Multiple Mixed Lineage Leukemia (MLL) Fusion Proteins Suppress p53-mediated Response to DNA Damage*

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Chromosomal translocations involving the mixed lineage leukemia (MLL) gene are often observed in acute leukemias of both myeloid and lymphocytic origin. Expression of MLL fusion proteins is known to induce malignant transformation of normal blood progenitors; however, molecular mechanisms of this process are still poorly understood. In this study we investigated the effect of several frequently detected MLL fusion proteins on p53 transcriptional activity. Our data show that MLL-AF9, MLL-AF10, MLL-ENL, and MLL-ELL substantially down-regulate p53-mediated induction of p21, MDM2, and Bax in response to DNA damage. Furthermore, we identify the reduction in p53 acetylation by p300 as a major mechanism of the inhibitory effect of MLL leukemia fusions. Our data suggest that abrogation of p53 functional activity can be a common feature of MLL fusion-mediated leukemogenesis.

Reciprocal chromosomal rearrangements involving the mixed lineage leukemia (MLL) gene at the 11q23 locus are frequently detected in patients diagnosed with acute forms of both myeloid and lymphocytic leukemias (1, 2). As a result of these chromosomal aberrations, the N terminus of MLL is consistently fused in-frame to a number of partner proteins. Although more than 30 genes have been identified as fused to MLL in human leukemias, AF4, AF9, AF10, ENL, and ELL account for the absolute majority of recurrent MLL partners (3). The precise molecular mechanisms underlying the oncogenic function of MLL fusions are still poorly understood. We and others have recently shown that transient expression of MLL-ELL results in a potent and specific inhibition of p53 (4, 5), a critical tumor suppressor protein that mediates expression of multiple cell cycle regulatory and pro-apoptotic genes in response to stress (6). The disruption of p53 interactions with its co-activator p300 has been demonstrated to contribute to the MLL-ELL inhibitory effect on p53 (5).

In the present study, we systematically analyzed the effect of additional frequently detected MLL fusion proteins on p53 activity. Our results show that MLL-AF9, MLL-AF10, and MLL-ENL associate with p53 through their partner proteins and significantly down-regulate the transcriptional activity of p53 in reporter assays. Furthermore, stable cell lines expressing low levels of MLL-AF9, MLL-AF10, MLL-ENL, and MLL-ELL exhibit impaired endogenous p53 response to both ionizing radiation and adriamycin treatment. Although having no discernible effect on p53 protein levels, MLL fusions significantly suppress p53-mediated induction of p21, MDM2, and Bax in response to various types of DNA damage. We also find that MLL fusions inhibit stress-induced p300-mediated p53 acetylation, which could explain their inhibitory effect on p53. Collectively, our data identify p53 functional inactivation as a common characteristic of multiple MLL fusions.

EXPERIMENTAL PROCEDURES

Plasmid Design—pcDNA-FLAG-p53, Myc-p53, pcDNA-FLAG-p53(6KR), pCMV-EGFP-MLL, pCMV-EGFP-MLL-C7T, and pCMV-EGFP-MLL-ELL have been described previously (5). MLL-AF9, MLL-AF10, and MLL-ENL sequences were subcloned into the pcDNA-FLAG vector using standard techniques. Internal deletion in the MLL N terminus was generated by digestion of FLAG-tagged, full-length fusion constructs with HindIII and subsequent re-ligation. cDNAs encoding full-length MLL fusions were also cloned into the pBabePuro retroviral expression vector. The identities of all constructs were verified by restriction digest and DNA sequencing (Dana Farber Cancer Institute/Harvard Cancer Center Core facility).

Cell Culture, Transfection, and DNA Damage Treatments—H1299 and U2OS cells (American Type Culture Collection) were maintained in minimal essential medium (Cellgro) supplemented with 10% fetal bovine serum (Invitrogen), 2 mm-glutamine, 10 units of penicillin per milliliter, and 10 μg of streptomycin per milliliter at 37 °C in a 5% CO2 humidified atmosphere. HCT116 cells were maintained in McCoy’s 5A medium (Cellgro), whereas TK6 cells were grown in RPMI (Cellgro) with the supplements indicated above. Cells were transfected by the Lipofectamine 2000 (Invitrogen) method according to the manufacturer’s instructions. To induce DNA damage, cells were irradiated using the Philips industrial x-ray system or treated with adriamycin.

