed p27 at a relatively low level and JAB1 at a high level (Fig. 1). The expression levels of p27 in Karpas 299 cells were further analyzed immunohistochemically using a cell block. A subset (20%) of Karpas 299 cells was positive for p27, and 90% of these cells were positive for JAB1 (data not shown).

**Expression of p27 in Reactive Lymph Nodes and ALCL Tumors.** As has been shown by others, (14) p27 was detected mostly in the mantle and marginal zones of reactive lymphoid follicles. The highly proliferating germinal center cells were almost all p27 negative (Fig. 2a).

In ALCLs, the percentage of p27-positive tumor cells varied from 0 (totally absent) to 82.6% with a mean of 49.3 ± 19.6% and a median percentage of 0.8%. p27 was localized principally in the nucleus of tumor cells with variable staining intensity (Figs. 2, b and c). Using a 10% cutoff, p27 was positive in 12 (18.2%) ALCLs and negative in the remaining 44 tumors (81.8%). Of the 12 p27-positive ALCLs, 5 were ALK-positive, and 7 were ALK-negative ($P = 0.7$, Fisher’s exact test). p27 expression was not statistically associated with clinical and laboratory features. In a subset of 20 ALCL (8 ALK-positive and 12 ALK-negative), 3 were p27 positive, and 17 were p27 negative. The T187-phosphorylated form of p27 protein was evaluated using a polyclonal antibody (24) and full tissue sections in 20 ALCLs. Fifteen of 17 (92.3%) p27-negative (7 ALK-positive) and 1 of 3 (33%) p27-positive tumors (1 ALK-positive) assessed showed weak granular cytoplasmic staining for T187-phosphorylated p27 (Fig. 3).

**Expression of JAB1 in Reactive Lymphoid Tissues and ALCL Tumors.** JAB1 was detected in a large number of germinal center cells as well as in a small number of lymphocytes in the interfollicular areas (Fig. 4). JAB1 immunoreactivity was predominantly localized in the nucleus of lymphocytes, but a weaker cytoplasmic reaction was also observed in a variable number of lymphocytes. The basal layers of the squamous epithelium of the tonsils were consistently JAB1 positive, whereas the top layers of epithelium were usually JAB1 negative (data not shown).

The percentage of JAB1-positive tumor cells ranged from 0 to 100% with a mean of 70.8 ± 29.7% and a median percentage of 85%. Using a 10% cutoff for JAB1 expression, 47 of 53 (88.7%) ALCLs assessed were JAB1 positive predominantly at high levels (Fig. 5). Of the 47 JAB1-positive tumors, 15 were ALK-positive, and 32 were ALK-negative ($P > 0.9$, Fisher’s exact test). JAB1 expression (>10% positive tumor cells) was inversely associated with p27 positivity (Fig. 6). More specifically, 40 of 47 (85.1%) JAB1-positive tumors were p27 negative, and 4 of 6 (66.7%) JAB1-negative tumors were p27 positive ($P = 0.01$ by Fisher’s exact test). As continuous variables, p27 and JAB1 expression were also inversely correlated (Spearman $r = -0.27$, $P = 0.03$). However, two (4%) ALCLs expressed high levels (>50% positive tumor cells) of both p27 and JAB1. The expression of JAB1 did not significantly correlate with ALK status or clinical and laboratory parameters.

**Association of p27 and JAB1 Expression with Apoptotic Rate and PI.** Apoptotic rate was assessed previously for 50 of these ALCL tumors (21). In this study group, apoptotic rate did not significantly correlate with p27 or JAB1 expression (Table 1).

PI was evaluated in 41 ALCL tumors and ranged from 20.4 to 94.6%, with a mean of 68.8 ± 17.7. These results are similar to those reported by our group in a smaller subset of ALCLs (21) and other types of aggressive non-Hodgkin’s lymphoma (23). No significant correlation between PI and p27 or JAB1 was observed (Table 1).