Luciferase Assay—H1299 cells were co-transfected in 35-mm dishes with wild-type FLAG-p53, MLL fusions, and a PG13 reporter construct (B. Vogelstein, Johns Hopkins University School of Medicine) that contained the luciferase gene under the control of p53-responsive promoter. The pRL-TK plasmid (Promega) was included as transfection efficiency control. Total DNA amount was normalized using empty vector. Both Firefly (PG13) and Renilla (pRL-TK) luciferase activities were determined 24 h post-transfection using the Dual luciferase assay kit (Promega).

Preparation of Whole Cell Extracts, Immunoprecipitation, and Western Blot Analysis—For transient transfections, cells were transfected in 60-mm plates and harvested at 24–48 h post-transfection. To obtain whole cell lysates, cells were lysed in 100 μl of RIPA lysis buffer (10 mm Tris-HCl, pH 7.5, 1 mm EDTA, 1% Nonidet P-40, 0.1% SDS, 150 mm NaCl, 1 mm dithiothreitol, 10% glycerol, 0.2% sodium deoxycholate, and protease inhibitors) by incubating on ice for 30 min, and the extracts were centrifuged at 13,000 rpm for 15 min to remove cellular debris. Protein concentrations were determined using the Bio-Rad protein assay. For immunoprecipitation analysis, cell extracts were...
prepared in high salt lysis buffer (50 mM HEPES, pH 7.5, 1 mM EDTA, 2.5 mM EGTA, 0.4 mM NaCl, 1% Triton X-100, 1 mM dithiothreitol, 0.2 mM phenylmethylsulfonyl fluoride, and protease inhibitors) and then di-
luted 15-fold in 0.5% Triton X-100 using salt- and detergent-free
buffer and incubated with anti-FLAG agarose (Sigma) overnight at
4 °C. After the addition of 5× loading buffer, samples were incubated at
95 °C for 5 min and resolved by SDS-PAGE. Proteins were transferred
onto nitrocellulose membranes (Schleicher & Schuell) and probed with
the antibodies anti-FLAG (M5; Sigma), anti-p53 (Ab-6; Calbiochem), an-
ti-actin (AC-15; Sigma), and anti-green fluorescent protein (Clon-
tech). Proteins were visualized with an enhanced chemiluminescence
method. Proteins were visualized with an enhanced chemiluminescence
detection system (PerkinElmer Life Sciences). Densitometry measure-
ments were carried out on selected scanned Western blot images using
Scion Image J software (Scion Corporation).

Retrovirus Infection—Phoenix Amphi Φ cells were transfected with
pBABEpuro vectors encoding MLL-AF9, MLL-AF10, MLL-ENL, MLL-
ELL, and MLL-ELLΔCT (10 μg), pCG-gagpol (5 μg), and pCG-VSVG (1 μg)
(Dr. R. Mulligan, Harvard Medical School) by the calcium-phos-
phate method. Retroviral supernatant was harvested 48 h post-trans-
faction. U2OS, HCT116, and TK6 cells were infected by incubation with
retroviral supernatants and Polybrene (4 μg/ml) for 24 h followed by
selection in puromycin (1.5 μg/ml)-containing media for 5 days.

Preparation of Total RNA and RT-PCR—500 ng of total RNA was
depurified from each cell line using the RNaseasy kit according to
manufacturer's instructions (Qiagen). RNA was then used as a template in
RT-PCR, which was performed using the OneStep RT-PCR kit (Qiagen).
Forward primer for all reactions was 5'-AGAAAAGAGTTGCTCCAAAA-
CCACCCATTG-3' for MLL. Reverse primers varied depending on the
MLL fusion being amplified as follows: MLL-AF9, 5'-CTTGTTCACTT-
TACATTCGTATTT-3'; MLL-AF10, 5'-AGTCGAATTTAAATT-
GTGCTTCATAA-3'; MLL-ENL, 5'-AGAACGACCTTCCCTGCCG-
TCTCCCTCTGTT-3'; and both MLL-ELL and MLL-ELLΔCT, 5'-TTAA-
TATCATGACCCGCTTCCAGCTGGTGTCC-3'. PCR products were resolved on 1% agarose gel and stained with ethidium bromide.

RESULTS

MLL Fusions Suppress Transcriptional Activity of Exoge-
nous p53—We have previously demonstrated that MLL-ELL
can potently inhibit p53-driven transactivation, whereas MLL-
ELLΔCT has no such effect (5). To test the effect of additional
MLL fusions on p53 transcriptional activity, the expression
constructs encoding MLL-AF9, MLL-AF10, and MLL-ENL
(1A) were co-transfected with wild-type p53 and p53-
responsive luciferase reporter into p53−/− H1299 cells. MDM2,
which is known to suppress p53-mediated transactivation (7),
and MDM2 (Fig. 2B, lanes 1–15). In cells expressing vector
only, transcriptional activity of p53 was dramatically induced
as evidenced by the increased expression of endogenous p21
and MDM2 (Fig. 2B, lanes 1–3). However, in cells stably
expressing MLL fusions both p21 and MDM2 induction was
severely attenuated (Fig. 2B, compare lanes 1–3 to lanes 4–15).
To ascertain if the inhibitory effect exerted by MLL leukemic
fusions on p53 can be overcome by increasing the dose of IR,
cells were irradiated by 2, 5 and 10 Gy of IR, and cell lysates
were analyzed by Western blot 4 h post-irradiation. Once
again, p53 was induced in a dose-dependent manner in all cell
lines (Fig. 2C, lanes 1–20). Whereas vector-expressing cells
responded to increasing doses of IR by substantially up-regu-
lating p21 and MDM2, this effect was significantly less
pronounced in MLL fusion-expressing cells (Fig. 2C, compare
lanes 1–4 to lanes 5–20). Collectively, these data show that
MLL fusion proteins interfere with p53-mediated induction of
p21 and MDM2 in response to IR.

Expression of MLL Fusions Decreases p53 Acetylation by
p300 in Response to Ionizing Radiation—p300 is an important
co-activator of p53 transcriptional activity that acetilates sev-
eral critical lysine residues on the p53 C terminus (10). Our
previously published observations showed that reduction in
p300-mediated p53 acetylation in vivo contributes to the MLL-
ELL inhibitory effect on p53 (5). We asked if this mechanism
might be involved in the down-regulation of endogenous p53
activity by MLL-ELL and other MLL fusions.

To test this possibility, whole-cell lysates of irradiated U2OS
cells expressing MLL chimeras were probed with the antibody
that specifically detects p300-mediated acetylation of lysines
373 and 382 on p53. Following exposure to escalating doses of
IR, the fraction of acetylated p53 increased dramatically in
cells expressing vector only (Fig. 2C, lanes 1–4). In contrast,
only a marginal increase in p53 acetylation was observed in
cells stably expressing various MLL fusions (Fig. 2C, compare
lanes 1–4 to lanes 5–20). These results suggest that reduced
p53 acetylation by p300 could be responsible for the inhibitory
effect of MLL fusions on p53 activity.

MLL Fusions Suppress p53 Activity following Adriamycin
Treatment—To rule out the possibility that the suppression of
p53 function by MLL chimeras is restricted to IR, we utilized
adriamycin as a different type of DNA-damaging agent. p53 protein accumulated to similar levels in all U2OS stable lines following exposure to adriamycin (Fig. 2D, lanes 1–20). A significant increase in protein abundance of p21 and MDM2, as well as the pro-apoptotic regulator Bax, was observed in cells expressing vector only, indicative of increased p53 transcriptional activity (Fig. 2D, lanes 1–4). However, in cells stably expressing MLL fusions, the transactivation function of p53 was inhibited as evidenced by the reduced induction of p21, MDM2, and Bax (Fig. 2D, compare lanes 1–4 to lanes 5–20). These results indicate that MLL fusion proteins suppress the induction of multiple p53 transcriptional targets following exposure to several types of genotoxic stress.

The Inhibitory Effect of MLL Fusions on p53 Is Not Cell Type-specific—To exclude cell type-specific effects, we stably transduced another p53−/− cell line, HCT116 cells, with expression constructs encoding MLL chimeras. In addition, to confirm that the inhibitory effect on p53 requires the presence of a MLL partner protein, we generated cells stably expressing the MLL-ELLΔCT construct that failed to inhibit p53-mediated induction of p21 and MDM2 in transient transfections. The presence of fusion protein mRNA in these cells was confirmed by RT-PCR (Fig. 3A), and, in the case of MLL-ELL and its truncated mutant, by Western blot analysis with a highly sensitive anti-ELL antibody (Fig. 3B).