**Clinical Outcome.** Survival analysis was restricted to 54 patients with available complete follow-up data and results for p27 and JAB1 expression. In this group, 20 ALCLs were ALK-positive, and 34 ALCLs were ALK-negative. Using a cutoff of 10% for p27 expression, for the entire group, the 5-year PFS was 39.5% for patients with p27-positive tumors compared with 66.8% for patients with p27-negative tumors ($P = 0.005$ by Log-rank; Fig. 7a). In the ALK-positive ALCL group, the corresponding PFS at 5 years was 0% for patients with p27-positive tumors and 66% for patients with p27-negative tumors.
In the ALK-negative group, the 5-year PFS was 60% for patients with p27-positive tumors versus 66% for patients with p27-negative tumors (\(P = 0.0006\) by Log-rank; Fig. 7b). In the ALK-negative group, the 5-year overall survival was 60% for patients with p27-positive tumors versus 90.7% for patients with p27-negative tumors (\(P = 0.007\) by Log-rank; Fig. 8c).

Using the same cutoff, overall survival for all ALCL patients at 5 years was 45.7% versus 90.1% for patients with p27-positive versus p27-negative ALCL (\(P = 0.0004\) by Log-rank; Fig. 8a). In the ALK-positive ALCL group, the corresponding overall survival at 5 years was 0% for patients with p27-positive tumors and 92% for patients with p27-negative tumors (\(P = 0.03\) by Log-rank; Fig. 8b). In the ALK-negative group, the survival difference remained statistically significant when other cutoffs for p27 expression were used, including 5 or 20%, e.g., using a 5% cutoff for p27 expression, the 5-year PFS of all ALCL patients was 41% for those with p27-positive tumors compared with 68% for those with p27-negative tumors (\(P = 0.0012\) by Log-rank).

The survival difference remained statistically significant when other cutoffs for p27 expression were used, including 5 or 20%, e.g., using a 5% cutoff for p27 expression, the 5-year PFS of all ALCL patients was 41% for those with p27-positive tumors compared with 68% for those with p27-negative tumors (\(P = 0.0012\) by Log-rank).

JAB1 expression did not correlate with PFS or overall survival using various cutoffs (data not shown).

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**Fig. 2**  p27 expression in ALCL tumors. In a, p27 is predominantly detected in mantle and marginal zones of reactive lymphoid follicles and mostly negative in the germinal center cells. A number of small lymphocytes of the interfollicular areas was also positive for p27. b, a case of ALCL with 40% p27-positive tumor cells. p27 is localized in the nucleus of tumor cells with variable staining intensity. c, a case of ALCL with p27-negative tumor cells. Coexisting small reactive lymphocytes are positive for p27 and served as internal positive controls (DAB, hematoxylin counterstain, for all panels).

**Fig. 3**  T187-phosphorylated p27 is detected in the cytoplasm of tumor cells with a granular staining pattern.
DISCUSSION

In this study, we report that most ALCL tumors have low levels of p27 expression. In fact, p27 was detected in only 18% of ALCL cases if a 10% cutoff is used to define positivity (Figs. 2 and 6). These results are not surprising because previous studies have shown an inverse correlation between p27 expression and proliferative activity in other types of non-Hodgkin’s lymphomas (13–15), and ALCLs are usually highly proliferative (21).

We also report for the first time that JAB1 protein is overexpressed in most (89%) ALCLs and is inversely associated with p27 in ALCL cell lines and tumors. In addition, the T187-phosphorylated form of p27 is present in the cytoplasm of a subset of ALCL. Taken together, these observations support the concept that JAB1 mediates down-regulation of p27, possibly through increased p27 phosphorylation and degradation, as has been suggested by previous in vitro and in vivo studies using mouse animal models (11). These studies also showed that p27 phosphorylation and degradation require shuttling of p27 from the nucleus to the cytoplasm (11). To further study the mechanisms of JAB1-mediated degradation of p27 in ALCL, we have performed transfection experiments using a JAB1 adenovirus...
system developed recently in our laboratory. Our preliminary data demonstrate a significant decrease of p27 levels and a significant increase of S phase of the cell cycle in ALCL cell lines that overexpress adenoviral JAB1 after infection.4 It is likely that p27 down-regulation is not mediated only by JAB1/CSN5 monomer but also by the COP9 signalosome (CSN) complex. Recently, it has been reported that other components of the CSN complex, in addition to JAB1/CSN5, are capable of inducing p27 down-regulation when ectopically expressed, and this function may require nuclear export and phosphorylation of p27 (25).