When HCT116 cell lines expressing various MLL fusion pro-
proteins were challenged with 5 Gy of IR, p53 protein accumulated over time in all cell lines, as detected by Western blot (Fig. 3C, lanes 1–18). In vector- and MLL-ELLΔCT-expressing cells, increased p53 protein abundance was accompanied by substantial up-regulation of both p21 and MDM2 (Fig. 3C, lanes 1–3 and 16–18). On the contrary, in cell lines expressing full-length MLL fusions, p21 levels barely increased in response to IR, whereas the induction of MDM2 and Bax was attenuated (Fig. 3C, compare lanes 1–3 and 16–18 to lanes 4–15).

Next, to determine whether the inhibitory effect of MLL fusions on p53 activity persists over time, we examined the induction of Bax in HCT stable lines at 24 and 48 h following treatment with adriamycin. As shown in Fig. 3D, Bax up-regulation was substantially inhibited at these time points in cells that express full-length MLL fusions, but not in vector- or MLL-ELLΔCT-expressing cell lines.

Finally, to increase the relevance of our findings to leukemic disease, we used a retrovirus to stably introduce MLL fusion constructs into acute lymphoblastic leukemia TK6 cells that express wild-type p53. RT-PCR analysis confirmed the presence of leukemic fusion mRNA in TK6 cell lines (Fig. 4A), and the expression of MLL-ELL and MLL-ELLΔCT was further verified by Western blot (Fig. 4B). Upon exposure to IR, p53 levels increased over time in all TK6 stable lines; however, the fraction of acetylated p53 and the induction of p21 was reduced in MLL fusion-expressing cells but was not affected in either

FIG. 2. p53 acetylation and transcriptional activity in response to DNA damage is suppressed by MLL chimeras. A, total RNA was isolated from U2OS stable lines and used as a template in RT-PCR with specific primers as described under “Experimental Procedures.” Reaction products were resolved on an agarose gel and stained with ethidium bromide. B, U2OS cells expressing vector only or MLL fusion proteins were irradiated with 5 Gy of IR, and cell lysates were prepared 0, 3, and 6 h later and probed with the indicated antibody. Relative density of MDM2 and p21 protein bands is shown in arbitrary units on the y-axis. IB, immunoblot. C, U2OS stable lines were irradiated with 0, 2, 5 and 10 Gy of IR and incubated for an additional 4 h. Cell lysates were analyzed by Western blot (IB, immunoblot) using a panel of antibodies as shown. Protein band intensity was determined for MDM2 and p21 and is shown in arbitrary units on the y-axis. D, U2OS cells stably expressing MLL fusions were either treated with 0.4 μM adriamycin or mock-treated (0 h). Cell lysates prepared at 0, 3, 6, or 9 h after adriamycin addition were probed with the indicated antibody. Densitometry analysis was performed on MDM2, p21 and Bax protein bands (relative density is shown on the y-axis in arbitrary units). IB, immunoblot.
vector- or MLL-ELL-CT-expressing TK6 cells (Fig. 3C, compare lanes 1–3 and 16–18 to lanes 4–15). Taken together, these data show that the inhibitory effect of MLL fusion proteins on p53-mediated transcription persists over time following genotoxic injury and is not cell type-specific.

Transcriptional Activity of p53(6KR) Mutant Cannot Be Suppressed by MLL Fusion Proteins—We have observed a substantial reduction in p53 acetylation by p300 in response to stress in U2OS and TK6 cell lines stably expressing MLL fusion proteins. To determine whether this mechanism is primarily responsible for the inhibitory effect of MLL fusions on p53 transcriptional activity, we utilized p53 mutant (p53(6KR)) in which six C-terminal lysine residues (Lys-370, Lys-372, Lys-373, Lys-381, Lys-382, and Lys-386) have been substituted with arginines. Previously published reports have demonstrated that this mutant cannot be acetylated by p300 in vitro or in vivo (5, 11). We reasoned that if the disruption in p300-mediated p53 acetylation is the predominant mechanism of action by MLL fusion proteins, then the functional activity of p53(6KR) should not be affected by MLL chimeras.

To test this assumption, we co-expressed p53(6KR) with either MLL fusions or MDM2, which has previously been shown to be ineffective in either inhibiting or degrading acetylation-deficient p53 mutants (11, 12). Wild-type p53 was included as a positive control, and the induction of endogenous p21 and MDM2 was used as a readout of either mutant or wild-type p53 transcriptional activity. Consistent with previously published observations (13), p53(6KR) induced both p21 and MDM2, albeit to a lesser degree than wild-type p53 (Fig. 5, compare lanes 2 and 3). As expected, exogenous MDM2 expression did not have an effect on p53(6KR)-mediated induction of p21. Significantly, MLL chimeras also failed to further suppress p53(6KR)-mediated induction of endogenous p21 and MDM2 (Fig. 5, compare lane 3 to lanes 4–8), supporting the notion that interference with p53 acetylation by p300 plays a critical role in the inhibitory effect of MLL fusions.

**DISCUSSION**

Acute leukemias with 11q23 translocations are characterized by an aggressive clinical course, resistance to conventional
treatment regimens, and poor outcomes (1, 14). In this report, we show that some of the most frequently detected MLL fusion proteins inhibit p53 transcriptional activity, which may contribute not only to MLL leukemogenesis but also to radiotherapy and chemotherapy resistance.

Even though MLL chimeras were expressed at low levels under both transient and stable conditions in this study, they potentially suppressed p53 transactivation function. These observations are consistent with previous reports showing that despite low levels of expression, MLL fusions are fully capable of transforming normal bone marrow cells and causing leukemias in animal models (15). It has been suggested that high levels of MLL chimeras might be detrimental to cellular growth, whereas low expression facilitates malignant transformation (3).

Our results strongly implicate MLL partner proteins in the inhibition of p53 activity and physical binding to p53. The MLL-ELL/H9004CT mutant, which contained the MLL N terminus found in all fusions and an additional sequence comparable in length to some partner proteins, has consistently failed to suppress p53 activity in reporter assays and in response to DNA damage. ELL has been shown to mediate MLL-ELL binding to p53, and now we demonstrate that AF9, AF10, and ENL are also sufficient to induce p53 association with MLL fusion proteins carrying a large deletion in the MLL N terminus. AF9 and ENL are highly homologous proteins; however, there is little similarity between them and AF10 or ELL at the primary sequence level. Yet, an examination of the predicted secondary structure reveals that all of these partner proteins contain two conserved α-helical motifs fused to MLL (data not shown). These secondary structures might mediate their binding to p53, which con-
tains similar motifs in its N terminus.

Wild-type, full-length ELL suppresses p53 activity (5) and functions as a bona fide oncogene to transform normal fibroblasts (16). However, it remains to be determined whether wild-type AF9, AF10, or ENL are capable of affecting p53 function in a similar fashion in the absence of fusion to the MLL N terminus.

Our results demonstrate that stress-induced p53 acetylation by p300 is substantially inhibited by stable expression of MLL chimeras. A reduction in p53 acetylation has been convincingly linked to the down-regulation of its biological activity. For example, it has been shown that mutant p53 that is resistant to p300-mediated acetylation has an impaired ability to induce both cell cycle arrest and apoptosis (13). Furthermore, Sir2α and HDAC1 deacetylases, which actively remove acetyl moieties from the p53 C-terminal lysines, are known to have a significant inhibitory effect on the p53 function (17, 18). Yet, our current data as well as previously published observations (13) show that acetylation-deficient p53 retains residual transactivating function. We now demonstrate that p53(6KR) activity cannot be further reduced by MLL fusions, which helps explain why the inhibition of wild-type p53 by MLL chimeras is not complete. By reducing p300-mediated p53 acetylation, MLL fusions essentially convert p53 into an acetylation-deficient mutant that is still capable of inducing low-level expression of p53 downstream targets.

Exactly how MLL fusions reduce p53 acetylation by p300 remains under investigation. One possibility is that MLL chimeras disrupt the physical association of p300 with p53 by sharing a common binding site, as has been demonstrated for MLL-ELL (5). On the other hand, MLL fusions might recruit deacetylases to p53, which, in turn, inhibit its activity. Interestingly, the N terminus of MLL has recently been shown to directly interact with histone deacetylase 1 in vivo (19). Whereas the partner protein presence is clearly sufficient to promote p53 binding to MLL fusions, the MLL N terminus might be required for the functional suppression of p53 activity.

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