In a study group of 54 ALCL patients untreated previously

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**Table 1** Correlation of p27 and Jab1 expression with apoptotic rate and proliferation index in anaplastic large cell lymphoma

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*p = 0.4, b P = 0.7 by Mann-Whitney test.

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**Fig. 6** a and b, distribution of ALCL tumors (histograms) according to p27 (Fig. 6a) and JAB1 (Fig. 6b) expression levels. Y axis, percentage of tumors; X axis, percentage of positive tumor cells. c, bivariate regression plot showing the inverse correlation between p27 and JAB1 expression levels among ALCL tumors. Y axis, percentage of p27-positive ALCL tumors; X axis, percentage of JAB1-positive tumors.

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**Fig. 7** Correlation of p27 expression with PFS in ALCL. a, all patients; b, ALK-positive ALCL; c, ALK-negative ALCL.
with clinical follow-up, p27 expression correlated significantly with worse PFS and overall survival. This was true when ALK-positive and -negative ALCLs were analyzed together (Figs. 7 and 8) and in separate survival analyses performed for only ALK-positive or -negative groups. In the latter group, p27 expression only correlated with overall survival (Fig. 8c). The correlation between p27 expression and worse clinical outcome seems paradoxical in the light of p27 function, as many previous studies of a variety of human cancers have shown that p27 expression is often associated with low-grade tumors and favorable clinical outcome (reviewed by Slingerland and Pagano in Ref. 12). However, the association of high p27 expression with inferior patient survival in our ALCL study group is not entirely unexpected. In previous studies of other types of aggressive lymphoma, a subset of tumors has been reported to express anomalous high levels of p27 (26) and correlated with adverse clinical outcome (27, 28).

In this study, p27 was detected in >50% of tumor cells in four cases of ALCL. High p27 levels in a subset of high-grade lymphomas might represent abnormal accumulation of p27 protein, which is probably inactive when joined to cyclin D1/CDK4–6 complexes. The presence of inactive p27 may explain its inability to arrest tumor cells at G1 phase or induce apoptosis (29) in these ALCLs. Sanchez-Beato et al. (26) have reported overexpression and colocalization of p27 and cyclin D3 proteins in the absence of p27/CDK2 complexes in a subset of aggressive lymphomas, including diffuse large B-cell and Burkitt lymphomas. It has been suggested that high cyclin D3 levels could lead to stabilization of inactive p27 protein (26). We did not assess cyclin D3 expression in this study. Two of these four ALCLs also overexpressed JAB1. It is reasonable to speculate that JAB1-mediated p27 degradation is only one mechanism that down-regulates the expression of p27, and other mechanisms also may exist. In fact, these mechanisms may be complex and involve molecules that merit further investigation. One candidate is the F-box protein Skp2 (S phase kinase-associated protein 2; Refs. 30 and 31). Others have reported that Skp2 inversely correlates with p27 levels in human lymphomas, and its transgenic expression may contribute to lymphomagenesis, particularly in T-cell neoplasms (32, 33).

In summary, we have shown that p27, an important checkpoint regulator, is absent or expressed at low levels in both ALK-positive and -negative ALCLs, and its expression significantly correlated with inferior survival in patients untreated previously. Our findings also provide evidence that JAB1 is frequently expressed in ALCL and inversely correlates with p27, suggesting that JAB1-mediated degradation of p27 may play a role in the pathogenesis of ALCL.

REFERENCES


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